Production of bioactive substances by intestinal bacteria as a basis for explaining probiotic mechanisms: bacteriocins and CLA

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Abstract

The mechanisms by which intestinal bacteria achieve their associated health benefits can be complex and multifaceted. In this respect, the diverse microbial composition of the human gastrointestinal tract (GIT) provides an almost unlimited potential source of bioactive substances (pharmabiotics) which can directly or indirectly affect human health. Bacteriocins and fatty acids are just two examples of pharmabiotic substances which may contribute to probiotic functionality within the mammalian GIT. Bacteriocin production is believed to confer producing strains with a competitive advantage within complex microbial environments as a consequence of their associated antimicrobial activity. This has the potential to enable the establishment and prevalence of producing strains as well as directly inhibiting pathogens within the GIT. Consequently, these antimicrobial peptides and the associated intestinal producing strains may be exploited to beneficially influence microbial populations. Intestinal bacteria are also known to produce a diverse array of health-promoting fatty acids. Indeed, certain strains of intestinal bifidobacteria have been shown to produce conjugated linoleic acid (CLA), a fatty acid which has been associated with a variety of systemic health promoting effects. Recently, the ability to modulate the fatty acid composition of the liver and adipose tissue of the host upon oral administration of CLA-producing bifidobacteria and lactobacilli was demonstrated in a murine model. Importantly, this implies a potential therapeutic role for probiotics in the treatment of certain metabolic and immunoinflammatory disorders. Such examples serve to highlight the potential contribution of pharmabiotic production to probiotic functionality in relation to human health maintenance.

Introduction

It is estimated that the healthy human adult gastrointestinal tract (GIT) harbors approximately 10^{13} microorganisms (Ventura *et al.*, 2009). Initially developed at birth, the intestinal microbiotia is primarily comprised of high proportions of such microorganisms as bifidobacteria which are thought to be selected by breast or formula milk in the first weeks of life (Fanaro *et al.*, 2003; Martin *et al.*, 2009). Development of the adult microbiota is consistent with dominating populations of *Firmicutes* (including genera of *Clostridia* and lactic acid bacteria) and *Bacteroidetes*, while *Proteobacteria*, *Actinobacteria*, *Fusobacteria* and *Verrucomicrobia* are present to a lesser extent (Eckburg *et al.*, 2005). The complex intestinal biomass is predicted to consist of greater than 1000 different phylotypes comprised of both the permanent or autochthonous inhabitants which form the stable populations of the adult gut ecosystem, and the acquired allochthonous or transient flora, which are obtained from diet (such as probiotics) or from the environment. Probiotics are live microorganisms, most frequently species of lactobacilli and bifidobacteria, which when administered in adequate amounts, confer a health benefit on the host (FAO/WHO, 2001). Although such health benefits are strain-dependent (Helwig *et al.*, 2006), a single daily oral administration of 10^9 bacterial colony forming units (CFU) has generally been accepted as the optimal probiotic dose based on detection of the organism in human faeces (Tannock, 2003). However, in some instances higher quantities may be required (Gionchetti *et al.*, 2007; Larsen *et al.*, 2006; Lee & Lee, 2009; Mimura *et al.*, 2004), and thus the efficacious dosage may also be regarded as strain-dependent.

The intestinal microbiota is thought to have an integral role in human nutrition, metabolism, epithelial development, immune modulation, regulation of fat storage and protection against pathogens (Backhed *et al.*, 2004; Claus *et al.*, 2008; Corr *et al.*, 2007; Lee *et al.*, 2003;

Martin *et al.*, 2010; Martin *et al.*, 2008b; Wells *et al.*, 2010). Indeed, fluctuations in the composition of the intestinal ecosystem have been associated with various disease states including inflammatory immune disorders, obesity and cancer (Backhed, 2010; Davis & Milner, 2009; Scanlan *et al.*, 2006). In this respect, probiotic interventions may beneficially influence the intestinal microbial ecology, intestinal homeostasis and host metabolism and, ultimately, the health of the host. Strain-specific microbial derived bioactive molecules, collectively termed "pharmabiotics" which include live or dead microorganisms as well as bacterial constituents and metabolites, may mediate many such interactions within the GIT (Shanahan *et al.*, 2009). For example, production of antimicrobial peptides such as bacteriocins may beneficially modulate the intestinal ecology by the specific inhibition of pathogens (Corr *et al.*, 2007).

Probiotics interact with the intestinal epithelial cells directly via cell components such as DNA, lipoteichoic acids and cell-surface polysaccharides (Ghadimi *et al.*, 2010; Jijon *et al.*, 2004; Lebeer *et al.*, 2010; Pedersen *et al.*, 2005) but also indirectly, through the production of bioactive metabolites (Heuvelin *et al.*, 2009; Menard *et al.*, 2004; Tao *et al.*, 2006; Yan *et al.*, 2007). Microbial-derived peptides and polysaccharides can activate signaling pathways and influence factors such as cytokine secretion and gut permeability, thereby enhancing epithelial barrier function. For example, a bioactive peptide secreted by *Bifidobacterium infantis* increased transepithelial resistance of human T84 cells by altering the expression of tight junction proteins (claudins and occludin) and cytokines (IFN-γ) via a MAP-kinase-dependent mechanism (Ewaschuk *et al.*, 2008). *B. infantis* conditioned medium also reduced colonic permeability and improved colitis in IL-10 deficient mice (Ewaschuk *et al.*, 2008). Furthermore, the anti-inflammatory activity mediated by a bioactive polysaccharide PSA produced by the gut commensal *Bacteriodes fragilis* protected mice against *Helicobacter hepaticus* induced colitis

(Mazmanian *et al.*, 2008). Therefore certain members of the intestinal microbiota can enhance gut barrier function and maintain intestinal homeostasis indicating a potential therapeutic role for probiotics in the prevention and treatment of gastrointestinal diseases.

In addition to having local effects in the gut, the intestinal microbiota is thought to possess the capacity to influence the overall metabolic homeostasis of the host. Indeed, germ free mice exhibited altered metabolic profiles of the colon, liver and kidney compared with conventional animals (Claus *et al.*, 2008). The colon of germ free animals was characterized by an increase in raffinose and reduced levels of amino acids, ammonia, 5-aminovalerate and short chain fatty acids (SCFA) as well as other metabolites involved in energy pathways (Claus *et al.*, 2008). Moreover, extra-intestinally, elevated levels of taurine, trimethylamine-*N*-oxide (TMAO) and bile acids were evident in the liver of germ free animals. In addition, higher levels of choline, betaine, *myo*-inositol and *scyllo*-inositol in the kidneys of germ-free mice were linked with a hypertonic environment which was associated with renal dysfunction in previous studies (Claus *et al.*, 2008). The extensive metabolic capability of intestinal microorganisms, such as bifidobacteria, is thought to provide them with a competitive advantage within the GIT. For example, it was recently suggested that the predominance of *Bifidobacterium breve* populations characteristic of the infant microbiota may be attributed to an operon dedicated to the degradation of starch, amylopectin and pullulan exclusively present in this species (Kleerebezem & Vaughan, 2009). This undoubtedly contributes to the ability of bifidobacteria to colonize early in life given that human milk and colostrum contain a wide variety of complex sugars. It has also been established that interventions with such probiotic strains can modulate the metabolic phenotype of the host in a very specific manner. For instance, the administration of *Lactobacillus paracasei* or *Lactobacillus rhamnosus* (in the presence or absence of galactosyl oligosaccharide

prebiotics) increased bifidobacteria and reduced *Clostridium perfringens* and *Staphylococcus aureus* populations of germ free mice inoculated with a model of human baby microbiota compared with control animals (Martin *et al.*, 2008a; Martin *et al.*, 2008b). The resulting alterations in lipid metabolism involved a decrease in hepatic triglycerides and an increase in long chain poly unsaturated fatty acids (PUFA) and correlated with a reduction in plasma lipoprotein levels. The modulation of amino acid, methylamine and SCFA metabolism as well as glycogenesis and gluconeogenesis were also reported upon exposure to the probiotics (Martin *et al.*, 2008a; Martin *et al.*, 2008b). As discussed in greater detail below, the gut microbiota may also modulate the fatty acid composition of the liver, brain and adipose tissue of the host via synthesis of bioactive fatty acids such as conjugated linoleic acid (CLA) (Wall *et al.*, 2010; Wall *et al.*, 2009). Anti-inflammatory and anti-cancer properties are among the wide array of health promoting effects associated with isomers of CLA (Cook *et al.*, 1993; Ha *et al.*, 1987). Therefore, production of such bioactive metabolites may also be considered an important probiotic trait.

It is thus evident that the commensal microbiota has an almost infinite potential for metabolite production, many of these are pharmabiotic substances which can positively influence human health. In this review, we specifically examine the ability of the gut flora to produce antimicrobial peptides, namely bacteriocins, and bioactive fatty acids such as CLA and discuss their contribution to probiotic functionality.

Bacteriocin production as a basis for probiotic functionality

Introduction

Bacteriocins are ribosomally synthesized antimicrobial peptides produced by a wide variety of bacterial species which also posses a cognate immunity system for self-protection. For the most part, bacteriocins have a narrow spectrum of activity, inhibiting strains closely related to the producer. Consequently, it is thought that these peptides assist the producers to compete within their specific ecological niche. However, some bacteriocins possess a broad spectrum of inhibition, such as nisin which is active against numerous gram positive targets (Le Blay *et al.*, 2007). Such broad spectrum bacteriocins and/or their associated food grade producers, may be exploited to prevent the growth of undesirable spoilage organisms in food (Cotter *et al.*, 2005). The production of organic acids and hydrogen peroxide may also contribute to the antimicrobial activity of probiotic bacteria (Pridmore *et al.*, 2008; Ryan *et al.*, 2008). Although they could potentially reach high concentrations in certain local regions of the gut, these compounds act in a non-targeted manner and their contribution to probiotic functionality has not been investigated as extensively.

Colicins and microcins are well characterized bacteriocins produced by and active against strains of *Escherichia coli* and closely related species of *Enterobacteriaceae*. Colicins are generally plasmid determined antimicrobials and are often encoded with a lysis protein which, when induced, activates phospholipase A resulting in cell death and release of the bacteriocin (Snijder & Dijkstra, 2000). In such instances, colicin production is a lethal event for the producing cells. Colicin proteins have a molecular mass of 25-80 kDa and are comprised of three functional domains. The central domain is involved in the recognition and binding of outer membrane proteins on target cells such as the vitamin B12 receptor BtuB, the siderophore receptors FepA, Cir, and the nucleoside receptor Tsx which can also act as colicin receptors (Bradley & Howard, 1992; Buchanan *et al.*, 2007; Di Masi *et al.*, 1973). The Tol/Ton transport

systems of sensitive bacteria are exploited by the N-terminal domain for translocation of the colicin across the outer membrane of the target cell (Davies & Reeves, 1975a; Davies & Reeves, 1975b). In the case of pore-forming colicins, the C-terminal domain interacts with the inner membrane (Lakey & Slatin, 2001) or alternatively, with DNA or RNA in the cytoplasm in the case of endonuclease colicins (James *et al.*, 2002). Uniquely, colicin M inhibits peptidoglycan synthesis via enzymatic digestion of the bond between the lipid moiety and the pyrophosphoryl group of the peptidoglycan intermediate lipid II (El Ghachi *et al.*, 2006). In contrast, microcins are a highly diverse collective of 14 low molecular mass peptides (< 10 kDa) (Duquesne *et al.*, 2007). These antimicrobials are subclassified based on the presence and localisation of posttranslational modifications, the organisation of the gene cluster and the leader sequence (Duquesne *et al.*, 2007). Class I microcins are less than 5 kDa and require extensive posttranslational modification for activity (Duquesne *et al.*, 2009; Metlitskaya *et al.*, 2006; Roy *et al.*, 1999). Such modifications give rise to thiazole and oxazole rings which give microcin B17 its characteristic structure (Bayer *et al.*, 1995), a nucleotide-heptapeptide which is characteristic of microcin C7/C51 (Guijarro *et al.*, 1995; Metlitskaya *et al.*, 1995) and a lasso structure found in the cyclic microcin J25 peptide (Wilson *et al.*, 2003). The higher molecular mass microcins (5-10 kDa) comprise class II, which are further subdivided based on the presence of disulfide bonds in class IIa (microcins L, V and 24). Conversely, class IIb microcins are distinguished by post translational modifications at the C-terminus of the mature peptide and are devoid of disulfide bonds (microcins E492, M, H and I) (Duquesne *et al.*, 2007). Like colicins, microcins exploit siderophore receptors and the TonB uptake system of the target cells (Destoumieux-Garzon *et al.*, 2006; Destoumieux-Garzon *et al.*, 2003; Duquesne *et al.*, 2007). However, their mechanisms of action vary considerably as could be expected from their structural diversity.

Class I microcins specifically target intracellular enzymes responsible for DNA/RNA structure or synthesis. For example, microcin B17 inhibits DNA gyrase (Vizan *et al.,* 1991), microcin C7/C51 inhibits the aspartly tRNA synthase (Metlitskaya *et al.*, 2006) while microcin J25 targets RNA polymerase (Adelman *et al.*, 2004). Class II microcins on the other hand, are thought to permeabilise the inner membrane of target cells. It was recently shown that microcin E492 activity requires the mannose phosphotransferase system of target cells (Bieler *et al.*, 2010; Bieler *et al.,* 2006), similar to class IIa and several class IId bacteriocins of Gram positive bacteria (Diep *et al.*, 2007; Kjos *et al.*, 2009).

Bacteriocins produced by Gram positive organisms have been differentiated into two classes (Class I and Class II) on the basis of modifications of their precursor peptides which introduce characteristic structural features (Cotter *et al.,* 2005). Class I peptides are those which undergo post-translational modification and, until recently, consisted of the lantibiotics exclusively. In this respect, lantibiotics are characterized by extensive post-translational modifications which introduce the thioether amino acids lanthionine and methyllanthionine (resulting in the formation of intramolecular ring structures). However, a recently updated classification scheme for bacteriocins proposed the subdivision of class I due to the identification of novel bacteriocins which contain post-translational modifications atypical of lantibiotics (Rea *et al.*, 2010b). Now designated class Ia, many of the lantibiotic group exert their antimicrobial activity through an interaction with the peptidoglycan precursor lipid II which in turn causes disruption of cell wall biosynthesis and/or pore formation thereby compromising the integrity of the cytoplasmic membrane of target cells (Pag & Sahl, 2002). Nisin, the most well known and extensively studied lantibiotic, is capable of both mechanisms (Wiedemann *et al.*, 2001), which at least partially accounts for the potent activity of this bacteriocin. However, other targets have

206 also been identified for lantibiotics, for example, the membrane phospholipid
207 phosohatidylethanolamine serves as a docking molecule for cinnamycin (Machaidze & Seelig,
208 2003). Further subdivisions of the diverse lantibiotic group have been proposed based on
209 structure, mechanism of action, pathway of maturation and the presence or absence of
210 antimicrobial activity (Cotter *et al.*, 2005; Jung, 1991; Pag & Sahl, 2002; Willey & van der
211 Donk, 2007). The inclusion of two new subclasses of post-translationally modified bacteriocins
212 has also been proposed. The labyrinthopeptins A1, A2 and A3 produced by *Actinomadura*
213 *namibiensis* DSM 6313 constitute class Ib which are distinguished by the presence of labionin
214 (Meindl *et al.*, 2010) and the novel sactibiotics, class Ic, contain the sulphur to α carbon linkage-
215 containing antibiotics thuricin CD and subtilosin A produced by *Bacillus thuringiensis* and
216 *Bacillus subtilis*, respectively (Kawulka *et al.*, 2004; Rea *et al.*, 2010c).
217 The unmodified class II bacteriocins are more diverse and generally function through
218 membrane permeabilisation of the target cells, causing dissipation of the proton motive force.
219 This class has been further subdivided into four distinct groups (Nissen-Meyer *et al.*, 2009).
220 Class IIa is comprised of the *Listeria*-active pediocin-like bacteriocins which possess a
221 conserved N-terminal motif Y-G-N-G-V and at least one disulfide bridge linking two cysteine
222 residues (Drider *et al.*, 2006). These are the most extensively studied unmodified bacteriocins
223 due to their associated antilisterial activity and given that they are generally produced by food
224 grade lactic acid bacteria (LAB). Recently, mannose phosphotransferase systems (PTS) were
225 identified as target receptors for class IIa bacteriocins where a positive correlation was observed
226 between the expression levels of the mannose PTS components of target microorganisms and
227 bacteriocin sensitivity (Kjos *et al.*, 2009; Opsata *et al.*, 2010). Class IIb two-peptide bacteriocins
228 such as abp118 require the presence of two complementary peptide components for optimal

antimicrobial activity (Oppegard *et al.*, 2007). These bacteriocins form ion-selective channels in their target cell membranes. Cyclic peptides such as gassericin A differentiate class IIc (Arakawa *et al.*, 2010). Finally, class IId bacteriocins are a diverse group of peptides with equally diverse mechanisms of action, as highlighted by the following examples. Bacteriocins of this variety have been shown to act via mechanisms of targeted pore formation involving mannose PTS receptor binding in the case of lactococcin A and lactococcin B (Diep *et al.*, 2007), by general membrane disruption as proposed for the leaderless bacteriocin aurocin A53 (Netz *et al.*, 2002), and also by the inhibition of cell division through interactions with lipid II in the case of lactococin 972 (Martinez *et al.*, 2008). In addition, it was recently established that this bacteriocin also effects prophage induction in a prophage/host-specific manner, revealing a novel mechanism of inhibition mediated by lactococin 972 (Madera *et al.*, 2009).

There has been a particular focus in recent years on GIT bacteria that are bacteriocin producers. Bacteriocins produced by intestinal microorganisms generally have narrow inhibitory spectra and thus may be suitable for therapeutic biomedical applications. Thuricin CD, abp118 and microcin C7 are examples of bacteriocins derived from intestinal isolates whose narrow inhibitory spectra include the intestinal pathogens *Clostridium difficile*, *Listeria monocytogenes*, *E. coli* and *Shigella flexneri*, respectively (Corr *et al.*, 2007; Cursino *et al.*, 2006; Rea *et al.*, 2010c). In such instances, *in situ* bacteriocin production may be advantageous in that, it may overcome negating effects such as proteolysis during gastric transit. Moreover, production of bacteriocins may confer a competitive advantage to the producer over closely related organisms and as such, contribute to dominance. Therefore, the intestinal microbiota have been the subject of several studies designed to identify novel bacteriocins produced by gut bacteria.

Bacteriocin production by intestinal bacteria

The intestinal microbiota has been identified as a rich source of potentially probiotic bacteria which produce novel antimicrobial and, more specifically, antipathogenic bacteriocins (Table 1). Veritably, bacteriocin production has long been touted as a potential probiotic trait since before any direct evidence existed as to substantiate this. Colicins and microcins are found at particularly high frequencies in isolates of human origin (Gillor *et al.*, 2008; Gordon & O'Brien, 2006; Smajs *et al.*, 2010; Smarda & Obdrzalek, 2001). It is notable that a common observation of studies mining intestinal sources for bacteriocin-producing isolates is the frequent isolation of a single producing strain or of a number of genetically distinct strains or even species from within a sample, niche or host which all produce the same bacteriocin (Arakawa *et al.*, 2010; Gordon & O'Brien, 2006; Marcille *et al.*, 2002; Smajs *et al.*, 2010). This trend was also evident from a recent screening study in our laboratory which revealed that of 84 antimicrobial producing intestinal lactic acid bacteria (LAB) isolates, there were just 24 distinct strains identified (corresponding to 71% redundancy) (O'Shea *et al.*, 2009). Furthermore, nine of these individual isolates were *Streptococcus bovis* which, while genetically distinct, displayed similarity with respect to their inhibitory spectra and the protease sensitivity of the antimicrobials which they produced. It is likely that all of these strains produce similar or even identical bacteriocins especially considering that each displayed cross-immunity (O'Shea *et al.*, 2009). While such redundancy has been attributed to the biased nature of culture based approaches in terms of selective media and indicators strains employed (Marcille *et al.*, 2002; Millette *et al.*, 2007; O'Shea *et al.*, 2009; Toure *et al.*, 2003), it is likely that the competitive advantage provided by the production of these specific antimicrobials is also a contributory factor. Culture-based screening procedures also suffer by virtue of the fact that environmental factors influence

bacteriocin regulation, and in the absence of the appropriate signal bacteriocin production may be overlooked or undetected. In addition, selective pressures may influence the antimicrobial phenotype of the bacteriocin producing cell once outside the host (Lee *et al.*, 2008; Toure *et al.*, 2003; Vriezen *et al.*, 2009). Alternative molecular or genomic appraoches overcome the limitations of culture based screening techniques. Notably, the increasing availability of microbial genomes and development of bioinformatic systems, such as BAGEL the web based genome mining tool (de Jong *et al.*, 2010), can facilitate *in silico* screening. The power of this approach was recently demonstrated with the identification of a novel two-component lantibiotic, lichenicidin, which exhibited anti-*Listeria* activity as well as the ability to inhibit antibiotic-resistant *Staphylococcus aureus* and enterococci (Begley *et al.*, 2009). Considering the high proportion of GIT-associated microbes which can not be cultured, emerging high-throughput sequencing technologies and functional metagenomics-based approaches will be crucial with respect to the identification of genes potentially encoding novel bacteriocins within the genomes of previously uncharacterized intestinal inhabitants. It is possible that such bacteriocins may well be produced efficiently in the gut but may not be detected *in vitro* in the laboratory environment.

Bacteriocin regulation and adaptation to the GIT

The physiological conditions encountered in the GIT are undoubtedly important factors influencing bacteriocin production *in vivo*. For example, it is known that bacteriocin production by Gram-positive bacteria is frequently tightly regulated by quorum sensing mechanisms which are cell density dependant (Kleerebezem & Quadri, 2001). In such cases, the accumulation of a highly specific secreted peptide pheromone or induction factor acts as an indicator of cell density. When present at sufficient concentrations, this inducer is sensed by a cognate

membrane-associated histidine kinase causing phosphorylation of the intracellular response regulator which then activates expression of the regulated operon(s) responsible for bacteriocin synthesis and secretion (Kleerebezem & Quadri, 2001). In several cases, the bacteriocin peptides themselves also serve as signaling peptides and thus autoregulate their own synthesis (Kleerebezem, 2004). However, bacteriocin production has also frequently been noted to be an environment-sensitive phenotype. Factors such as temperature can influence bacteriocin synthesis as is the case for sakacin A, which only occurs when the associated producing strains, *Lactobacillus sakei* Lb706 or *Lactobacillus curvatus* LTH1174, are grown at 25-30°C (Diep *et al.*, 2000). In the extreme case of *Enterococcus faecium* L50, enterocins L50, P and Q are each produced optimally at different growth temperatures (Cintas *et al.*, 2000).

Interestingly, different mechanisms can also exist within a species. For example, different induction peptides regulate plantaricin production from otherwise highly conserved bacteriocin operons in *Lactobacillus plantarum* C11 and *L. plantarum* NC8. While accumulation of the pheromone peptide plantaricin A, which is constitutively expressed at basal levels, mediates plantaricin production in *L. plantarum* C11 (Hauge *et al.*, 1998), bacteriocin production by strain *L. plantarum* NC8 instead requires the presence of specific inducer bacteria (Maldonado *et al.*, 2004a; Maldonado *et al.*, 2004b). This suggests that, in some cases, bacteriocin production necessitates a competitive environment such as that of the GIT. However, the corollary can also be true. Of several clinical methicillin-resistant *S. aureus* (MRSA) isolates, production of the lantibiotic Bsa was associated with community acquired isolates but was absent from hospital acquired/health care-associated strains (Daly *et al.*, 2010). The lack of antimicrobial activity among hospital acquired/health care-associated isolates was ascribed to an adaptive response of these strains to a health care environment where the presence of antibiotics

eliminated much of the surrounding competitive flora. It is also not uncommon for multiple bacteriocins to coexist within a strain. In such instances, bacteriocin production in response to different environmental stimuli may further enhance the competitive advantage of the producing strain. This is expemlified by mutacin production in the dental caries patient isolate *Streptococcus mutans* UA140. It was found that narrow spectrum mutacin IV was almost exclusively produced in liquid medium and thus is likely important for the primary colonization of the tooth surface by S. mutans. However, production of the broad spectrum lantibiotic mutacin I could only be achieved on a membrane or solid medium suggesting that the competitive environment of biofilm-like growth on the densely colonized tooth surface may be a prerequisite for mutacin I production by the same strain (Qi *et al.*, 2001). Thus, it is tempting to suggest that *S. mutans* adapts to increasingly competitive environments in the oral cavity through the production of different bacteriocins. A similar phenomenon has been noted in the gut in the form of the trypsin-dependent production of the lantibiotic ruminococcin A by the strictly anaerobic intestinal isolate *Ruminococcus gnavus* E1 (Gomez *et al.*, 2002). The importance of the intestinal protease was confirmed *in vivo* as the faeces of rats monoassociated with the producing strain was devoid of antimicrobial activity following oral ingestion of a trypsin inhibitor (Ramare *et al.*, 1993). This effect was correlated with the successful colonization of subsequently administered ruminococcin A-sensitive *Clostridium perfringens*. Following cessation of the trypsin inhibitor treatment, faecal antimicrobial activity reappeared and within three days *C. perfringens* was no longer detectable, thereby confirming both trypsin dependence and the production and efficacy of ruminococcin A *in vivo*. This was further substantiated by the loss of antimicrobial activity and reduced faecal proteolytic activity after ligature of the pancreatic bile duct of the rats which contrasted with the situation in an operated non-ligatured control group. Following oral ingestion

of trypsin, an increase in both proteolytic and antimicrobial activity was detected in the faeces of the ligatured rats (Ramare et al., 1993). A model for the transcriptional activation of ruminococcin A production proposed the trypsin-dependent activation of a specific (pre)inducer peptide (Gomez et al., 2002). Although the thioether bridges of lantibiotics offer some resistance to protease activity (Bierbaum *et al.*, 1996; Moll *et al.*, 2009; Ottenwalder *et al.*, 1995; Rink *et al.*, 2010; Suda *et al.*, 2010), typically exposure to intestinal proteases such as trypsin is detrimental to bacteriocin activity. Consequently, both engineering and encapsulation strategies have been investigated to overcome the adverse effects of proteolysis of bacteriocins within the GIT (O'Shea *et al.*, 2010; Stern *et al.*, 2006). However, the trypsin-dependant synthesis of ruminococcin A not only suggests that this antimicrobial activity plays a role in bacterial interactions in the gut, but also indicates that bacteriocin production may be an adaptive response of the producing strain to the physiology of the gut ecosystem.

Largely under the control of the SOS response, colicin biosynthesis can also be induced by many environmental stresses (Cascales *et al.*, 2007; Kuhar & Zgur-Bertok, 1999). Notably, temperature has similarly been shown to affect colicin production (Cavard, 1995; Kennedy, 1971; Kuhar & Zgur-Bertok, 1999; Smajs & Weinstock, 2001). In the case of colicin K, production was induced at 37°C while only basal levels of production were detected at 22°C (Kuhar & Zgur-Bertok, 1999) indicating adaptation to physiological conditions. It has also been established that nutrient depletion and hence a competitive environment are important factors influencing the production of both colicins (Cascales *et al.*, 2007; Kuhar & Zgur-Bertok, 1999) and microcins (Duquesne *et al.*, 2007). In particular, microcin production is stimulated under conditions of iron limitation (Azpiroz & Lavina, 2004; Boyer & Tai, 1998). While this may be unlikely in the gut, it has been suggested that microcins may mediate competition for iron at

extra-intestinal bodily sites, thereby assisting pathogenesis of the producing strains (Gordon, 2009; Jeziorowski & Gordon, 2007).

Bacteriocin genotypes and selective pressures of the GIT

As noted above, it is possible that the high level of redundancy of bacteriocin producing strains in intestinally derived samples may be due to their numerical prominence, by virtue of bacteriocin synthesis. In support of this, a culture-independent real-time PCR assay revealed that *pedA* homologues, responsible for the production of pediocin PA-1, are widely distributed among members of the infant microbiota, as revealed by their detection in the faeces of 11 of 17 individuals investigated (Mathys *et al.*, 2007). A number of other bacteriocin structural genes, or homologues thereof, have also been frequently identified in several independent studies, as for the class IIb bacteriocin abp118. More specifically, Southern analysis has revealed the widespread dissemination of *abp118* α and β homologues in intestinally derived *Lactobacillus salivarius* isolates of human, avian and porcine origin (Li *et al.*, 2007). In separate studies, these genes were identified in the extensively studied probiotic *L. salivarius* CECT 5713 which was isolated from the breast milk and infant faeces of a mother and child pair (Jimenez *et al.*, 2010) as well as in the vaginal isolate *L. salivarius* CRL1328 (Pingitore *et al.*, 2009). In addition, a high frequency of the genetic determinants for salivaricin P, a natural variant of abp118, was observed in porcine derived intestinal *L. salivarius* isolates (Barrett *et al.*, 2007a). The frequency with which abp118 homologues are identified is indicative of the wide distribution of this genotype in *L. salivarius*, an autochthonous inhabitant of the GIT. A high frequency of colicin and microcin production has also been detected among human intestinal *E. coli* isolates (Gordon & O'Brien, 2006; Smajs *et al.*, 2010; Smarda & Obdrzalek, 2001). The observation that pediocin

PA-1, abp118 and colicins are plasmid-encoded features is likely to be significant. Indeed, bacteriocin loci are frequently located on mobile genetic elements such as plasmids and conjugative transposons and may frequently undergo horizontal transfer between related strains, thus potentially explaining their prevalence within GIT microorganisms. Notably, the *in vivo* transmission of a bacteriocin-rich megaplasmid of *Streptococcus salivarius* was recently demonstrated (Wescombe *et al.*, 2006a), which may explain the relative abundance of lantibiotic producing *S. salivarius* observed within the oral cavity (Simpson *et al.*, 1995).

A number of other bacteriocins have frequently emerged following investigations of gut microorganisms. The structural gene for the anti-*Clostridium* bacteriocin ruminococcin A was confirmed in seven distinct strains isolated from the faeces of neonates, healthy adults and adults with chronic pouchitis (Marcille et al., 2002). Interestingly, four of the *rumA*-positive strains were isolated from a single sample from a healthy child and belonged to three different species i.e. *R. gnavus*, *Runimococcus hansenii* and *Clostridium nexile*. Similarly, the identical circular bacteriocins gassericin A and reutericin 6 produced by *Lactobacillus gasseri* LA39 and *Lactobacillus reuteri* LA6, respectively, were isolated from a single neonatal fecal sample (Arakawa *et al.*, 2010; Kawai *et al.*, 2004; Toba *et al.*, 1991). Further compelling evidence for the competitive role of bacteriocins in the gut was obtained when it was established that a minimally cultured intestinal isolate *Bifidobacterium longum* DJO10A undergoes genome reduction in response to growth in a pure culture fermentation environment over 1,000 generations (Lee *et al.*, 2008). The loss of genetic loci responsible for lantibiotic production as well as oligosaccharide and polyol metabolism, each important features for bacterial competition in the large intestine, was observed. This finding, combined with the fact that the level of bacteriocin production by intestinal *Bifidobacterium* isolates can be low (Toure et al., 2003), may

explain why few bifidobacteria-associated bacteriocins have been identified to date despite a number of screening studies specifically targeting this important intestinal resident (Anand *et al.*, 1984; Gagnon *et al.*, 2004; Lievin *et al.*, 2000; Meghrous *et al.*, 1990; Zinedine & Faid, 2007). Moreover, the lantibiotic-deficient derivative of *B. longum* DJO10A demonstrated increased growth rates suggesting that the corresponding genome reduction favored the *in vitro* growth environment. However, this derivative had a significantly reduced competitive ability against *E. coli* and *Clostridium difficile* relative to the parent strain in a simulated anaerobic fecal environment (Lee et al., 2008). This example of specific gene loss is indicative of the co-evolution of the host and intestinal microbiota while also providing evidence that bacteriocin production is advantageous to the human intestinal microbiota. Typically, bacteriocins derived from intestinal bacteria display narrow inhibitory spectra and have been implicated in two proposed mechanisms of probiotic functionality, namely improved colonization and protection via pathogen inhibition. These are each discussed here.

Bacteriocins and improved colonization in the GIT

While several bacteriocins exhibit potent broad spectrum anti-pathogenic activity, the majority merely inhibit closely related commensal microorganisms. However, both broad and narrow spectrum bacteriocins can potentially provide the producing strain with a competitive advantage within complex environments. Interestingly, bacteriocin 32 which is widely disseminated among clinical *E. faecium* isolates, possesses the characteristic sequence motif of pediocin-like class IIa bacteriocins but lacks the characteristic anti-*Listeria* activity associated with this group (Inoue et al., 2006). Instead bacteriocin 32-producing isolates were found to be antagonistic to other *E. faecium* as well as the closely related species *Enterococcus hirae* and *Enterococcus durans*.

436 Similarly, salivaricin T, isolated from neonate faeces, lacks the anti-listerial activity
437 characteristic of two-component bacteriocins widely distributed in intestinal *L. salivarius* isolates
438 (O'Shea *et al*., unpublished data). This suggests that, both bacteriocin-32 and salivaricin T have
439 evolved to facilitate the establishment and survival of their respective producing strains, over
440 closely related competing microbes, within the GIT.
441 The ecological advantage of bacteriocin-producing strains may be exploited to
442 beneficially influence GIT populations, and could provide an effective mechanism for
443 replacement therapies *in vivo*. Indeed, bacteriocin mediated intra- and interspecies competition
444 has led to the successful establishment and predominance of the lantibiotic-producing
445 commercial probiotic *S. salivarius* K12 within the oral cavity. The lantibiotic-producing strains
446 superseded a co-administered lantibiotic-negative *S. salivarius* K12 derivative *in vivo*
447 (Wescombe *et al.*, 2006a). Salivaricin A also suppressed black-pigmented bacteria in saliva and
448 the efficacy of the strain K12 with respect to replacement therapy for halitosis and the prevention
449 of streptococcal pharyngitis has been demonstrated (Burton *et al.*, 2006; Horz *et al.*, 2007; Tagg,
450 2004). In other studies, a link has also been established between the production of the lantibiotic
451 mutacin 1140 and the ability of the producing mutans streptococci to persistently colonize the
452 oral cavity of humans (Hillman *et al.*, 1987; Hillman *et al.*, 1985). In this case, a lactate
453 dehydrogenase (LDH)-deficient derivative of the mutacin 1140-producing strain was generated.
454 This mutant successfully displaced indigenous *S. mutans* and reduced the incidence and severity
455 of dental caries in both gnotobiotic and conventional rats given that its ability to produce acid
456 was greatly reduced (Hillman, 2002; Hillman *et al.*, 2000). Bacteriocin production also seems to
457 enhance the competitiveness of strains located more distally in the GIT. It was repoted that a
458 salivaricin P-producing strain *L. salivarius* DPC6005 prevailed over four other co-administered

prospective probiotic strains (two *Lactobacillus murinus* strains, and a single *Lactobacillus pentosus* and *Pediococcus pentosaceus* strain) within the ileum digesta and mucosa of pigs (Walsh *et al.,* 2008). It is tempting to suggest that in this case, salivaricin P production may have provided *L. salivarius* DPC6005 with a competitive advantage *in vivo*. The predominance of this strain within the ileum is of significance given that administration of the five strain probiotic formulation alleviated *Salmonella* infection in pigs (Casey *et al.,* 2007) (as the ileum is also the main site of *Salmonella* invasion within the porcine GIT (Salyers & Whitt, 2002)).

Bacteriocin-mediated enhanced competitiveness may also contribute to the ability of potential pathogens to colonise specific niches. For example, the production of class IIb Blp bacteriocins by *Streptococcus pneumonae* enabled this strain to successfully colonize the mouse nasopharynx and to displace co-administered bacteriocin-negative *S. pneumoniae* populations (Dawid *et al.,* 2007). A further example includes six colicin-producing *E. coli* strains reported to persist in the GIT of mice over a non-producing isogenic control for 112 days following a single administration to the streptomycin treated animals (Gillor *et al.,* 2009). These findings demonstrate that colicinogeny assists colonization and persistence of pathogenic and probiotic *E. coli* strains within the GIT. Ovarall, these studies corroborate the theory that bacteriocin production affords the producing strains a competitive advantage which, in the context of the GIT, increases the efficacy of bacteriocin mediated colonization at various sites and results in the modulation of the indigenous microbiota in a specific manner.

Bacteriocins and pathogen inhibition in the GIT

There are numerous examples of the use of a bacteriocin or a bacteriocin-producing probiotic to control pathogens in the GIT or models thereof. Colicins and microcins exhibit considerable

potential for the inhibition of enteric pathogens (Cursino *et al.*, 2006). One widely used probiotic *E. coli* strain Nissle 1917 produces microcins H47 and M (Patzer *et al.*, 2003). This strain was found effective for reducing the colonization of bacterial pathogens (Lodinova-Zadnikova & Sonnenborn, 1997) and for treating diarrhea (Henker *et al.*, 2007; Henker *et al.*, 2008) in children as well as for the treatment of inflammatory bowel disease (Schultz, 2008). *E. coli* Nissle 1917 also inhibited the invasion of intestinal epithelial INT407 cells by *Yersinia enterocolitica*, *Shigella flexneri*, *Legionella pneumophila* and *Listeria monocytogenes* while invasion by *Salmonella enterica* serovar Typhimurium was reduced by 70% (Altenhoefer *et al.*, 2004). However, this protective effect was not attributed to microcin production by this strain as a bacteriocin-negative isogenic mutant was as effective as the parent strain (Altenhoefer *et al.*, 2004). Another non-pathogenic *E. coli* strain H22 which produces microcin C7, colicins E1 and Ib, aerobactin and a bacteriophage was found to inhibit a range of enteric pathogens *in vitro* (Cursino *et al.*, 2006). As *S. flexneri* only exhibited sensitivity to microcin C7, the *in vivo* inhibition of this pathogen was specifically attributed to the activity of this bacteriocin, when both *E. coli* H22 and *S. flexneri* were co-administered to mice (Cursino *et al.*, 2006).

In vitro studies indicate that the broad spectrum lantibiotic lacticin 3147 has the potential to be employed in the treatment for *C. difficile*-associated diarrhea (CDAD) (Rea *et al.*, 2007). The MIC_{50} (3.6 μg ml^{-1}) of this bacteriocin with respect to clinical *C. difficile* isolates was comparable to those of metronidazole and vancomycin (0.5-4.0 μg ml^{-1}), two antibiotics currently used for the treatment of this disease. Moreover, addition of a food grade (milk-based) lacticin 3147 powder to an anaerobic faecal fermentation completely eliminated *C. difficile* (10^6 CFU ml^{-1}) within 30 minutes, but also reduced lactobacilli and bifidobacteria populations by 3-log units (Rea *et al.*, 2007). The concentrations of lacticin 3147 required to bring about this

reduction of *C. difficile* were also much higher than the corresponding levels of metronidazole/vancomycin required in a simulated human distal colon model (Rea *et al.*, 2010a). A further investigation of the collateral damage to other members of the GIT microbiota arising from administration of these antimicrobials was achieved through high-throughput pyrosequencing specific of the V4 variable region of the 16s rRNA gene. This revealed dramatic impacts on the relative proportions of the dominant phyla of the microbiota in that all three antimicrobial treatments resulted in a shift from *Firmicutes* to *Proteobacertia* as well as dramatically reducing *Bacteriodetes* compared to the control (no antimicrobial) (Rea *et al.*, 2010a). The efficacy of another antimicrobial which possesses a narrow inhibitory spectrum inclusive of *C. difficile*, namely thuricin CD, was also tested using this model system and was found comparable to the conventional antibiotics with respect to the inhibition of *C. difficile* (Rea *et al.*, 2010a). In contrast however, thuricin CD did not significantly alter the relative proportions of the dominant populations in the simulated colonic environment compared to the control. As such, this two-component sactibiotic would appear to be an improved antibiotic alternative for the treatment of CDAD. In addition to overcoming the adverse effects of antibiotics on the indigenous gut microbiota, the use of such natural alternatives could also reduce the development and spread of antibiotic resistance in pathogenic bacteria.

There are a number of other examples of the use of bacteriocins and bacteriocin-producing probiotics with respect to controlling pathogens in the GIT. As previously noted, it has been established that production of ruminococcin A in rats monoassociated with a producing strain was associated with protection against *C. perfringens* and *C. difficile* (Ramare *et al.*, 1993). Likewise a human intestinal *Pediococcus acidilactici* isolate producing the anti-*Listeria* bacteriocin pediocin PA-1 has been found to successfully eliminate vancomycin-resistant *E.*

faecium (VRE) in mice (Millette *et al.*, 2008). In this case, the eradication of VRE was directly attributed to pediocin PA-1 production as a bacteriocin-negative derivative of the producing strain did not impact on the VRE populations in mice, relative to the control group. Moreover, reoccurrence of VRE was not apparant upon cessation of treatment with the bacteriocin-producing strain unlike the bacitracin treated control animals. This benefit was attributed to the minimal impact of the bacteriocin on the commensal gut flora, again highlighting the advantage and efficacy of bacteriocins over broad spectrum antibiotics (Millette et al., 2008). Corr *et al*., also demonstrated the power of utilizing bacteriocin-producing probiotics when they established that administration of the abp118-producing *L. salivarius* UCC118 significantly reduced infection levels of *Listeria monocytogenes* in mice (Corr et al., 2007). This protective effect was not apparent when a *L. monocytogenes* mutant expressing the dedicated abp118 immunity protein was employed (Corr *et al.*, 2007), thereby confirming that the anti-infective properties of this probiotic were specifically bacteriocin-mediated.

These studies confirm that bacteriocin production can contribute to the probiotic functionality of intestinal LAB and in some cases may be directly responsible for it. Thus narrow spectrum bacteriocins and intestinal producers thereof have exceptional potential with respect to beneficially modulating the gastrointestinal microbiota and in particular with respect to the inhibition of specific gastrointestinal pathogens. In addition, bacteriocin production may contribute to the potential anti-cancer properties of intestinal bacteria considering that several have exhibited inhibitory activity towards human cells (Booth *et al.*, 1996; Chumchalova & Smarda, 2003; Hetz *et al.*, 2002; Lagos *et al.*, 2009; Lancaster *et al.*, 2007; Smarda, 1983; Watanabe & Saito, 1980) although it should be pointed out that as yet, this is far less well understood.

Fatty acid production as a basis for explaining probiotic mechanisms

Introduction

Another example of pharmabiotic production by intestinal bacteria is their ability to produce health promoting bioactive fatty acids such as conjugated linoleic acid (CLA). Produced from free linoleic acid (*cis*-9, *cis*-12 18:2 octadecadienoic acid) by the microbial enzyme linoleic acid isomerase (Kepler *et al.*, 1966), CLA has been associated with a multitude of local and systemic health promoting effects *in vitro* and *in vivo*. These include anti-carcinogenic (Ha *et al.*, 1987), anti-atherogeneic (Lee *et al.*, 1994), anti-adipogeneic (Park *et al.*, 1997), anti-diabetogenic (Houseknecht *et al.*, 1998) and anti-inflammatory (Cook *et al.*, 1993) activities. It is well established that CLA is produced in the rumen due to the isomerase activity of bacteria such as *Butyrivibrio fibriosolvens* (Kepler *et al.*, 1966; Wallace *et al.*, 2007). In addition, the endogenous conversion of *trans*-vaccenic acid (*trans*-11 18:1) to CLA via delta-9 desaturase activity occurs within the mammary gland (Griinari *et al.*, 2000). Consequently, ruminant derived meat and dairy products have traditionally been a primary source of dietary CLA intake for humans (Jiang *et al.*, 1999). However, animal studies which revealed that conventional, but not germ-free, rats were capable of CLA production (Chin *et al.*, 1994), triggered investigations into the capacity of non-ruminant microbes for linoleic acid metabolism (Coakley *et al.*, 2003; Jiang *et al.*, 1998; Kim & Liu, 2002; Lin *et al.*, 1999).

Although there are 28 naturally occurring positional and geometric CLA isomers, *cis*-9, *trans*-11 CLA is regarded as one of the major bioactive isomers as it is the predominant isomer present in the diet, constituting greater than 90 % of the CLA content in milk fat (Stanton *et al.*, 2003). The biological effects of CLA have been attributed to two possible mechanisms of action.

Firstly, CLA is known to cause a decrease in the synthesis of arachidonic acid-derived eicosanoids such as prostaglandins and leukotrienes involved in inflammation and cancer (Belury, 2002). This may occur via displacement of arachidonic acid (C20:4) from cell membrane phospholipids or alternatively by the intervention of the cyclooxygenase and lipoxygenase pathways which are responsible for the synthesis of these eicosanoids. Modulation of gene expression presents a second possible mechanism of action, whereby CLA mediates activation of transcription factors such as peroxisome proliferator-activated receptors (PPARs) impacting on cell processes such as lipid metabolism, apoptosis and immune function (Belury, 2002).

While CLA has shown considerable promise as a bioactive agent, animal studies have demonstrated that an estimated daily intake of approximately 3 g of CLA may be required to realize the associated physiological benefits (Ip *et al*., 1994). This figure is considerably greater than the estimated average human daily intake of 0.1-1.0 g of CLA (Chin *et al.*, 1992; Mushtaq *et al.*, 2010). To address this, strategies to increase the levels of dietary CLA have been investigated such as dietary intervention of ruminants which can result in an elevation in the CLA content of milk (Lawless *et al.*, 1998; Stanton *et al.*, 1997). Further efforts included the manipulation of dairy starter cultures, capable of the isomerization of free lineoleic acid, to influence the CLA content of yoghurt and cheese (Kim & Liu, 2002; Lin *et al.*, 1999). Moreover, evidence of CLA production by species of the human intestinal microbiota, particularly bifidobacteria has more recently emerged (Barrett *et al.*, 2007b; Coakley *et al.*, 2003). Therefore, probiotic intervention with such bacteria has the potential to contribute to the *in situ* microbial conjugation of linoleic acid and thus, provide a potential alternative with respect to enhancing bioavailable CLA.

CLA production by intestinal bacteria

Like certain rumen bacteria, several strains of propionibacteria and of LAB commonly used as dairy starter cultures have the capacity to produce CLA from free linoleic acid during dairy fermentation (Hennessy *et al.*, 2007). Importantly, the screening of potential probiotic species present in culture collections, (Coakley *et al.*, 2003; Kim & Liu, 2002; Kishino *et al.*, 2002; Lin *et al.*, 1999; Ogawa *et al.*, 2001), as well as human faecal samples (Barrett *et al.*, 2007b; Oh *et al.*, 2003; Rosberg-Cody *et al.*, 2004) has also revealed the varying efficacy of lactobacilli and bifidobacteria of human intestinal origin for linoleic acid conjugation (Table 2). One study focussed on four human intestinally-derived strains, two *Lactobacillus acidophilus* and two *Lactobacillus casei* isolates, which were found to exhibit isomerase activity in both MRS broth and skim milk supplemented with 0.2 mg ml^{-1} free linoleic acid (Alonso *et al.*, 2003). The proportions of the isomers produced were similar for each of the four strains in both media, with the highest (117-132 µg ml^{-1}) and lowest (54-61 µg ml^{-1}) total CLA produced by *L. acidophilus* isolates L1 and O16, respectively. Greater than 90% of total CLA corresponded to the *cis*-9, *trans*-11 isomer and low concentrations of *trans*-10, *cis*-12 CLA were also detected. A similar assessment of an array of LAB and bifidobacteria revealed the efficacy of intestinal species of *Bifidobacterium*, particularly *Bifidobacterium breve*, with respect to CLA production from free linoleic acid (Coakley et al., 2003). Considerable interspecies variation was also evident in the capacity for linoleic acid conjugation in this study (with conversion levels varying from 3 - 65%). *Cis*-9, *trans*-11 CLA was the predominant isomer in each case, with *trans*-9, *trans*-11 CLA also being detected but at low concentrations (Coakley *et al.*, 2003). High-throughput screening of human stools for probiotics with a CLA-producing phenotype consistently favored

620 the isolation of *B. breve*, (Barrett *et al.*, 2007b; Oh *et al.*, 2003; Rosberg-Cody *et al.*, 2004)
621 highlighting the exceptional efficacy of this species in this regard.
622 Analysis of 30 strains typical of the intestinal community revealed that *B. breve* and
623 propionibacteria produce a range of CLA isomers. In contrast, lactobacilli, *Butyrivibrio*
624 *fibrisolvens* and bacteria of the *Clostridium* clade, such as species of *Roseburia*, were found to
625 metabolize linoleic acid to vaccenic acid or hydroxyl fatty acid (10-OH-18:1) end products
626 (Devillard *et al.*, 2007). Incubation of the hydroxyl fatty acid products with human faeces
627 indicated that they may serve as a precursor of the *cis*-9, *trans*-11 isomer in the mixed human
628 intestinal community (Devillard *et al.*, 2007). These findings are in agreement with previous
629 studies which reported that hydroxyl fatty acids are formed as an intermediate during CLA
630 production (Ogawa *et al.*, 2005; Ogawa *et al.*, 2001) Indeed, a myosin–cross-reactive protein
631 found in bifidobacteria has recently been found to catalyse the conversion of linoleic acid to a
632 hydroxylated intermediate (Rosberg-Cody *et al.*, 2010). Endogenous CLA production via the
633 delta-9 desaturase catalyzed conversion of vaccenic acid to *cis*-9, *trans*-11 CLA in human tissues
634 is also thought to contribute to the level of CLA available in the body (Turpeinen *et al.*, 2002).
635 Interestingly however, Devillard *et al.*, also established a correlation between the composition of
636 the intestinal microbiota and the variation in linoleic acid metabolism of individual human
637 subjects (Devillard *et al.*, 2009). It was apparent that higher proportions of *Bacteroidetes* in the
638 intestinal microbiota were concomitant with the extensive metabolism of linoleic acid to stearic
639 acid and minor accumulation of the *cis*-9, *trans*-11 CLA isomer. Conversely, CLA accumulation
640 was much higher from the faeces of an individual with higher quantities of *Firmicutes*. In
641 addition, the level of the *trans*-10, *cis*-12 isomer detected was found to exceed that of *cis*-9,
642 *trans*-11 CLA in this individual. This is an important consideration due to emerging evidence of

643 isomer-specific physiological effects of CLA (Churruca *et al.*, 2009). Although both *cis*-9, *trans*-
644 11 and *trans*-10, *cis*-12 isomers have been implicated in the anticancer activity of CLA, these
645 effects were predominantly associated with *cis*-9, *trans*-11 CLA (Kelley *et al.*, 2007).
646 Alternatively, the *trans*-10, *cis*-12 isomer has been largely associated with antiobesity effects
647 (Brown & McIntosh, 2003; Herrmann *et al.*, 2009).
648
649 *Bioactivity of CLA produced by intestinal bacteria*
650 The production of multiple bioactive fatty acid metabolites may be associated with the health
651 promoting properties of bifidobacteria and other microbes within the GIT and, therefore, may be
652 considered a probiotic trait. Although *in vitro* studies established that the two primary isomers
653 formed by *B. breve* NCIMB 702258 imparted antiproliferative effects on SW480 and HT-29
654 colon cancer cell lines, *trans*-9, *trans*-11 CLA was more potent than *cis*-9, *trans*-11 CLA in each
655 case (Coakley *et al.*, 2006). In another study, incubation of either HT-29 or Caco-2 cancer cells
656 with the CLA metabolites (*cis*-9, *trans*-11 and *trans*-10, *cis*-12 isomers) of VSL3, an eight strain
657 probiotic combination, resulted in a dose dependent reduction in viability. VSL3 consists of *L.*
658 *acidophilus, L. delbreuckii* subsp *bulgaricus, L. casei, L. plantarum, B. breve, B. infantis, B.*
659 *longum* and *Streptococcus thermophilus,* each of which were shown to produce CLA *in vitro*.
660 Furthermore, when this probiotic mixture was fed to mice, a 100-fold increase in the capacity of
661 the faecal content for the formation of CLA under anaerobic conditions, was observed
662 (Ewaschuk et al., 2006).
663 The amount of linoleic acid available for CLA production in the large intestine will vary
664 depending on both the amount ingested and the efficacy of absorption in the small intestine.
665 However, it is estimated that humans excrete approximately 20 mg of linoleic acid on a daily

basis (Edionwe & Kies, 2001). As the intestinal absorption of long chain fatty acids in the colon is minimal, it is likely that microbial CLA formed in the colon would primarily mediate beneficial effects at a local level. Significantly, however, systemic increases in CLA have also been attributed to microbial isomerase activity in the colon. Indeed, CLA has previously been implicated in local beneficial immunomodulatory activity (Bassaganya-Riera & Hontecillas, 2010; Bassaganya-Riera *et al.*, 2004; O'Shea *et al.*, 2004), and anti colon cancer effects (Evans *et al.*, 2010; Miller *et al.*, 2002), as well as systemic effects such as the contribution to the maintenance of metabolic homeostasis (Guri *et al.*, 2008). It is tempting to suggest that microbial CLA production within the gut may be a contributing factor to these effects.

Modulation of the fatty acid composition of host tissues upon dietary supplementation with a combination of *B. breve* NCIMB 702258 and linoleic acid revealed the *in situ* production of CLA in the GIT of mice and pigs (Wall *et al.*, 2009). Following daily administration of 90 mg linoleic acid and 1×10^9 CFU *B. breve* per mouse for eight weeks, liver, large intestinal and faecal concentrations of *cis*-9, *trans*-11 CLA increased by more than 2-fold in healthy BALB/c mice relative to the control group fed linoleic acid alone. An increase in CLA was also observed in the small intestine and caecal contents of this group. Similarly, a 1.5-fold increase in the *cis*-9, *trans*-11 isomer was observed in the liver of pigs administered a combination of sunflower oil, containing 63 % linoleic acid, and 1×10^{10} CFU *B. breve* each day for 21 days, relative to unsupplemented control animals. The greatest increase in tissue CLA concentrations was observed in severe combined immunodeficient (SCID) mice following daily administration of 90 mg linoleic acid and 1×10^9 CFU *B. breve* for a period of 10 weeks. Indeed, liver *cis*-9, *trans*-11 CLA concentrations increased 4-fold, while 3 and 2-fold increases were detected in the large intestine and caecal contents, compared to a control group which received linoleic acid alone.

689 Interestingly, eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) levels were
690 significantly elevated in adipose tissue of SCID mice who were fed *B. breve* alone. Notably, this
691 was coupled with a significant reduction in the levels of proinflammatory cytokines in the
692 splenocytes of these animals relative to the unsupplemented control group (Wall *et al*., 2009). It
693 is possible that such alterations of tissue n-3 PUFA concentrations may be responsible for the
694 anti-inflammatory effects resulting from the intake of *B. breve*. A more recent study
695 demonstrated that administration of the same strain, *B. breve* NCIMB 702258, at a level of 1 ×
696 10^9 CFU/day in combination with alpha-linolenic acid (90 mg/day), (the metabolic precursor for
697 n-3 PUFA such as EPA and DHA) for eight weeks, increased adipose tissue and liver EPA and
698 DHA levels of mice relative to control animals (Wall *et al.*, 2010). Interestingly, this effect was
699 associated with a decrease in arachidonic acid levels. It is thus likely that this effect was
700 accompanied by an increase in the production of EPA-derived anti-inflammatory eicosanoids
701 and reduced arachidonic acid-derived proinflammatory eicosanoids. Administration of *B. breve*
702 alone or a combination of *B. breve* and alpha-linolenic acid was also associated with increased
703 levels of DHA in the brain compared to control mice that received alpha-linolenic acid alone or
704 an unsupplemented diet (Wall *et al*., 2010). Collectively, these data suggest that such
705 metabolically active linoleic acid-conjugating strains could provide a possible therapeutic
706 approach for alleviation of metabolic disorders such as non-alcoholic fatty liver disease
707 (NAFLD), via elevation of the levels of CLA in the liver (Nagao *et al.*, 2005), and
708 immunoinflammatory disorders such as Crohn's disease and inflammatory bowel disease (IBD)
709 through fatty acid-mediated anti-inflammatory activity.
710 Bioproduction of CLA by the human intestinal isolate *Lactobacillus rhamnosus* PL60
711 resulted in elevated serum levels of *trans*-10, *cis*-12 CLA in a murine model (Lee *et al.*, 2006).

712 Following a single inoculation of 1×10^9 CFU, *L. rhamnosus* PL60 was detected in faeces of
713 mice at levels greater than 1×10^8 CFU/g for the first 48hrs and lower thereafter for up to 96hrs
714 (Lee *et al.*, 2006). The *cis*-9, *trans*-11 isomer was detected in the sera of mice administered *L.*
715 *rhamnosus* PL60 as well as the sera of *L. rhamnosus* GG or PBS-fed control animals. In contrast,
716 detection of *trans*-10, *cis*-12 CLA was unique to the sera of mice fed *L. rhamnosus* PL60 (Lee et
717 al., 2006). Daily administration of *L. rhamnosus* PL60 for eight weeks significantly reduced the
718 body weight of diet-induced obese (DIO) mice, without reducing energy intake, compared to the
719 unsupplemented control group (Lee *et al.*, 2006). Lee and coworkers also demonstrated the
720 antiobesity effects of CLA-producing *L. plantarum* PL62 in DIO mice (Lee *et al.*, 2007). Lower
721 body weight as well as serum glucose and leptin levels of DIO mice fed *L. plantarum* PL62 for 8
722 weeks, relative to control animals, was attributed to the efficacy of this strain for *trans*-10, *cis*-12
723 CLA production (Lee et al., 2007). Moreover, bacterial production of CLA in humans, as a
724 consequence of the oral ingestion of *L. rhamnosus* PL60, has recently been demonstrated (Lee &
725 Lee, 2009). Daily consumption of 1×10^{12} CFU *L. rhamnosus* PL60 for 21 days increased the
726 blood levels of both *cis*-9, *trans*-11 and *trans*-10, *cis*-12 CLA isomers over the baseline of four
727 individuals. *L. rhamnosus* PL60 was detected in faeces one week after intake commenced.
728 Concentrations of *cis*-9, *trans*-11 CLA increased from baseline levels of 1.69-10.19 μg ml^{-1} on
729 day 0 to 1.76-23.31 μg ml^{-1} on day 21 in different subjects (Lee & Lee, 2009). Concentrations of
730 *trans*-10, *cis*-12 CLA ranged from 0-1.68 μg ml^{-1} on day 0 to concentrations of 0.71-3.42 μg ml^{-1}
731 on day 21. It was suggested that the difference in the CLA concentrations in the individuals may
732 be due to the survival/attachment rate of *L. rhamnosus* PL60 coupled with the efficiency of CLA
733 production. Interestingly, the enhanced CLA concentrations were correlated with reduced leptin
734 concentrations in these individuals (Lee & Lee, 2009), as previously observed in mice (Lee et al.,

2006). This finding thus provides strong evidence that linoleic acid-conjugating probiotics may provide an effective approach for obesity and cancer treatment, as well as an array of health promoting effects in humans.

Conclusions and potential for the future

Undeniably the intestinal microbiota is a virtually unlimited source of pharmabiotic molecules. This review focused on the role of two distinct pharmabiotic families, bacteriocins and isomers of CLA, in probiosis and importantly, evidence was found to support the production and bioactivity of each of these metabolites *in vivo*. However, short chain fatty acids such as acetate, propionate and butyrate as well as γ-aminobutyric acid (GABA) are a major energy source for the body which also possess several therapeutic properties (Mills *et al.*, 2009) and are but a few other relevant examples of bioactive pharmabiotic metabolites of intestinal bacteria. Although *in vitro* and animal studies have revealed that the production of bioactives considerably contribute to probiotic functionality within the GIT, in many cases these findings have yet to be confirmed in human studies. More comprehensive investigations on the mechanisms of action of pharmabiotic molecules, factors influencing the metabolic activity of probiotics *in vivo*, as well as detailed human studies will be crucial with respect to further verifying the role of specific probiotics in health and disease.

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760 **References**

761 Adelman K., Yuzenkova J., La Porta A., Zenkin N., Lee J., Lis J. T., Borukhov S., Wang M. D.,
762 and Severinov K. (2004). Molecular mechanism of transcription inhibition by peptide
763 antibiotic Microcin J25. *Mol Cell* **14:** 753-62.

764 Aguilar A., Baquero F., Martinez J. L., and Asensio C. (1983). Microcin 15n: a second antibiotic
765 from *Escherichia coli* LP15. *J Antibiot (Tokyo)* **36:** 325-7.

766 Aguilar A., Perez-Diaz J. C., Baquero F., and Asensio C. (1982). Microcin 15m from
767 *Escherichia coli*: mechanism of antibiotic action. *Antimicrob Agents Chemother* **21:** 381-
768 6.

769 Alonso L., Cuesta E. P., and Gilliland S. E. (2003). Production of free conjugated linoleic acid
770 by *Lactobacillus acidophilus* and *Lactobacillus casei* of human intestinal origin. *J Dairy*
771 *Sci* **86:** 1941-6.

772 Altenhoefer A., Oswald S., Sonnenborn U., Enders C., Schulze J., Hacker J., and Oelschlaeger T.
773 A. (2004). The probiotic *Escherichia coli* strain Nissle 1917 interferes with invasion of
774 human intestinal epithelial cells by different enteroinvasive bacterial pathogens. *FEMS*
775 *Immunol Med Microbiol* **40:** 223-9.

776 Anand S. K., Srinivasan R. A., and Rao L. K. (1984). Antibacterial activity associated with
777 *Bifidobacterium bifidum*. *Cultured Dairy Products Journal* **2:** 6-8.

778 Arakawa K., Kawai Y., Ito Y., Nakamura K., Chujo T., Nishimura J., Kitazawa H., and Saito T.
779 (2010). HPLC purification and re-evaluation of chemical identity of two circular
780 bacteriocins, gassericin A and reutericin 6. *Lett Appl Microbiol* **50:** 406-11.

781 Azpiroz M. F., and Lavina M. (2004). Involvement of enterobactin synthesis pathway in
782 production of microcin H47. *Antimicrob Agents Chemother* **48:** 1235-41.
783 Backhed F. (2010). 99th Dahlem conference on infection, inflammation and chronic
784 inflammatory disorders: the normal gut microbiota in health and disease. *Clin Exp*
785 *Immunol* **160:** 80-4.
786 Backhed F., Ding H., Wang T., Hooper L. V., Koh G. Y., Nagy A., Semenkovich C. F., and
787 Gordon J. I. (2004). The gut microbiota as an environmental factor that regulates fat
788 storage. *Proc Natl Acad Sci U S A* **101:** 15718-23.
789 Barrett E., Hayes M., O'Connor P., Gardiner G., Fitzgerald G., Stanton C., Ross R. P., and Hill
790 C. (2007a). Salivaricin P: one of a family of two component anti-listerial bacteriocins
791 produced by intestinal isolates of *Lactobacillus salivarius*. *Appl. Environ. Microbiol.* **73:**
792 3719-3723.
793 Barrett E., Ross R. P., Fitzgerald G. F., and Stanton C. (2007b). Rapid screening method for
794 analyzing the conjugated linoleic acid production capabilities of bacterial cultures. *Appl*
795 *Environ Microbiol* **73:** 2333-7.
796 Bassaganya-Riera J., and Hontecillas R. (2010). Dietary conjugated linoleic acid and n-3
797 polyunsaturated fatty acids in inflammatory bowel disease. *Curr Opin Clin Nutr Metab*
798 *Care* **13:** 569-73.
799 Bassaganya-Riera J., Reynolds K., Martino-Catt S., Cui Y., Hennighausen L., Gonzalez F.,
800 Rohrer J., Benninghoff A. U., and Hontecillas R. (2004). Activation of PPAR gamma and
801 delta by conjugated linoleic acid mediates protection from experimental inflammatory
802 bowel disease. *Gastroenterology* **127:** 777-91.

803 Bayer A., Freund S., and Jung G. (1995). Post-translational heterocyclic backbone modifications
804 in the 43-peptide antibiotic microcin B17. Structure elucidation and NMR study of a
805 13C,15N-labelled gyrase inhibitor. *Eur J Biochem* **234:** 414-26.
806 Begley M., Cotter P. D., Hill C., and Ross R. P. (2009). Identification of a novel two-peptide
807 lantibiotic, lichenicidin, following rational genome mining for LanM proteins. *Appl*
808 *Environ Microbiol* **75:** 5451-60.
809 Belury M. A. (2002). Dietary conjugated linoleic acid in health: physiological effects and
810 mechanisms of action. *Annu Rev Nutr* **22:** 505-31.
811 Bieler S., Silva F., and Belin D. (2010). The polypeptide core of Microcin E492 stably associates
812 with the mannose permease and interferes with mannose metabolism. *Res Microbiol* **161:**
813 706-10.
814 Bieler S., Silva F., Soto C., and Belin D. (2006). Bactericidal activity of both secreted and
815 nonsecreted microcin E492 requires the mannose permease. *J Bacteriol* **188:** 7049-61.
816 Bierbaum G., Szekat C., Josten M., Heidrich C., Kempter C., Jung G., and Sahl H. G. (1996).
817 Engineering of a novel thioether bridge and role of modified residues in the lantibiotic
818 Pep5. *Appl Environ Microbiol* **62:** 385-92.
819 Birri D. J., Brede D. A., Forberg T., Holo H., and Nes I. F. (2010). Molecular and genetic
820 characterization of a novel bacteriocin locus in *Enterococcus avium* isolates from infants.
821 *Appl Environ Microbiol* **76:** 483-92.
822 Booth M. C., Bogie C. P., Sahl H. G., Siezen R. J., Hatter K. L., and Gilmore M. S. (1996).
823 Structural analysis and proteolytic activation of *Enterococcus faecalis* cytolysin, a novel
824 lantibiotic. *Mol Microbiol* **21:** 1175-84.

825 Boyer A. E., and Tai P. C. (1998). Characterization of the cvaA and cvi promoters of the colicin
826 V export system: iron-dependent transcription of cvaA is modulated by downstream
827 sequences. *J Bacteriol* **180:** 1662-72.
828 Bradley D. E., and Howard S. P. (1992). A new colicin that adsorbs to outer-membrane protein
829 Tsx but is dependent on the tonB instead of the tolQ membrane transport system. *J Gen*
830 *Microbiol* **138:** 2721-4.
831 Brown J. M., and McIntosh M. K. (2003). Conjugated linoleic acid in humans: regulation of
832 adiposity and insulin sensitivity. *J Nutr* **133:** 3041-6.
833 Buchanan S. K., Lukacik P., Grizot S., Ghirlando R., Ali M. M., Barnard T. J., Jakes K. S.,
834 Kienker P. K., and Esser L. (2007). Structure of colicin I receptor bound to the R-domain
835 of colicin Ia: implications for protein import. *EMBO J* **26:** 2594-604.
836 Burton J. P., Chilcott C. N., Moore C. J., Speiser G., and Tagg J. R. (2006). A preliminary study
837 of the effect of probiotic *Streptococcus salivarius* K12 on oral malodour parameters. *J*
838 *Appl Microbiol* **100:** 754-64.
839 Cascales E., Buchanan S. K., Duche D., Kleanthous C., Lloubes R., Postle K., Riley M., Slatin
840 S., and Cavard D. (2007). Colicin biology. *Microbiol Mol Biol Rev* **71:** 158-229.
841 Casey P. G., Gardiner G. E., Casey G., Bradshaw B., Lawlor P. G., Lynch P. B., Leonard F. C.,
842 Stanton C., Ross R. P., Fitzgerald G. F., and Hill C. (2007). A five-strain probiotic
843 combination reduces pathogen shedding and alleviates disease signs in pigs challenged
844 with *Salmonella enterica* Serovar Typhimurium. *Appl Environ Microbiol* **73:** 1858-63.
845 Cavard D. (1995). Effects of temperature and of heat shock on the expression and action of the
846 colicin A lysis protein. *J Bacteriol* **177:** 5189-92.

847 Chikindas M. L., Novak J., Driessen A. J., Konings W. N., Schilling K. M., and Caufield P. W.
848 (1995). Mutacin II, a bactericidal antibiotic from *Streptococcus mutans*. *Antimicrob*
849 *Agents Chemother* **39:** 2656-60.
850 Chin S. F., Liu W., Storkson J. M., Ha Y. L., and Pariza M. W. (1992). Dietary sources of
851 conjugated dienoic isomers of linoleic acid, a newly recognized class of anticarcinogens.
852 *Journal of Food Composition and Analysis* **5:** 185-197.
853 Chin S. F., Storkson J. M., Liu W., Albright K. J., and Pariza M. W. (1994). Conjugated linoleic
854 acid (9,11- and 10,12-octadecadienoic acid) is produced in conventional but not germ-
855 free rats fed linoleic acid. *J Nutr* **124:** 694-701.
856 Chumchalova J., and Smarda J. (2003). Human tumor cells are selectively inhibited by colicins.
857 *Folia Microbiol (Praha)* **48:** 111-5.
858 Churruca I., Fernandez-Quintela A., and Portillo M. P. (2009). Conjugated linoleic acid isomers:
859 differences in metabolism and biological effects. *Biofactors* **35:** 105-11.
860 Cintas L. M., Casaus P., Herranz C., Havarstein L. S., Holo H., Hernandez P. E., and Nes I. F.
861 (2000). Biochemical and genetic evidence that *Enterococcus faecium* L50 produces
862 enterocins L50A and L50B, the sec-dependent enterocin P, and a novel bacteriocin
863 secreted without an N-terminal extension termed enterocin Q. *J Bacteriol* **182:** 6806-14.
864 Claus S. P., Tsang T. M., Wang Y., Cloarec O., Skordi E., Martin F. P., Rezzi S., Ross A.,
865 Kochhar S., Holmes E., and Nicholson J. K. (2008). Systemic multicompartmental effects
866 of the gut microbiome on mouse metabolic phenotypes. *Mol Syst Biol* **4:** 219.
867 Coakley M., Johnson M. C., McGrath E., Rahman S., Ross R. P., Fitzgerald G. F., Devery R.,
868 and Stanton C. (2006). Intestinal bifidobacteria that produce trans-9, trans-11 conjugated

linoleic acid: a fatty acid with antiproliferative activity against human colon SW480 and HT-29 cancer cells. *Nutr Cancer* **56:** 95-102.

Coakley M., Ross R. P., Nordgren M., Fitzgerald G., Devery R., and Stanton C. (2003). Conjugated linoleic acid biosynthesis by human-derived *Bifidobacterium* species. *J Appl Microbiol* **94:** 138-45.

Cook M. E., Miller C. C., Park Y., and Pariza M. (1993). Immune modulation by altered nutrient metabolism: nutritional control of immune-induced growth depression. *Poult Sci* **72:** 1301-5.

Corr S. C., Li Y., Riedel C. U., O'Toole P. W., Hill C., and Gahan C. G. (2007). Bacteriocin production as a mechanism for the antiinfective activity of *Lactobacillus salivarius* UCC118. *Proc Natl Acad Sci U S A* **104:** 7617-21.

Cotter P. D., Hill C., and Ross R. P. (2005). Bacteriocins: developing innate immunity for food. *Nat Rev Microbiol* **3:** 777-88.

Cursino L., Smajs D., Smarda J., Nardi R. M., Nicoli J. R., Chartone-Souza E., and Nascimento A. M. (2006). Exoproducts of the *Escherichia coli* strain H22 inhibiting some enteric pathogens both *in vitro* and *in vivo*. *J Appl Microbiol* **100:** 821-9.

Dabard J., Bridonneau C., Phillipe C., Anglade P., Molle D., Nardi M., Ladire M., Girardin H., Marcille F., Gomez A., and Fons M. (2001). Ruminococcin A, a new lantibiotic produced by a *Ruminococcus gnavus* strain isolated from human feces. *Appl Environ Microbiol* **67:** 4111-8.

Daly K. M., Upton M., Sandiford S. K., Draper L. A., Wescombe P. A., Jack R. W., O'Connor P. M., Rossney A., Gotz F., Hill C., Cotter P. D., Ross R. P., and Tagg J. R. (2010).

Production of the Bsa lantibiotic by community-acquired *Staphylococcus aureus* strains. *J Bacteriol* **192:** 1131-42.

Davies J. K., and Reeves P. (1975a). Genetics of resistance to colicins in *Escherichia coli* K-12: cross-resistance among colicins of group A. *J Bacteriol* **123:** 102-17.

Davies J. K., and Reeves P. (1975b). Genetics of resistance to colicins in *Escherichia coli* K-12: cross-resistance among colicins of group B. *J Bacteriol* **123:** 96-101.

Davis C. D., and Milner J. A. (2009). Gastrointestinal microflora, food components and colon cancer prevention. *J Nutr Biochem* **20:** 743-52.

Dawid S., Roche A. M., and Weiser J. N. (2007). The blp bacteriocins of *Streptococcus pneumoniae* mediate intraspecies competition both *in vitro* and *in vivo*. *Infect Immun* **75:** 443-51.

de Jong A., van Heel A. J., Kok J., and Kuipers O. P. (2010). BAGEL2: mining for bacteriocins in genomic data. *Nucleic Acids Res* **38 Suppl:** W647-51.

de Lorenzo V. (1984). Isolation and characterization of microcin E492 from *Klebsiella pneumoniae*. *Arch Microbiol* **139:** 72-5.

del Campo R., Tenorio C., Jimenez-Diaz R., Rubio C., Gomez-Lus R., Baquero F., and Torres C. (2001). Bacteriocin production in vancomycin-resistant and vancomycin-susceptible *Enterococcus* isolates of different origins. *Antimicrob Agents Chemother* **45:** 905-12.

Destoumieux-Garzon D., Peduzzi J., Thomas X., Djediat C., and Rebuffat S. (2006). Parasitism of iron-siderophore receptors of *Escherichia coli* by the siderophore-peptide microcin E492m and its unmodified counterpart. *Biometals* **19:** 181-91.

Destoumieux-Garzon D., Thomas X., Santamaria M., Goulard C., Barthelemy M., Boscher B., Bessin Y., Molle G., Pons A. M., Letellier L., Peduzzi J., and Rebuffat S. (2003).

914 Microcin E492 antibacterial activity: evidence for a TonB-dependent inner membrane
915 permeabilization on *Escherichia coli*. *Mol Microbiol* **49:** 1031-41.
916 Devillard E., McIntosh F. M., Duncan S. H., and Wallace R. J. (2007). Metabolism of linoleic
917 acid by human gut bacteria: different routes for biosynthesis of conjugated linoleic acid. *J*
918 *Bacteriol* **189:** 2566-70.
919 Devillard E., McIntosh F. M., Paillard D., Thomas N. A., Shingfield K. J., and Wallace R. J.
920 (2009). Differences between human subjects in the composition of the faecal bacterial
921 community and faecal metabolism of linoleic acid. *Microbiology* **155:** 513-20.
922 Di Masi D. R., White J. C., Schnaitman C. A., and Bradbeer C. (1973). Transport of vitamin B12
923 in *Escherichia coli*: common receptor sites for vitamin B12 and the E colicins on the
924 outer membrane of the cell envelope. *J Bacteriol* **115:** 506-13.
925 Diep D. B., Axelsson L., Grefsli C., and Nes I. F. (2000). The synthesis of the bacteriocin
926 sakacin A is a temperature-sensitive process regulated by a pheromone peptide through a
927 three-component regulatory system. *Microbiology* **146 (Pt 9):** 2155-60.
928 Diep D. B., Skaugen M., Salehian Z., Holo H., and Nes I. F. (2007). Common mechanisms of
929 target cell recognition and immunity for class II bacteriocins. *Proc Natl Acad Sci U S A*
930 **104:** 2384-9.
931 Drider D., Fimland G., Hechard Y., McMullen L. M., and Prevost H. (2006). The continuing
932 story of class IIa bacteriocins. *Microbiol Mol Biol Rev* **70:** 564-82.
933 Duquesne S., Destoumieux-Garzon D., Peduzzi J., and Rebuffat S. (2007). Microcins, gene-
934 encoded antibacterial peptides from enterobacteria. *Nat Prod Rep* **24:** 708-34.
935 Duquesne S., Destoumieux-Garzon D., Zirah S., Knappe T. A., Goulard C., Peduzzi J., Marahiel
936 M. A., and Rebuffat S. (2009). Post-translational modification and folding of a lasso-type

gene-encoded antimicrobial peptide require two enzymes only in *Escherichia coli*. *Adv Exp Med Biol* **611:** 35-6.

Eckburg P. B., Bik E. M., Bernstein C. N., Purdom E., Dethlefsen L., Sargent M., Gill S. R., Nelson K. E., and Relman D. A. (2005). Diversity of the human intestinal microbial flora. *Science* **308:** 1635-8.

Edionwe A. O., and Kies C. (2001). Comparison of palm and mixtures of refined palm and soybean oils on serum lipids and fecal fat and fatty acid excretions of adult humans. *Plant Foods Hum Nutr* **56:** 157-65.

El Ghachi M., Bouhss A., Barreteau H., Touze T., Auger G., Blanot D., and Mengin-Lecreulx D. (2006). Colicin M exerts its bacteriolytic effect via enzymatic degradation of undecaprenyl phosphate-linked peptidoglycan precursors. *J Biol Chem* **281:** 22761-72.

Evans N. P., Misyak S. A., Schmelz E. M., Guri A. J., Hontecillas R., and Bassaganya-Riera J. (2010). Conjugated linoleic acid ameliorates inflammation-induced colorectal cancer in mice through activation of PPARgamma. *J Nutr* **140:** 515-21.

Ewaschuk J. B., Diaz H., Meddings L., Diederichs B., Dmytrash A., Backer J., Looijer-van Langen M., and Madsen K. L. (2008). Secreted bioactive factors from *Bifidobacterium infantis* enhance epithelial cell barrier function. *Am J Physiol Gastrointest Liver Physiol* **295:** G1025-34.

Ewaschuk J. B., Walker J. W., Diaz H., and Madsen K. L. (2006). Bioproduction of conjugated linoleic acid by probiotic bacteria occurs *in vitro* and *in vivo* in mice. *J Nutr* **136:** 1483-7.

Fanaro S., Chierici R., Guerrini P., and Vigi V. (2003). Intestinal microflora in early infancy: composition and development. *Acta Paediatr Suppl* **91:** 48-55.

959 FAO/WHO (2001). Evaluation of Health and Nutritional Properties of Probiotics in Food
960 Including Powder Milk with Live Lactic Acid Bacteria. *Cordoba, Argentina: Joint*
961 *FAO/WHO Expert Consultation, Food and Agriculture Organisation of the United*
962 *Nations*.
963 Flynn S., van Sinderen D., Thornton G. M., Holo H., Nes I. F., and Collins J. K. (2002).
964 Characterization of the genetic locus responsible for the production of ABP-118, a novel
965 bacteriocin produced by the probiotic bacterium *Lactobacillus salivarius* subsp.
966 *salivarius* UCC118. *Microbiology* **148:** 973-84.
967 Gagnon M., Kheadr E. E., Le Blay G., and Fliss I. (2004). *In vitro* inhibition of *Escherichia coli*
968 O157:H7 by bifidobacterial strains of human origin. *Int J Food Microbiol* **92:** 69-78.
969 Ghadimi D., Vrese M., Heller K. J., and Schrezenmeir J. (2010). Effect of natural commensal-
970 origin DNA on toll-like receptor 9 (TLR9) signaling cascade, chemokine IL-8
971 expression, and barrier integritiy of polarized intestinal epithelial cells. *Inflamm Bowel*
972 *Dis* **16:** 410-27.
973 Gillor O., Etzion A., and Riley M. A. (2008). The dual role of bacteriocins as anti- and
974 probiotics. *Appl Microbiol Biotechnol* **81:** 591-606.
975 Gillor O., Giladi I., and Riley M. A. (2009). Persistence of colicinogenic *Escherichia coli* in the
976 mouse gastrointestinal tract. *BMC Microbiol* **9:** 165.
977 Gionchetti P., Rizzello F., Morselli C., Poggioli G., Tambasco R., Calabrese C., Brigidi P., Vitali
978 B., Straforini G., and Campieri M. (2007). High-dose probiotics for the treatment of
979 active pouchitis. *Dis Colon Rectum* **50:** 2075-82; discussion 2082-4.
980 Gomez A., Ladire M., Marcille F., and Fons M. (2002). Trypsin mediates growth phase-
981 dependent transcriptional tegulation of genes involved in biosynthesis of ruminococcin

A, a lantibiotic produced by a *Ruminococcus gnavus* strain from a human intestinal microbiota. *J Bacteriol* **184:** 18-28.

Gordon D. M. (2009). The potential of bacteriocin-producing probiotics and associated caveats. *Future Microbiol* **4:** 941-3.

Gordon D. M., and O'Brien C. L. (2006). Bacteriocin diversity and the frequency of multiple bacteriocin production in *Escherichia coli*. *Microbiology* **152:** 3239-44.

Griinari J. M., Corl B. A., Lacy S. H., Chouinard P. Y., Nurmela K. V., and Bauman D. E. (2000). Conjugated linoleic acid is synthesized endogenously in lactating dairy cows by Delta(9)-desaturase. *J Nutr* **130:** 2285-91.

Guijarro J. I., Gonzalez-Pastor J. E., Baleux F., San Millan J. L., Castilla M. A., Rico M., Moreno F., and Delepierre M. (1995). Chemical structure and translation inhibition studies of the antibiotic microcin C7. *J Biol Chem* **270:** 23520-32.

Guri A. J., Hontecillas R., and Bassaganya-Riera J. (2008). Dietary modulators of peroxisome proliferator-activated receptors: implications for the prevention and treatment of metabolic syndrome. *J Nutrigenet Nutrigenomics* **1:** 126-35.

Ha Y. L., Grimm N. K., and Pariza M. W. (1987). Anticarcinogens from fried ground beef: heat-altered derivatives of linoleic acid. *Carcinogenesis* **8:** 1881-7.

Hale J. D., Balakrishnan B., and Tagg J. R. (2004). Genetic basis for mutacin N and of its relationship to mutacin I. *Indian J Med Res* **119 Suppl:** 247-51.

Hauge H. H., Mantzilas D., Moll G. N., Konings W. N., Driessen A. J., Eijsink V. G., and Nissen-Meyer J. (1998). Plantaricin A is an amphiphilic alpha-helical bacteriocin-like pheromone which exerts antimicrobial and pheromone activities through different mechanisms. *Biochemistry* **37:** 16026-32.

1005 Helwig U., Lammers K. M., Rizzello F., Brigidi P., Rohleder V., Caramelli E., Gionchetti P.,
1006 Schrezenmeir J., Foelsch U. R., Schreiber S., and Campieri M. (2006). Lactobacilli,
1007 bifidobacteria and *E. coli* Nissle induce pro- and anti-inflammatory cytokines in
1008 peripheral blood mononuclear cells. *World J Gastroenterol* **12:** 5978-86.
1009 Henker J., Laass M., Blokhin B. M., Bolbot Y. K., Maydannik V. G., Elze M., Wolff C., and
1010 Schulze J. (2007). The probiotic *Escherichia coli* strain Nissle 1917 (EcN) stops acute
1011 diarrhoea in infants and toddlers. *Eur J Pediatr* **166:** 311-8.
1012 Henker J., Laass M. W., Blokhin B. M., Maydannik V. G., Bolbot Y. K., Elze M., Wolff C.,
1013 Schreiner A., and Schulze J. (2008). Probiotic *Escherichia coli* Nissle 1917 versus
1014 placebo for treating diarrhea of greater than 4 days duration in infants and toddlers.
1015 *Pediatr Infect Dis J* **27:** 494-9.
1016 Hennessy A. A., Ross R. P., Stanton C., Devery R., and Murphy J. J. (2007). Development of
1017 dairy based functional foods enriched in conjugated linoleic acid with special reference to
1018 rumenic acid. *In* "Functional Dairy Products, Volume 2" (M. Saarela, Ed.), pp. 443-495,
1019 Woodhead Publishing Limited Cambridge, UK.
1020 Herrmann J., Rubin D., Hasler R., Helwig U., Pfeuffer M., Auinger A., Laue C., Winkler P.,
1021 Schreiber S., Bell D., and Schrezenmeir J. (2009). Isomer-specific effects of CLA on
1022 gene expression in human adipose tissue depending on PPARgamma2 P12A
1023 polymorphism: a double blind, randomized, controlled cross-over study. *Lipids Health*
1024 *Dis* **8:** 35.
1025 Hetz C., Bono M. R., Barros L. F., and Lagos R. (2002). Microcin E492, a channel-forming
1026 bacteriocin from *Klebsiella pneumoniae*, induces apoptosis in some human cell lines.
1027 *Proc Natl Acad Sci U S A* **99:** 2696-701.

1028 Heuvelin E., Lebreton C., Grangette C., Pot B., Cerf-Bensussan N., and Heyman M. (2009).
1029 Mechanisms involved in alleviation of intestinal inflammation by *Bifidobacterium breve*
1030 soluble factors. *PLoS One* **4:** e5184.
1031 Hillman J. D. (2002). Genetically modified *Streptococcus mutans* for the prevention of dental
1032 caries. *Antonie Van Leeuwenhoek* **82:** 361-6.
1033 Hillman J. D., Brooks T. A., Michalek S. M., Harmon C. C., Snoep J. L., and van Der Weijden
1034 C. C. (2000). Construction and characterization of an effector strain of *Streptococcus*
1035 *mutans* for replacement therapy of dental caries. *Infect Immun* **68:** 543-9.
1036 Hillman J. D., Dzuback A. L., and Andrews S. W. (1987). Colonization of the Human Oral
1037 Cavity by a *Streptococcus mutans* Mutant Producing Increased bacteriocin. *J Dent Res*
1038 **66:** 1092-1094.
1039 Hillman J. D., Novak J., Sagura E., Gutierrez J. A., Brooks T. A., Crowley P. J., Hess M., Azizi
1040 A., Leung K., Cvitkovitch D., and Bleiweis A. S. (1998). Genetic and biochemical
1041 analysis of mutacin 1140, a lantibiotic from *Streptococcus mutans*. *Infect Immun* **66:**
1042 2743-9.
1043 Hillman J. D., Yaphe B. I., and Johnson K. P. (1985). Colonization of the Human Oral Cavity by
1044 a Strain of *Streptococcus mutans*. *J Dent Res* **64:** 1272-1274.
1045 Horz H. P., Meinelt A., Houben B., and Conrads G. (2007). Distribution and persistence of
1046 probiotic *Streptococcus salivarius* K12 in the human oral cavity as determined by real-
1047 time quantitative polymerase chain reaction. *Oral Microbiol Immunol* **22:** 126-30.
1048 Houseknecht K. L., Vanden Heuvel J. P., Moya-Camarena S. Y., Portocarrero C. P., Peck L. W.,
1049 Nickel K. P., and Belury M. A. (1998). Dietary conjugated linoleic acid normalizes

impaired glucose tolerance in the Zucker diabetic fatty fa/fa rat. *Biochem Biophys Res Commun* **244:** 678-82.

Hyink O., Balakrishnan M., and Tagg J. R. (2005). *Streptococcus rattus* strain BHT produces both a class I two-component lantibiotic and a class II bacteriocin. *FEMS Microbiol Lett* **252:** 235-41.

Hyink O., Wescombe P. A., Upton M., Ragland N., Burton J. P., and Tagg J. R. (2007). Salivaricin A2 and the novel lantibiotic salivaricin B are encoded at adjacent loci on a 190-kilobase transmissible megaplasmid in the oral probiotic strain *Streptococcus salivarius* K12. *Appl Environ Microbiol* **73:** 1107-13.

Hynes W. L., Ferretti J. J., and Tagg J. R. (1993). Cloning of the gene encoding Streptococcin A-FF22, a novel lantibiotic produced by *Streptococcus pyogenes*, and determination of its nucleotide sequence. *Appl Environ Microbiol* **59:** 1969-71.

Inoue T., Tomita H., and Ike Y. (2006). Bac 32, a novel bacteriocin widely disseminated among clinical isolates of *Enterococcus faecium*. *Antimicrob Agents Chemother* **50:** 1202-12.

Ip C., Singh M., Thompson H. J., and Scimeca J. A. (1994). Conjugated linoleic acid suppresses mammary carcinogenesis and proliferative activity of the mammary gland in the rat. *Cancer Res* **54:** 1212-5.

James R., Penfold C. N., Moore G. R., and Kleanthous C. (2002). Killing of *E. coli* cells by E group nuclease colicins. *Biochimie* **84:** 381-9.

Jeziorowski A., and Gordon D. M. (2007). Evolution of microcin V and colicin Ia plasmids in *Escherichia coli*. *J Bacteriol* **189:** 7045-52.

Jiang J., Bjorck L., and Fonden R. (1998). Production of conjugated linoleic acid by dairy starter cultures. *J Appl Microbiol* **85:** 95-102.

1073 Jiang J., Wolk A., and Vessby B. (1999). Relation between the intake of milk fat and the
1074 occurrence of conjugated linoleic acid in human adipose tissue. *Am J Clin Nutr* **70:** 21-7.
1075 Jijon H., Backer J., Diaz H., Yeung H., Thiel D., McKaigney C., De Simone C., and Madsen K.
1076 (2004). DNA from probiotic bacteria modulates murine and human epithelial and
1077 immune function. *Gastroenterology* **126:** 1358-73.
1078 Jimenez E., Martin R., Maldonado A., Martin V., Gomez de Segura A., Fernandez L., and
1079 Rodriguez J. M. (2010). Complete Genome Sequence of *Lactobacillus salivarius* CECT
1080 5713, a Probiotic Strain Isolated from Human Milk and Infant Feces. *J Bacteriol* **192:**
1081 5266-7.
1082 Jung G. (1991). Lantibiotics-ribosomally synthesised biologically active polypeptides containing
1083 sulfide bridges and α, β-didehydroamino acids. *Angew. Chem. Int. Ed* **30:** 1051-1068.
1084 Kang B. S., Seo J. G., Lee G. S., Kim J. H., Kim S. Y., Han Y. W., Kang H., Kim H. O., Rhee J.
1085 H., Chung M. J., and Park Y. M. (2009). Antimicrobial activity of enterocins from
1086 *Enterococcus faecalis* SL-5 against *Propionibacterium acnes*, the causative agent in acne
1087 vulgaris, and its therapeutic effect. *J Microbiol* **47:** 101-9.
1088 Kang J. H., and Lee M. S. (2005). Characterization of a bacteriocin produced by *Enterococcus*
1089 *faecium* GM-1 isolated from an infant. *J Appl Microbiol* **98:** 1169-76.
1090 Kawai Y., Ishii Y., Arakawa K., Uemura K., Saitoh B., Nishimura J., Kitazawa H., Yamazaki Y.,
1091 Tateno Y., Itoh T., and Saito T. (2004). Structural and functional differences in two
1092 cyclic bacteriocins with the same sequences produced by lactobacilli. *Appl Environ*
1093 *Microbiol* **70:** 2906-11.

1094 Kawai Y., Saitoh B., Takahashi O., Kitazawa H., Saito T., Nakajima H., and Itoh T. (2000).
1095 Primary amino acid and DNA sequences of gassericin T, a lactacin F-family bacteriocin
1096 produced by *Lactobacillus gasseri* SBT2055. *Biosci Biotechnol Biochem* **64:** 2201-8.
1097 Kawulka K. E., Sprules T., Diaper C. M., Whittal R. M., McKay R. T., Mercier P., Zuber P., and
1098 Vederas J. C. (2004). Structure of subtilosin A, a cyclic antimicrobial peptide from
1099 *Bacillus subtilis* with unusual sulfur to alpha-carbon cross-links: formation and reduction
1100 of alpha-thio-alpha-amino acid derivatives. *Biochemistry* **43:** 3385-95.
1101 Kelley N. S., Hubbard N. E., and Erickson K. L. (2007). Conjugated linoleic acid isomers and
1102 cancer. *J Nutr* **137:** 2599-607.
1103 Kennedy C. K. (1971). Induction of colicin production by high temperature or inhibition of
1104 protein synthesis. *J Bacteriol* **108:** 10-9.
1105 Kepler C. R., Hirons K. P., McNeill J. J., and Tove S. B. (1966). Intermediates and products of
1106 the biohydrogenation of linoleic acid by *Butyrinvibrio fibrisolvens*. *J Biol Chem* **241:**
1107 1350-4.
1108 Kim Y. J., and Liu R. H. (2002). Increase of conjugated linoleic acid content in milk by
1109 fermentation with lactic acid bacteria. *Journal of Food Science* **67**.
1110 Kishino S., Ogawa J., Omura Y., Matsumura K., and Shimizu S. (2002). Conjugated linoleic acid
1111 production from linoleic acid by lactic acid bacteria. *Journal of American Oil Chemists'*
1112 *Society* **79:** 159-163.
1113 Kjos M., Nes I. F., and Diep D. B. (2009). Class II one-peptide bacteriocins target a
1114 phylogenetically defined subgroup of mannose phosphotransferase systems on sensitive
1115 cells. *Microbiology* **155:** 2949-61.

1116 Kleerebezem M. (2004). Quorum sensing control of lantibiotic production; nisin and subtilin
1117 autoregulate their own biosynthesis. *Peptides* **25:** 1405-14.
1118 Kleerebezem M., Boekhorst J., van Kranenburg R., Molenaar D., Kuipers O. P., Leer R.,
1119 Tarchini R., Peters S. A., Sandbrink H. M., Fiers M. W., Stiekema W., Lankhorst R. M.,
1120 Bron P. A., Hoffer S. M., Groot M. N., Kerkhoven R., de Vries M., Ursing B., de Vos W.
1121 M., and Siezen R. J. (2003). Complete genome sequence of *Lactobacillus plantarum*
1122 WCFS1. *Proc Natl Acad Sci U S A* **100:** 1990-5.
1123 Kleerebezem M., and Quadri L. E. (2001). Peptide pheromone-dependent regulation of
1124 antimicrobial peptide production in Gram-positive bacteria: a case of multicellular
1125 behavior. *Peptides* **22:** 1579-96.
1126 Kleerebezem M., and Vaughan E. E. (2009). Probiotic and gut lactobacilli and bifidobacteria:
1127 molecular approaches to study diversity and activity. *Annu Rev Microbiol* **63:** 269-90.
1128 Kuhar I., and Zgur-Bertok D. (1999). Transcription regulation of the colicin K cka gene reveals
1129 induction of colicin synthesis by differential responses to environmental signals. *J*
1130 *Bacteriol* **181:** 7373-80.
1131 Lagos R., Tello M., Mercado G., Garcia V., and Monasterio O. (2009). Antibacterial and
1132 antitumorigenic properties of microcin E492, a pore-forming bacteriocin. *Curr Pharm*
1133 *Biotechnol* **10:** 74-85.
1134 Lakey J. H., and Slatin S. L. (2001). Pore-forming colicins and their relatives. *Curr Top*
1135 *Microbiol Immunol* **257:** 131-61.
1136 Lancaster L. E., Wintermeyer W., and Rodnina M. V. (2007). Colicins and their potential in
1137 cancer treatment. *Blood Cells Mol Dis* **38:** 15-8.

1138 Larsen C. N., Nielsen S., Kaestel P., Brockmann E., Bennedsen M., Christensen H. R., Eskesen
1139 D. C., Jacobsen B. L., and Michaelsen K. F. (2006). Dose-response study of probiotic
1140 bacteria *Bifidobacterium animalis* subsp lactis BB-12 and *Lactobacillus paracasei* subsp.
1141 *paracasei* CRL-341 in healthy young adults. *Eur J Clin Nutr* **60:** 1284-93.
1142 Lavina M., Gaggero C., and Moreno F. (1990). Microcin H47, a chromosome-encoded microcin
1143 antibiotic of *Escherichia coli*. *J Bacteriol* **172:** 6585-8.
1144 Lawless F., Murphy J. J., Harrington D., Devery R., and Stanton C. (1998). Elevation of
1145 conjugated cis-9, trans-11-octadecadienoic acid in bovine milk because of dietary
1146 supplementation. *J Dairy Sci* **81:** 3259-67.
1147 Le Blay G., Lacroix C., Zihler A., and Fliss I. (2007). *In vitro* inhibition activity of nisin A, nisin
1148 Z, pediocin PA-1 and antibiotics against common intestinal bacteria. *Lett Appl Microbiol*
1149 **45:** 252-7.
1150 Lebeer S., Vanderleyden J., and De Keersmaecker S. C. (2010). Host interactions of probiotic
1151 bacterial surface molecules: comparison with commensals and pathogens. *Nat Rev*
1152 *Microbiol* **8:** 171-84.
1153 Lee H. Y., Park J. H., Seok S. H., Baek M. W., Kim D. J., Lee K. E., Paek K. S., and Lee Y.
1154 (2006). Human originated bacteria, *Lactobacillus rhamnosus* PL60, produce conjugated
1155 linoleic acid and show anti-obesity effects in diet-induced obese mice. *Biochim Biophys*
1156 *Acta* **1761:** 736-44.
1157 Lee J. H., Karamychev V. N., Kozyavkin S. A., Mills D., Pavlov A. R., Pavlova N. V.,
1158 Polouchine N. N., Richardson P. M., Shakhova V. V., Slesarev A. I., Weimer B., and
1159 O'Sullivan D. J. (2008). Comparative genomic analysis of the gut bacterium

Bifidobacterium longum reveals loci susceptible to deletion during pure culture growth. *BMC Genomics* **9:** 247.

Lee K., and Lee Y. (2009). Production of c9,t11- and t10,c12-conjugated linoleic acids in humans by *Lactobacillus rhamnosus* PL60. *J Microbiol Biotechnol* **19:** 1617-9.

Lee K., Paek K., Lee H. Y., Park J. H., and Lee Y. (2007). Antiobesity effect of trans-10,cis-12-conjugated linoleic acid-producing *Lactobacillus plantarum* PL62 on diet-induced obese mice. *J Appl Microbiol* **103:** 1140-6.

Lee K. N., Kritchevsky D., and Pariza M. W. (1994). Conjugated linoleic acid and atherosclerosis in rabbits. *Atherosclerosis* **108:** 19-25.

Lee Y. K., Puong K. Y., Ouwehand A. C., and Salminen S. (2003). Displacement of bacterial pathogens from mucus and Caco-2 cell surface by lactobacilli. *J Med Microbiol* **52:** 925-30.

Li Y., Canchaya C., Fang F., Raftis E., Ryan K. A., van Pijkeren J. P., van Sinderen D., and O'Toole P. W. (2007). Distribution of megaplasmids in *Lactobacillus salivarius* and other lactobacilli. *J Bacteriol* **189:** 6128-39.

Lievin V., Peiffer I., Hudault S., Rochat F., Brassart D., Neeser J. R., and Servin A. L. (2000). *Bifidobacterium* strains from resident infant human gastrointestinal microflora exert antimicrobial activity. *Gut* **47:** 646-52.

Lin T. Y., Lin C. W., and Lee C. H. (1999). Conjugated linoleic acid concentration as affected by lactic cultures and added linoleic acid. *Food Chemistry* **67:** 1-5.

Lodinova-Zadnikova R., and Sonnenborn U. (1997). Effect of preventive administration of a nonpathogenic *Escherichia coli* strain on the colonization of the intestine with microbial pathogens in newborn infants. *Biol Neonate* **71:** 224-32.

1183 Machaidze G., and Seelig J. (2003). Specific binding of cinnamycin (Ro 09-0198) to
1184 phosphatidylethanolamine. Comparison between micellar and membrane environments.
1185 *Biochemistry* **42:** 12570-6.
1186 Madera C., Garcia P., Rodriguez A., Suarez J. E., and Martinez B. (2009). Prophage induction in
1187 *Lactococcus lactis* by the bacteriocin Lactococcin 972. *Int J Food Microbiol* **129:** 99-
1188 102.
1189 Majhenic A. C., Venema K., Allison G. E., Matijasic B. B., Rogelj I., and Klaenhammer T. R.
1190 (2004). DNA analysis of the genes encoding acidocin LF221 A and acidocin LF221 B,
1191 two bacteriocins produced by *Lactobacillus gasseri* LF221. *Appl Microbiol Biotechnol*
1192 **63:** 705-14.
1193 Maldonado A., Jimenez-Diaz R., and Ruiz-Barba J. L. (2004a). Induction of plantaricin
1194 production in *Lactobacillus plantarum* NC8 after coculture with specific gram-positive
1195 bacteria is mediated by an autoinduction mechanism. *J Bacteriol* **186:** 1556-64.
1196 Maldonado A., Ruiz-Barba J. L., and Jimenez-Diaz R. (2004b). Production of plantaricin NC8
1197 by Lactobacillus plantarum NC8 is induced in the presence of different types of gram-
1198 positive bacteria. *Arch Microbiol* **181:** 8-16.
1199 Marcille F., Gomez A., Joubert P., Ladire M., Veau G., Clara A., Gavini F., Willems A., and
1200 Fons M. (2002). Distribution of genes encoding the trypsin-dependent lantibiotic
1201 ruminococcin A among bacteria isolated from human fecal microbiota. *Appl Environ*
1202 *Microbiol* **68:** 3424-31.
1203 Martin F. P., Sprenger N., Montoliu I., Rezzi S., Kochhar S., and Nicholson J. K. (2010). Dietary
1204 Modulation of Gut Functional Ecology Studied by Fecal Metabonomics. *J Proteome Res*.

Martin F. P., Wang Y., Sprenger N., Yap I. K., Lundstedt T., Lek P., Rezzi S., Ramadan Z., van Bladeren P., Fay L. B., Kochhar S., Lindon J. C., Holmes E., and Nicholson J. K. (2008a). Probiotic modulation of symbiotic gut microbial-host metabolic interactions in a humanized microbiome mouse model. *Mol Syst Biol* **4:** 157.

Martin F. P., Wang Y., Sprenger N., Yap I. K., Rezzi S., Ramadan Z., Pere-Trepat E., Rochat F., Cherbut C., van Bladeren P., Fay L. B., Kochhar S., Lindon J. C., Holmes E., and Nicholson J. K. (2008b). Top-down systems biology integration of conditional prebiotic modulated transgenomic interactions in a humanized microbiome mouse model. *Mol Syst Biol* **4:** 205.

Martin R., Jimenez E., Heilig H., Fernandez L., Marin M. L., Zoetendal E. G., and Rodriguez J. M. (2009). Isolation of bifidobacteria from breast milk and assessment of the bifidobacterial population by PCR-denaturing gradient gel electrophoresis and quantitative real-time PCR. *Appl Environ Microbiol* **75:** 965-9.

Martinez B., Bottiger T., Schneider T., Rodriguez A., Sahl H. G., and Wiedemann I. (2008). Specific interaction of the unmodified bacteriocin Lactococcin 972 with the cell wall precursor lipid II. *Appl Environ Microbiol* **74:** 4666-70.

Mathys S., von Ah U., Lacroix C., Staub E., Mini R., Cereghetti T., and Meile L. (2007). Detection of the pediocin gene pedA in strains from human faeces by real-time PCR and characterization of *Pediococcus acidilactici* UVA1. *BMC Biotechnol* **7:** 55.

Mazmanian S. K., Round J. L., and Kasper D. L. (2008). A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature* **453:** 620-5.

Meghrous J., Eulogy P., Junelles A. M., Ballongue J., and Petitdemange H. (1990). Screening of bifidobacteria strains for bacteriocin production. *Biotechnology Letters* **12:** 575-580.

1228 Meindl K., Schmiederer T., Schneider K., Reicke A., Butz D., Keller S., Guhring H., Vertesy L.,
1229 Wink J., Hoffmann H., Bronstrup M., Sheldrick G. M., and Sussmuth R. D. (2010).
1230 Labyrinthopeptins: a new class of carbacyclic lantibiotics. *Angew Chem Int Ed Engl* **49:**
1231 1151-4.
1232 Menard S., Candalh C., Bambou J. C., Terpend K., Cerf-Bensussan N., and Heyman M. (2004).
1233 Lactic acid bacteria secrete metabolites retaining anti-inflammatory properties after
1234 intestinal transport. *Gut* **53:** 821-8.
1235 Metlitskaya A., Kazakov T., Kommer A., Pavlova O., Praetorius-Ibba M., Ibba M.,
1236 Krasheninnikov I., Kolb V., Khmel I., and Severinov K. (2006). Aspartyl-tRNA
1237 synthetase is the target of peptide nucleotide antibiotic Microcin C. *J Biol Chem* **281:**
1238 18033-42.
1239 Metlitskaya A. Z., Katrukha G. S., Shashkov A. S., Zaitsev D. A., Egorov T. A., and Khmel I. A.
1240 (1995). Structure of microcin C51, a new antibiotic with a broad spectrum of activity.
1241 *FEBS Lett* **357:** 235-8.
1242 Miller A., Stanton C., and Devery R. (2002). Cis 9, trans 11- and trans 10, cis 12-conjugated
1243 linoleic acid isomers induce apoptosis in cultured SW480 cells. *Anticancer Res* **22:** 3879-
1244 87.
1245 Millette M., Cornut G., Dupont C., Shareck F., Archambault D., and Lacroix M. (2008).
1246 Capacity of human nisin- and pediocin-producing lactic Acid bacteria to reduce intestinal
1247 colonization by vancomycin-resistant enterococci. *Appl Environ Microbiol* **74:** 1997-
1248 2003.

1249 Millette M., Dupont C., Archambault D., and Lacroix M. (2007). Partial characterization of
1250 bacteriocins produced by human *Lactococcus lactis* and *Pediococccus acidilactici*
1251 isolates. *J Appl Microbiol* **102:** 274-82.
1252 Mills S., Ross R. P., Fitzgerald G., and Stanton C. (2009). Microbial Production of Bioactive
1253 Metabolites. *In* "Dairy Fats and Related Products" (A. Y. Tamime, Ed.), pp. 257-285,
1254 Wiley-Blackwell, Oxford, UK.
1255 Mimura T., Rizzello F., Helwig U., Poggioli G., Schreiber S., Talbot I. C., Nicholls R. J.,
1256 Gionchetti P., Campieri M., and Kamm M. A. (2004). Once daily high dose probiotic
1257 therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut* **53:**
1258 108-14.
1259 Moll G. N., Kuipers A., de Vries L., Bosma T., and Rink R. (2009). A biological stabilization
1260 technology for peptide drugs: enzymatic introduction of thioether-bridges *Drug*
1261 *Discovery Today: Technologies* **6:** e13-e18.
1262 Mota-Meira M., Lacroix C., LaPointe G., and Lavoie M. C. (1997). Purification and structure of
1263 mutacin B-Ny266: a new lantibiotic produced by *Streptococcus mutans*. *FEBS Lett* **410:**
1264 275-9.
1265 Mushtaq S., Heather Mangiapane E., and Hunter K. A. (2010). Estimation of cis-9, trans-11
1266 conjugated linoleic acid content in UK foods and assessment of dietary intake in a cohort
1267 of healthy adults. *Br J Nutr* **103:** 1366-74.
1268 Nagao K., Inoue N., Wang Y. M., Shirouchi B., and Yanagita T. (2005). Dietary conjugated
1269 linoleic acid alleviates nonalcoholic fatty liver disease in Zucker (fa/fa) rats. *J Nutr* **135:**
1270 9-13.

Netz D. J., Bastos Mdo C., and Sahl H. G. (2002). Mode of action of the antimicrobial peptide aureocin A53 from *Staphylococcus aureus*. *Appl Environ Microbiol* **68:** 5274-80.

Nissen-Meyer J., Rogne P., Oppegard C., Haugen H. S., and Kristiansen P. E. (2009). Structure-function relationships of the non-lanthionine-containing peptide (class II) bacteriocins produced by gram-positive bacteria. *Curr Pharm Biotechnol* **10:** 19-37.

O'Shea E. F., Gardiner G. E., O'Connor P. M., Mills S., Ross R. P., and Hill C. (2009). Characterization of enterocin- and salivaricin-producing lactic acid bacteria from the mammalian gastrointestinal tract. *FEMS Microbiol Lett* **291:** 24-34.

O'Shea E. F., O'Connor P. M., Cotter P. D., Ross R. P., and Hill C. (2010). Synthesis of trypsin-resistant variants of the Listeria-active bacteriocin salivaricin P. *Appl Environ Microbiol* **76:** 5356-62.

O'Shea M., Bassaganya-Riera J., and Mohede I. C. (2004). Immunomodulatory properties of conjugated linoleic acid. *Am J Clin Nutr* **79:** 1199S-1206S.

Ogawa J., Kishino S., Ando A., Sugimoto S., Mihara K., and Shimizu S. (2005). Production of conjugated fatty acids by lactic acid bacteria. *J Biosci Bioeng* **100:** 355-64.

Ogawa J., Matsumura K., Kishino S., Omura Y., and Shimizu S. (2001). Conjugated linoleic acid accumulation via 10-hydroxy-12-octadecaenoic acid during microaerobic transformation of linoleic acid by *Lactobacillus acidophilus*. *Appl Environ Microbiol* **67:** 1246-52.

Oh D. K., Hong G. H., Lee Y., Min S., and Cho S. K. (2003). Production of conjugated linoleic acid by isolated *Bifidobacterium* strains. *World Journal of Microbiology & Biotechnology* **19:** 907-912.

1292 Oppegard C., Rogne P., Emanuelsen L., Kristiansen P. E., Fimland G., and Nissen-Meyer J.
1293 (2007). The two-peptide class II bacteriocins: structure, production, and mode of action. *J*
1294 *Mol Microbiol Biotechnol* **13:** 210-9.
1295 Opsata M., Nes I. F., and Holo H. (2010). Class IIa bacteriocin resistance in *Enterococcus*
1296 *faecalis* V583: The mannose PTS operon mediates global transcriptional responses. *BMC*
1297 *Microbiol* **10:** 224.
1298 Ottenwalder B., Kupke T., Brecht S., Gnau V., Metzger J., Jung G., and Gotz F. (1995). Isolation
1299 and characterization of genetically engineered gallidermin and epidermin analogs. *Appl*
1300 *Environ Microbiol* **61:** 3894-903.
1301 Pag U., and Sahl H. G. (2002). Multiple activities in lantibiotics--models for the design of novel
1302 antibiotics? *Curr Pharm Des* **8:** 815-33.
1303 Park Y., Albright K. J., Liu W., Storkson J. M., Cook M. E., and Pariza M. W. (1997). Effect of
1304 conjugated linoleic acid on body composition in mice. *Lipids* **32:** 853-8.
1305 Patzer S. I., Baquero M. R., Bravo D., Moreno F., and Hantke K. (2003). The colicin G, H and X
1306 determinants encode microcins M and H47, which might utilize the catecholate
1307 siderophore receptors FepA, Cir, Fiu and IroN. *Microbiology* **149:** 2557-70.
1308 Pedersen G., Andresen L., Matthiessen M. W., Rask-Madsen J., and Brynskov J. (2005).
1309 Expression of Toll-like receptor 9 and response to bacterial CpG oligodeoxynucleotides
1310 in human intestinal epithelium. *Clin Exp Immunol* **141:** 298-306.
1311 Pingitore V. E., Hebert E. M., Nader-Macias M. E., and Sesma F. (2009). Characterization of
1312 salivaricin CRL 1328, a two-peptide bacteriocin produced by *Lactobacillus salivarius*
1313 CRL 1328 isolated from the human vagina. *Res Microbiol* **160:** 401-8.

1314 Poey M. E., Azpiroz M. F., and Lavina M. (2006). Comparative analysis of chromosome-
1315 encoded microcins. *Antimicrob Agents Chemother* **50:** 1411-8.
1316 Pridmore R. D., Berger B., Desiere F., Vilanova D., Barretto C., Pittet A. C., Zwahlen M. C.,
1317 Rouvet M., Altermann E., Barrangou R., Mollet B., Mercenier A., Klaenhammer T.,
1318 Arigoni F., and Schell M. A. (2004). The genome sequence of the probiotic intestinal
1319 bacterium *Lactobacillus johnsonii* NCC 533. *Proc Natl Acad Sci U S A* **101:** 2512-7.
1320 Pridmore R. D., Pittet A. C., Praplan F., and Cavadini C. (2008). Hydrogen peroxide production
1321 by *Lactobacillus johnsonii* NCC 533 and its role in anti-*Salmonella* activity. *FEMS*
1322 *Microbiol Lett* **283:** 210-5.
1323 Qi F., Chen P., and Caufield P. W. (1999). Purification of mutacin III from group III
1324 *Streptococcus mutans* UA787 and genetic analyses of mutacin III biosynthesis genes.
1325 *Appl Environ Microbiol* **65:** 3880-7.
1326 Qi F., Chen P., and Caufield P. W. (2001). The group I strain of *Streptococcus mutans*, UA140,
1327 produces both the lantibiotic mutacin I and a nonlantibiotic bacteriocin, mutacin IV. *Appl*
1328 *Environ Microbiol* **67:** 15-21.
1329 Ramare F., Nicoli J., Dabard J., Corring T., Ladire M., Gueugneau A. M., and Raibaud P.
1330 (1993). Trypsin-dependent production of an antibacterial substance by a human
1331 *Peptostreptococcus* strain in gnotobiotic rats and *in vitro*. *Appl Environ Microbiol* **59:**
1332 2876-83.
1333 Rea M. C., Clayton E., O'Connor P. M., Shanahan F., Kiely B., Ross R. P., and Hill C. (2007).
1334 Antimicrobial activity of lacticin 3,147 against clinical *Clostridium difficile* strains. *J*
1335 *Med Microbiol* **56:** 940-6.

Rea M. C., Dobson A., O'Sullivan O., Crispie F., Fouhy F., Cotter P. D., Shanahan F., Kiely B., Hill C., and Ross R. P. (2010a). Effect of broad and narrow spectrum antimicrobials on *Clostridium difficile* and microbial diversity in a model of the distal colon. *Proc Natl Acad Sci U S A***:** (in press).

Rea M. C., Ross R. P., Cotter P. D., and Hill C. (2010b). Classification of Bacteriocins from Gram Positive Bacteria *In* "Prokaryotic Antimicrobial Peptides" (D. Drider, Ed.), Spriger, New York.

Rea M. C., Sit C. S., Clayton E., O'Connor P. M., Whittal R. M., Zheng J., Vederas J. C., Ross R. P., and Hill C. (2010c). Thuricin CD, a posttranslationally modified bacteriocin with a narrow spectrum of activity against *Clostridium difficile*. *Proc Natl Acad Sci U S A* **107:** 9352-7.

Rink R., Arkema-Meter A., Baudoin I., Post E., Kuipers A., Nelemans S. A., Akanbi M. H., and Moll G. N. (2010). To protect peptide pharmaceuticals against peptidases. *J Pharmacol Toxicol Methods* **61:** 210-8.

Robson C. L., Wescombe P. A., Klesse N. A., and Tagg J. R. (2007). Isolation and partial characterization of the *Streptococcus mutans* type AII lantibiotic mutacin K8. *Microbiology* **153:** 1631-41.

Rosberg-Cody E., Liavonchanka A., Gobel C., Ross R. P., O'Sullivan O., Fitzgerald G., Feussner I., and Stanton C. (2010). Myosin-cross-reactive antigen (MCRA) protein from *Bifidobacterium breve* is a FAD-dependent fatty acid hydratase which has a function in stress protection. *BMC Biochem* **In press**.

1357 Rosberg-Cody E., Ross R. P., Hussey S., Ryan C. A., Murphy B. P., Fitzgerald G. F., Devery R.,
1358 and Stanton C. (2004). Mining the microbiota of the neonatal gastrointestinal tract for
1359 conjugated linoleic acid-producing bifidobacteria. *Appl Environ Microbiol* **70:** 4635-41.
1360 Ross K. F., Ronson C. W., and Tagg J. R. (1993). Isolation and characterization of the lantibiotic
1361 salivaricin A and its structural gene salA from *Streptococcus salivarius* 20P3. *Appl*
1362 *Environ Microbiol* **59:** 2014-21.
1363 Roy R. S., Allen O., and Walsh C. T. (1999). Expressed protein ligation to probe regiospecificity
1364 of heterocyclization in the peptide antibiotic microcin B17. *Chem Biol* **6:** 789-99.
1365 Ryan K. A., Daly P., Li Y., Hooton C., and O'Toole P. W. (2008). Strain-specific inhibition of
1366 *Helicobacter pylori* by *Lactobacillus salivarius* and other lactobacilli. *J Antimicrob*
1367 *Chemother* **61:** 831-4.
1368 Salomon R. A., and Farias R. N. (1992). Microcin 25, a novel antimicrobial peptide produced by
1369 *Escherichia coli*. *J Bacteriol* **174:** 7428-35.
1370 Salyers A. A., and Whitt D. D. (2002). *Salmonella* Species. *In* "Bacterial Pathogenesis, a
1371 Molecular Approach 2nd Edition" (D. D. Whitt, Ed.), pp. 381-397, ASM Press,
1372 Washington, DC.
1373 Scanlan P. D., Shanahan F., O'Mahony C., and Marchesi J. R. (2006). Culture-independent
1374 analyses of temporal variation of the dominant fecal microbiota and targeted bacterial
1375 subgroups in Crohn's disease. *J Clin Microbiol* **44:** 3980-8.
1376 Schultz M. (2008). Clinical use of *E. coli* Nissle 1917 in inflammatory bowel disease. *Inflamm*
1377 *Bowel Dis* **14:** 1012-8.
1378 Shanahan F., Stanton C., Ross R. P., and Hill C. (2009). Pharmabiotics: Bioactives from Mining
1379 Host-Microbe-Dietary Interactions. *Functional Food Reviews* **1:** 20-15.

Simpson W. J., Ragland N. L., Ronson C. W., and Tagg J. R. (1995). A lantibiotic gene family widely distributed in *Streptococcus salivarius* and *Streptococcus pyogenes*. *Dev Biol Stand* **85:** 639-43.

Smajs D., Micenkova L., Smarda J., Vrba M., Sevcikova A., Valisova Z., and Woznicova V. (2010). Bacteriocin synthesis in uropathogenic and commensal *Escherichia coli*: colicin E1 is a potential virulence factor. *BMC Microbiol* **10:** 288.

Smajs D., and Weinstock G. M. (2001). The iron- and temperature-regulated cjrBC genes of *Shigella* and enteroinvasive *Escherichia coli* strains code for colicin Js uptake. *J Bacteriol* **183:** 3958-66.

Smarda J. (1983). The action of colicins on eukaryotic cells. *Journal of Toxicology. Toxin Reviews* **2:** 1-76.

Smarda J., and Obdrzalek V. (2001). Incidence of colicinogenic strains among human *Escherichia coli*. *J Basic Microbiol* **41:** 367-74.

Snijder H. J., and Dijkstra B. W. (2000). Bacterial phospholipase A: structure and function of an integral membrane phospholipase. *Biochim Biophys Acta* **1488:** 91-101.

Stanton C., Lawless F., Kjellmer G., Harrington D., Devery R., Connolly J. F., and Murphy J. (1997). Dietary influences on bovine milk *cis*-9, *trans*-11-conjugated linoleic acid content. *J Food Sci* **62:** 1083-1086.

Stanton C., Murphy J., McGrath E., and Devery R. (2003). Animal Feeding Strategies for Conjugated Linoleic Acid Enrichment of Milk. *In* "Advances in Conjugated Linoleic Acid Research, Volume 2" (J. L. Sebedio, W. W. Christie, and R. Adolf, Eds.), pp. 123-145, AOCS Press, Champaign, IL.

Stern N. J., Svetoch E. A., Eruslanov B. V., Perelygin V. V., Mitsevich E. V., Mitsevich I. P., Pokhilenko V. D., Levchuk V. P., Svetoch O. E., and Seal B. S. (2006). Isolation of a *Lactobacillus salivarius* strain and purification of its bacteriocin, which is inhibitory to *Campylobacter jejuni* in the chicken gastrointestinal system. *Antimicrob Agents Chemother* **50:** 3111-6.

Suda S., Westerbeek A., O'Connor P. M., Ross R. P., Hill C., and Cotter P. D. (2010). Effect of bioengineering lacticin 3147 lanthionine bridges on specific activity and resistance to heat and proteases. *Chem Biol* **17:** 1151-60.

Tagg J. R. (2004). Prevention of streptococcal pharyngitis by anti-*Streptococcus pyogenes* bacteriocin-like inhibitory substances (BLIS) produced by *Streptococcus salivarius*. *Indian J Med Res* **119 Suppl:** 13-6.

Tannock G. W. (2003). Probiotics: time for a dose of realism. *Curr Issues Intest Microbiol* **4:** 33-42.

Tao Y., Drabik K. A., Waypa T. S., Musch M. W., Alverdy J. C., Schneewind O., Chang E. B., and Petrof E. O. (2006). Soluble factors from *Lactobacillus* GG activate MAPKs and induce cytoprotective heat shock proteins in intestinal epithelial cells. *Am J Physiol Cell Physiol* **290:** C1018-30.

Toba T., Yoshioka E., and Itoh T. (1991). Potential of *Lactobacillus gasseri* isolated from infant faeces to produce bacteriocin. *Lett Appl Microbiol* **12:** 228-231.

Toure R., Kheadr E., Lacroix C., Moroni O., and Fliss I. (2003). Production of antibacterial substances by bifidobacterial isolates from infant stool active against *Listeria monocytogenes*. *J Appl Microbiol* **95:** 1058-69.

1424 Turpeinen A. M., Mutanen M., Aro A., Salminen I., Basu S., Palmquist D. L., and Griinari J. M.
1425 (2002). Bioconversion of vaccenic acid to conjugated linoleic acid in humans. *Am J Clin*
1426 *Nutr* **76:** 504-10.
1427 Upton M., Tagg J. R., Wescombe P., and Jenkinson H. F. (2001). Intra- and interspecies
1428 signaling between *Streptococcus salivarius* and *Streptococcus pyogenes* mediated by
1429 SalA and SalA1 lantibiotic peptides. *J Bacteriol* **183:** 3931-8.
1430 Ventura M., Turroni F., Canchaya C., Vaughan E. E., O'Toole P. W., and van Sinderen D.
1431 (2009). Microbial diversity in the human intestine and novel insights from metagenomics.
1432 *Front Biosci* **14:** 3214-21.
1433 Vizan J. L., Hernandez-Chico C., del Castillo I., and Moreno F. (1991). The peptide antibiotic
1434 microcin B17 induces double-strand cleavage of DNA mediated by *E. coli* DNA gyrase.
1435 *EMBO J* **10:** 467-76.
1436 Vriezen J. A., Valliere M., and Riley M. A. (2009). The evolution of reduced microbial killing.
1437 *Genome Biol Evol* **1:** 400-8.
1438 Wall R., Ross R. P., Shanahan F., O'Mahony L., Kiely B., Quigley E., Dinan T. G., Fitzgerald
1439 G., and Stanton C. (2010). Impact of administered *Bifidobacterium* on murine host fatty
1440 acid composition. *Lipids* **45:** 429-36.
1441 Wall R., Ross R. P., Shanahan F., O'Mahony L., O'Mahony C., Coakley M., Hart O., Lawlor P.,
1442 Quigley E. M., Kiely B., Fitzgerald G. F., and Stanton C. (2009). Metabolic activity of
1443 the enteric microbiota influences the fatty acid composition of murine and porcine liver
1444 and adipose tissues. *Am J Clin Nutr* **89:** 1393-401.

1445 Wallace R. J., McKain N., Shingfield K. J., and Devillard E. (2007). Isomers of conjugated
1446 linoleic acids are synthesized via different mechanisms in ruminal digesta and bacteria. *J*
1447 *Lipid Res* **48:** 2247-54.
1448 Walsh M. C., Gardiner G. E., Hart O. M., Lawlor P. G., Daly M., Lynch B., Richert B. T.,
1449 Radcliffe S., Giblin L., Hill C., Fitzgerald G. F., Stanton C., and Ross P. (2008).
1450 Predominance of a bacteriocin-producing *Lactobacillus salivarius* component of a five-
1451 strain probiotic in the porcine ileum and effects on host immune phenotype. *FEMS*
1452 *Microbiol Ecol* **64:** 317-27.
1453 Watanabe T., and Saito H. (1980). Cytotoxicity of pyocin S2 to tumor and normal cells and its
1454 interaction with cell surfaces. *Biochim Biophys Acta* **633:** 77-86.
1455 Wells J. M., Rossi O., Meijerink M., and van Baarlen P. (2010). Microbes and Health Sackler
1456 Colloquium: Epithelial crosstalk at the microbiota-mucosal interface. *Proc Natl Acad Sci*
1457 *U S A*.
1458 Wescombe P. A., Burton J. P., Cadieux P. A., Klesse N. A., Hyink O., Heng N. C., Chilcott C.
1459 N., Reid G., and Tagg J. R. (2006a). Megaplasmids encode differing combinations of
1460 lantibiotics in *Streptococcus salivarius*. *Antonie Van Leeuwenhoek* **90:** 269-80.
1461 Wescombe P. A., and Tagg J. R. (2003). Purification and characterization of streptin, a type A1
1462 lantibiotic produced by *Streptococcus pyogenes*. *Appl Environ Microbiol* **69:** 2737-47.
1463 Wescombe P. A., Upton M., Dierksen K. P., Ragland N. L., Sivabalan S., Wirawan R. E., Inglis
1464 M. A., Moore C. J., Walker G. V., Chilcott C. N., Jenkinson H. F., and Tagg J. R.
1465 (2006b). Production of the lantibiotic salivaricin A and its variants by oral streptococci
1466 and use of a specific induction assay to detect their presence in human saliva. *Appl*
1467 *Environ Microbiol* **72:** 1459-66.

1468 Wiedemann I., Breukink E., van Kraaij C., Kuipers O. P., Bierbaum G., de Kruijff B., and Sahl
1469 H. G. (2001). Specific binding of nisin to the peptidoglycan precursor lipid II combines
1470 pore formation and inhibition of cell wall biosynthesis for potent antibiotic activity. *J*
1471 *Biol Chem* **276:** 1772-9.
1472 Willey J. M., and van der Donk W. A. (2007). Lantibiotics: peptides of diverse structure and
1473 function. *Annu Rev Microbiol* **61:** 477-501.
1474 Wilson K. A., Kalkum M., Ottesen J., Yuzenkova J., Chait B. T., Landick R., Muir T., Severinov
1475 K., and Darst S. A. (2003). Structure of microcin J25, a peptide inhibitor of bacterial
1476 RNA polymerase, is a lassoed tail. *J Am Chem Soc* **125:** 12475-83.
1477 Yan F., Cao H., Cover T. L., Whitehead R., Washington M. K., and Polk D. B. (2007). Soluble
1478 proteins produced by probiotic bacteria regulate intestinal epithelial cell survival and
1479 growth. *Gastroenterology* **132:** 562-75.
1480 Yildirim Z., Winters D. K., and Johnson M. G. (1999). Purification, amino acid sequence and
1481 mode of action of bifidocin B produced by *Bifidobacterium bifidum* NCFB 1454. *J Appl*
1482 *Microbiol* **86:** 45-54.
1483 Zhu W. M., Liu W., and Wu D. Q. (2000). Isolation and characterization of a new bacteriocin
1484 from *Lactobacillus gasseri* KT7. *J Appl Microbiol* **88:** 877-86.
1485 Zinedine A., and Faid M. (2007). Isaolation and characterisation of strains of bifidobacteria with
1486 probiotic properties *In vitro*. *World Journal of Dairy and Food Science* **2:** 28-34.

Table 1. Bacteriocins produced by intestinal bacteria.

Classification	Bacteriocin		Producing organism	Source	Reference
Bacteriocins produced by gram-negative bacteria					
Colicins					
Group A	Colicin E1-E9		*Escherichia coli*	Human feaces	(Gorden and O'Brien, 2006; Smajs et al., 2010)
	Colicin K		*Escherichia coli*	Human feaces	(Gorden and O'Brien, 2006)
	Colicin N		*Escherichia coli*	Human feaces	(Smajs et al., 2010)
	Colicin S4		*Escherichia coli*	Human feaces	(Smajs et al., 2010)
	Colicin U		*Escherichia coli*	Human feaces	(Smajs et al., 2010)
	Colicin Y		*Escherichia coli*	Human feaces	(Smajs et al., 2010)
Group B	Colicin B		*Escherichia coli*	Human feaces	(Gorden and O'Brien, 2006)
	Colicin Ia		*Escherichia coli*	Human feaces	(Gorden and O'Brien, 2006)
	Colicin Ib		*Escherichia coli*	Human feaces	(Smajs et al., 2010)
	Colicin M		*Escherichia coli*	Human feaces	(Gorden and O'Brien, 2006)
	Colicin 5		*Escherichia coli*	Human feaces	(Smajs et al., 2010)
Unclassified	Colicin Js		*Escherichia coli*	Human feaces	(Smajs et al., 2010)
Microcins					
Class I	Microcin B17		*Escherichia coli*	Human feaces	(Gorden and O'Brien, 2006)
	Microcin C7/C51		*Escherichia coli*	Human feaces	(Gorden and O'Brien, 2006)
	Microcin J25		*Escherichia coli*	Human feaces	(Salomon and Farias, 1992)
	Microcin 15m		*Escherichia coli* LP15	Human feaces	(Aguilar et al., 1982)
	Microcin 15n		*Escherichia coli* LP15	Human feaces	(Aguilar et al., 1983)
Class IIa	Microcin V		*Escherichia coli*	Human feaces	(Gorden and O'Brien, 2006)
	Microcin L		*Escherichia coli*	Human feaces	(Gorden and O'Brien, 2006)
Class IIb	Microcin E492		*Klebsiella pneumoniae* RYC492	Human feaces	(de Lorenzo, 1984)
	Microcin H47		*Escherichia coli* H47	Human feaces	(Lavina, Gaggero and Moreno, 1990)
	Microcin I47		*Escherichia coli* H48	Human feaces	(Poey, Azpiroz and Lavina, 2006)
	Microcin M		*Escherichia coli* Nissle 1917	Human feaces	(Patzer et al., 2003)
Pyocin	Pyocin S2		*Pseudomonas aeruginosa* 42A	Clinical isolate	(Abdi-Ali et al, 2004)
Bacteriocins produced by gram-positive bacteria					
Class I (modified)					
Class Ia Lantibiotics					
	BHT A		*Streptococcus rattus, Streptococcus mutans*	Oral cavity	(Hyink et al., 2005)
	Cytolysin	cylLL/cylLS	*Enterococcus faecalis*	Human feaces	(Haas & Gilmore, 1999)
	Mutacin I		*Streptococcus mutans* UA140	Oral cavity	(Qi et al., 2001)
	Mutacin II		*Streptococcus mutans* T8	Oral cavity	(Chikindas et al., 1995)
	Mutacin III		*Streptococcus mutans* UA787	Oral cavity	(Qi et al., 1999)
	Mutacin K8		*Streptococcus mutans* K8	Oral cavity	(Robson et al., 2007)
	Mutacin 1140		*Streptococcus mutans* JH1000	Oral cavity	(Hillman et al., 1998)

1489 **Table 1.** (continued)

Classification	Bacteriocin		Producing organism	Source	Reference
	Mutacin B-Ny226		*Streptococcus mutans* Ny226	Oral cavity	(Mota-Meira et al., 1997)
	Nisin Z		*Lactococcus lactis* MM19	Human feaces	(Millette et al., 2008)
	Ruminococcin A		*Clostridium nexile*, *Ruminococcus gnavus* E1, Ruminococcus hansenii	Human feaces	(Dabard et al., 2001; Marcille et al, 2002)
	Salivaricin A		*Streptococcus salivarius* 20P3	Oral cavity	(Ross et al., 1993)
	Salivaricin A1		*Streptococcus pyogenes*	Oral cavity	(Upton et al., 2001)
	Salivaricin A2-A5		*Streptococcus salivarius*	Oral cavity	(Wescombe et al., 2006b)
	Salivaricin B		*Streptococcus salivarius* K12	Oral cavity	(Hyink et al., 2007)
	Streptococcin A-FF22		*Streptococcus pyogenes* FF22	Throat	(Hynes et al., 1993)
	Streptin		*Streptococcus pyogenes*	Oral cavity	(Wescombe et al., 2003)
			Bifidobacterium longum DJO10A	Healthy adult faeces	(Lee et al., 2008)
Class Ic Sactibiotics	Thuracin CD	Trn-α/Trn-β	*Bacillus thuringiensis* DPC6431	Healthy adult faeces	(Rea et al., 2010c)
Class II (unmodified)					
Class IIa *Listeria*-active pediocin-like					
	Avicin A		*Enterococcus avium* 208/ XA83	Infant feaces	(Birri et al., 2010)
	Bacteriocin RC714		*Enterococcus faecium* RC714	Human faeces	(del Campo et al., 2001)
	Bacteriocin 32		*Enterococcus faecium* VRE200	Clinical isolate	(Inoue et al., 2006)
	Bacteriocin GM-1		*Enterococcus faecium* GM-1	Infant faeces	(Kang & Lee, 2005)
	Bifidocin B		*Bifidobacterium bifidum* NCFB 1454	Nursling stools	(Yildirim, Winters and Johnson, 1999)
	Enterocin A		*Enterococcus faecium* DPC6482	Infant faeces	(O'Shea et al., 2009)
	Pediocin PA-1		*Pediococcus acidilactici* UVA1	Breast fed infant faeces	(Mathys et al., 2007)
Class IIb two-component					
	Abp118	Abp118α/ Abp118β	*Lactobacillus salivarius* UCC118	Ileal-caecal region of human GIT	(Flynn et al., 2002)
	Blp	BlpM/BlpN	*Streptococcus pneumoniae*	Clinical isolate	(Dawid et al., 2007)
	Lactacin F	LafA/LafX	*Lactobacillus johnsonii* NCC 533	Human faeces	(Pridmore et al., 2004)
	Mutacin IV	NlmA/NlmB	*Streptococcus mutans* UA140	Oral cavity	(Qi et al., 2001)
	Plantaricin EF and JK	Pln E/F J/K	*Lactobacillus plantarum* WCFS1	Oral cavity	(Kleerebezem et al., 2003)
	Salivarcin T	SalTα/ SalTβ	*Lactobacillus salivarius* DPC6488	Infant faeces	(O'Shea et al., unpublished)
Class IIc cyclic	Gassericin A /Reutericin 6		*Lactobacillus gasseri* LA39, *Lactobacillus reuteri* LA6	Breast-fed infant faeces	(Toba et al., 1991)
Class IId one peptide non-pedicin-like linear bacteriocins					
	ESL5		*Enterococcus faecalis* SL-5	Human faeces	(Kang et al., 2009)
	Mutacin N		*Streptococcus mutans* N	Oral cavity	(Hale et al., 2004)
	BHT B		*Streptococcus rattus*, *Streptococcus mutans*	Oral cavity	(Hyink et al., 2005)
	Plantaricin A		*Lactobacillus plantarum* WCFS1	Oral cavity	(Kleerebezem et al., 2003)
	Gassericin T		*Lactobacillus gasseri* SBT2055	Healthy adult faeces	(Kawai et al., 2000)
	Gassericin KT7		*Lactobacillus gasseri* KT7	Breast-fed infant faeces	(Zhu, Liu & Wu, 2000)
	Acidocin LF221A/LF221B		*Lactobacillus gasseri* LF221A	Child fecal isolate	(Majhenic et al., 2004)
	Acidophilucin A		*Lactobacillus acidophilus* LAPT1060	Breast-fed infant faeces	(Toba et al., 1991)

1490

1491 **Table 2.** CLA produced by intestinal bacteria

Organism	Source	Medium	Linoleic acid (mg ml^{-1})	CLA (mg ml^{-1})			Alternative metabolites	Total CLA (mg ml^{-1})	Reference
				c-9, *t*-11 isomer	*t*-10, *c*-12 isomer	*t*-9, *t*-11 isomer			
Bifidobacterium adolescentis NCFB 2231	Adult intestine	cys-MRS	0.55	0.0006	0.0016	0.0006		0.0028	(Coakley et al., 2003)
Bifidobacterium adolescentis NCFB 2204	Adult intestine	cys-MRS	0.55	0.0016	0.0012	0.0007		0.0035	(Coakley et al., 2003)
Bifidobacterium adolescentis NCFB 2204	Adult intestine	M2	0.05	ND	ND	ND	68 % HFA		(Devillard et al., 2007)
Bifidobacterium angulatum NCFB 2236	Human faeces	cys-MRS	0.55	0.0006	0.0006	0.0000		0.0012	(Coakley et al., 2003)
Bifidobacterium bifidum NCFB 795	Unknown	cys-MRS	0.55	0.0010	0.0000	0.0000		0.0010	(Coakley et al., 2003)
Bifidobacterium bifidum (PFGE pattern A1)	Infant faeces	cys-MRS	0.50	ND	ND	ND		17.90%	(Rosberg-cody et al., 2004)
Bifidobacterium breve NCFB 2257	Infant intestine	cys-MRS	0.46	0.2232	0.0009	0.0070		0.2311	(Coakley et al., 2003)
Bifidobacterium breve NCFB 2258	Infant intestine	cys-MRS	0.55	0.3640	0.0000	0.0342		0.3982	(Coakley et al., 2003)
Bifidobacterium breve NCFB 2258	Infant intestine	cys-MRS	0.50	ND	ND	ND		36.70%	(Rosberg-cody et al., 2004)
Bifidobacterium breve NCFB 2258	Infant intestine	M2	0.05	95%	ND	ND		95.00%	(Devillard et al., 2007)
Bifidobacterium breve NCTC 11815	Infant intestine	cys-MRS	0.55	0.1987	0.0028	0.0136		0.2151	(Coakley et al., 2003)
Bifidobacterium breve NCIMB 8807	Nursling stools	cys-MRS	0.46	0.1229	0.0003	0.0047		0.1279	(Coakley et al., 2003)
Bifidobacterium breve NCIMB 8815	Nursling stools	cys-MRS	0.55	0.2238	0.0025	0.0158		0.2281	(Coakley et al., 2003)
Bifidobacterium breve KCTC 10462	Breast-fed infant faeces	cys-MRS	0.50	0.1600	ND	ND		0.0016	(Oh et al., 2003)
Bifidobacterium breve (PFGE pattern B)	Infant faeces	cys-MRS	0.50	ND	ND	ND		29.00%	(Rosberg-cody et al., 2004)
Bifidobacterium breve (PFGE pattern F1)	Infant faeces	cys-MRS	0.50	ND	ND	ND		7.70%	(Rosberg-cody et al., 2004)
Bifidobacterium breve (PFGE pattern F2)	Infant faeces	cys-MRS	0.50	ND	ND	ND		27.40%	(Rosberg-cody et al., 2004)
Bifidobacterium breve (PFGE pattern A)	*C. difficile* patient	cys-MRS	0.50	ND	ND	ND		76.65%	(Barrett et al., 2007)
Bifidobacterium breve (PFGE pattern C)	*C. difficile* patient	cys-MRS	0.50	ND	ND	ND		61.12%	(Barrett et al., 2007)
Bifidobacterium breve (PFGE pattern G)	*C. difficile* patient	cys-MRS	0.50	ND	ND	ND		27.20%	(Barrett et al., 2007)
Bifidobacterium breve (PFGE pattern H)	*C. difficile* patient	cys-MRS	0.50	ND	ND	ND		44.65%	(Barrett et al., 2007)
Bifidobacterium breve (PFGE pattern O)	*C. difficile* patient	cys-MRS	0.50	ND	ND	ND		21.53%	(Barrett et al., 2007)
Bifidobacterium breve (PFGE pattern P)	*C. difficile* patient	cys-MRS	0.50	ND	ND	ND		4.12%	(Barrett et al., 2007)

1492

1493 **Table 2.** (continued)

Organism	Source	Medium	Linoleic acid (mg ml^{-1})	CLA (mg ml^{-1})			Alternative metabolites	Total CLA (mg ml^{-1})	Reference
				c-9, *t*-11 isomer	*t*-10, *c*-12 isomer	*t*-9, *t*-11 isomer			
Bifidobacterium dentium (PFGE pattern L)	Infant faeces	cys-MRS	0.50	ND	ND	ND		12.55%	(Barrett et al., 2007)
Bifidobacterium dentium NCFB 2243	Dental caries	cys-MRS	0.55	0.1252	0.0014	0.0332		0.1598	(Coakley et al., 2003)
Bifidobacterium infantis NCFB 2205	Infant intestine	cys-MRS	0.55	0.0011	0.0016	0.0009		0.0036	(Coakley et al., 2003)
Bifidobacterium infantis NCFB 2256	Infant intestine	cys-MRS	0.55	0.0182	0.0018	0.0046		0.0246	(Coakley et al., 2003)
Bifidobacterium infantis NCFB 2256	Infant intestine	M2	0.05	ND	ND	ND	79 % HFA		(Devillard et al., 2007)
Bifidobacterium infantis (PFGE pattern D)	Adult faeces	cys-MRS	0.50	ND	ND	ND		18.11%	(Barrett et al., 2007)
Bifidobacterium lactis Bb12	Chr Hansen	cys-MRS	0.55	0.1539	0.0030	0.0134		0.2180	(Coakley et al., 2003)
Bifidobacterium longum (PFGE pattern E)	Infant faeces	cys-MRS	0.50	ND	ND	ND		3.20%	(Rosberg-cody et al., 2004)
Bifidobacterium longum (PFGE pattern B)	*C. difficile* patient	cys-MRS	0.50	ND	ND	ND		53.08%	(Barrett et al., 2007)
Bifidobacterium longum (PFGE pattern E)	Adult faeces	cys-MRS	0.50	ND	ND	ND		60.12%	(Barrett et al., 2007)
Bifidobacterium longum (PFGE pattern F)	Adult faeces	cys-MRS	0.50	ND	ND	ND		3.98%	(Barrett et al., 2007)
Bifidobacterium longum (PFGE pattern I)	Infant faeces	cys-MRS	0.50	ND	ND	ND		38.50%	(Barrett et al., 2007)
Bifidobacterium longum (PFGE pattern J)	Infant faeces	cys-MRS	0.50	ND	ND	ND		20.16%	(Barrett et al., 2007)
Bifidobacterium longum (PFGE pattern K)	Infant faeces	cys-MRS	0.50	ND	ND	ND		18.66%	(Barrett et al., 2007)
Bifidobacterium longum (PFGE pattern N)	Infant faeces	cys-MRS	0.50	ND	ND	ND		5.24%	(Barrett et al., 2007)
Bifidobacterium longum (PFGE pattern Q)	Adult faeces	cys-MRS	0.50	ND	ND	ND		3.68%	(Barrett et al., 2007)
Bifidobacterium longum (PFGE pattern R)	Infant faeces	cys-MRS	0.50	ND	ND	ND		6.31%	(Barrett et al., 2007)
Bifidobacterium pseudocatenulatum NCIMB 8811	Nursling stools	cys-MRS	0.55	0.0168	0.0020	0.0045		0.0233	(Coakley et al., 2003)
Bifidobacterium pseudocatenulatum KCTC 10208	Breast-fed infant faeces	cys-MRS	0.50	0.1350	ND	ND		0.1400	(Oh et al., 2003)
Bifidobacterium pseudocatenulatum (PFGE pattern M)	Infant faeces	cys-MRS	0.50	ND	ND	ND		2.60%	(Barrett et al., 2007)
Butyrivibrio fibrisolvens 16.4	Human faeces	M2	0.05	ND	ND	ND	100 % VA		(Devillard et al., 2007)
Eubacterium siraeum DSM 15702	Human faeces	M2	0.05	ND	ND	ND	26 % HFA		(Devillard et al., 2007)
Eubacterium ruminantium L2-50	Human faeces	M2	0.05	ND	ND	ND	38 % HFA		(Devillard et al., 2007)
Faecalibacterium prausnitzii L-2-6	Human faeces	M2	0.05	ND	ND	ND	32 % HFA		(Devillard et al., 2007)

1494

1495 **Table 2.** (continued)

Organism	Source	Medium	Linoleic acid (mg ml^{-1})	CLA (mg ml^{-1})			Alternative metabolites	Total CLA (mg ml^{-1})	Reference
				c-9, *t*-11 isomer	*t*-10, *c*-12 isomer	*t*-9, *t*-11 isomer			
Lactobacillus acidophilus L1	Human intestine	MRS	0.20	0.1150	0.0132	0.0007		0.1320	(Alonso et al., 2003)
Lactobacillus acidophilus L1	Human intestine	10 % RSM	0.20	0.1000	0.0100	0.0060		0.1160	(Alonso et al., 2003)
Lactobacillus acidophilus O16	Human intestine	MRS	0.20	0.0550	0.0050	0.0004		0.0610	(Alonso et al., 2003)
Lactobacillus acidophilus O16	Human intestine	10 % RSM	0.20	0.0450	0.0080	0.0010		0.0540	(Alonso et al., 2003)
Lactobacillus casei E5	Human intestine	MRS	0.20	0.0940	0.0140	0.0030		0.1110	(Alonso et al., 2003)
Lactobacillus casei E5	Human intestine	10 % RSM	0.20	0.0850	0.0120	0.0030		0.1000	(Alonso et al., 2003)
Lactobacillus casei E10	Human intestine	MRS	0.20	0.0710	0.0070	0.0025		0.0800	(Alonso et al., 2003)
Lactobacillus casei E10	Human intestine	10 % RSM	0.20	0.0610	0.0085	0.0020		0.0710	(Alonso et al., 2003)
Lactobacillus fermentum 7-2	Infant faeces	MRS	5.00	ND	ND	ND		ND	(Ham et al., 2002)
Lactobacillus plantarum PL62 (KACC 91104)	Infant faeces	10 % RSM	0.1 % (vol/vol)	0.0268	0.0064	ND		0.0332	(Lee et al., 2007)
Lactobacillus reuteri DSM 20016	Adult intestine	M2	0.05	ND	ND	ND	28 % HFA		(Devillard et al., 2007)
Lactobacillus rhamnosus PL60 (KACC 91105)	Infant faeces			2.836*	1.6025*	ND		4.4385*	(Lee *et al*., 2006)
Roseburia faecis M6/1	Human faeces	M2	0.05	ND	ND	ND	86 % HFA		(Devillard et al., 2007)
Roseburia faecis M88/1	Human faeces	M2	0.05	ND	ND	ND	76 % HFA		(Devillard et al., 2007)
Roseburia faecis M72/1	Human faeces	M2	0.05	ND	ND	ND	88 % HFA		(Devillard et al., 2007)
Roseburia hominis A2-183	Human faeces	M2	0.05	ND	ND	ND	100 % VA		(Devillard et al., 2007)
Roseburia hominis A2-181	Human faeces	M2	0.05	ND	ND	ND	100 % VA		(Devillard et al., 2007)
Roseburia intestinalis L1-82	Human faeces	M2	0.05	ND	ND	ND	84 % HFA		(Devillard et al., 2007)
Roseburia intestinalis L1-952	Human faeces	M2	0.05	ND	ND	ND	85 % HFA		(Devillard et al., 2007)
Roseburia inulinivorans A2-194	Human faeces	M2	0.05	ND	ND	ND	100 % VA		(Devillard et al., 2007)
Roseburia inulinivorans L1-83	Human faeces	M2	0.05	ND	ND	ND	100 % VA		(Devillard et al., 2007)

ND: Not Defined; HFA: Hydroxy Fatty Acid (10-OH-18:1); VA: Vaccenic Acid (trans-11-18:1); *CLA produced from crude enzyme prepared from cell lysate, rather than viable cells

HFA: Hydroxy Fatty Acid (10-OH-18:1)

VA: Vaccenic Acid (*trans*-11-18:1)

1496 *CLA produced from crude enzyme prepared from cell lysate, rather than viable cells