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MINIREVIEW

Bacteriocin Production: a Probiotic Trait?

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Bacteriocins are an abundant and diverse group of ribosomally synthesized antimicrobial peptides produced by bacteria and archaea. Traditionally, bacteriocin production has been considered an important trait in the selection of probiotic strains, but until recently, few studies have definitively demonstrated the impact of bacteriocin production on the ability of a strain to compete within complex microbial communities and/or positively influence the health of the host. Although research in this area is still in its infancy, there is intriguing evidence to suggest that bacteriocins may function in a number of ways within the gastrointestinal tract. Bacteriocins may facilitate the introduction of a producer into an established niche, directly inhibit the invasion of competing strains or pathogens, or modulate the composition of the microbiota and influence the host immune system. Here we review the role of bacteriocin production in complex microbial communities and their potential to enhance human health.

Probiotics are defined as "live microorganisms, which when consumed in adequate amounts, confer a health benefit on the host" (45). They are believed to enhance or maintain the ratio of beneficial to undesirable components in the human gastrointestinal (GI) microbiota (44). The majority of probiotics in use today include species of lactic acid bacteria (LAB), including lactobacilli, as well as bifidobacteria, nonpathogenic *Escherichia coli*, bacilli, and yeasts such as *Saccharomyces boulardii*. The scientific and clinical evidence in support of the therapeutic potential of probiotic bacteria in human health, and most notably with respect to GI health, has been increasing steadily (7). It is not surprising, then, that there is an ever greater interest in these potential biotherapeutic agents and the mechanisms by which they elicit their beneficial effects.

Several mechanisms of probiotic action have been described, the most common relating to their abilities to strengthen the intestinal barrier, to modulate the host immune system, and to produce antimicrobial substances (8). Indeed, the production of antimicrobials is often regarded *a priori* as an important trait in the context of bacterial fitness but also in terms of probiotic efficacy. Several probiotic bacteria produce a variety of antimicrobial compounds (e.g., short-chain fatty acids, hydrogen peroxide, nitric oxide, bacteriocins) that may enhance their ability to compete against other GI microbes and which could potentially inhibit pathogenic (disease-causing) bacteria (1, 6). Traditionally, bacteriocin production has been an important criterion in the selection of a probiotic strain, albeit that few studies have definitively demonstrated the impact of bacteriocin production on the ability of a strain to compete within the GI tract and/or positively influence the health of the host (9).

Bacteriocins are bacterially produced peptides that are active against other bacteria and against which the producer has a specific immunity mechanism (10, 30). They are produced by all major lineages of bacteria and archaea and constitute a heterogeneous group of peptides with respect to size, structure, mode of action, antimicrobial potency, immunity mechanisms and target cell receptors (21). Here we review the literature with respect to the role of bacteriocin production within complex microbial niches, and in particular in the GI tract, in terms of their impact on the prevalence of the producing strain, as well as on microbial diversity and the survival of pathogens. We conclude with suggestions for future work and the possible ways in which bacteriocins could potentially be applied to enhance health.

BACTERIOCIN FUNCTION: AN ECOLOGICAL PERSPECTIVE

It has been estimated that the vast majority of all bacteria and archaea produce at least one bacteriocin (29). The apparent ubiquity of this trait implies that bacteriocins play an important role, despite the associated energy costs imposed by their production (23). However, their exact ecological function has been the subject of much debate. It is possible that bacteriocins could contribute to probiotic functionality in a number of ways (Fig. 1). Bacteriocins may function as colonizing peptides, facilitating the introduction and/or dominance of a producer into an already occupied niche (48). Alternatively, bacteriocins may act as antimicrobial or killing peptides, directly inhibiting competing strains or pathogens (38). Lastly, bacteriocins may function as signaling peptides, either signaling other bacteria through quorum sensing and bacterial cross talk within microbial communities or signaling cells of the host immune system (12, 17, 24, 38, 40).

Bacteriocins as colonizing peptides. The high cell density typically associated with the GI tract may result in close cell-cell contact between members of the same or different species, promoting both cooperative and antagonistic microbial interactions (33). The production of antimicrobials may provide a mechanism by which producers can gain a competitive advantage over neighboring sensitive strains within this environment. In support of this hypothesis, Gillor et al. (23) demonstrated that *E. coli* producing the bacteriocin colicin was able to persist in the large intestine of streptomycin-treated mice for an extended period of time relative to their non-colicin-producing counterparts. Over time, the density of the noncolicinogenic strains decreased from 10^6 to 10^2 CFU/g feces, while that of colicin-producing strains remained significantly higher (23). In a similar study, Hillman et al. (25) noted a strong correlation between the ability of a *Streptococcus mutans*

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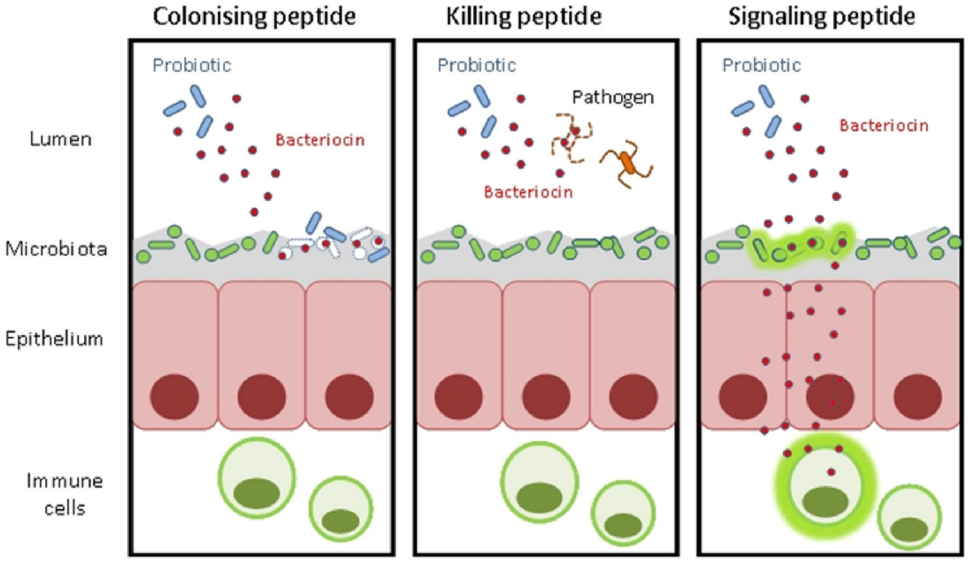

FIG 1 Mechanisms via which bacteriocin production could contribute to probiotic functionality. Bacteriocins may act as colonizing peptides, facilitating the competition of a probiotic with the resident microbiota (23); they may function as killing peptides, directly eliminating pathogens (9); or they may serve as signaling peptides, signaling other bacteria or the immune system (32, 40, 56).

strain to colonize the oral cavity and the production of the bacteriocin mutacin 1140. One mutacin-producing strain was shown to be stably maintained in human subjects, persisting for 14 years following a single administration (25–27). Although direct competition studies using isogenic non-bacteriocin-producing mutants were not performed in this case, the fact that no other strains of mutans streptococci were observed in saliva and plaque samples is indicative of the competitive dominance of this strain. It has also been established that the production of BlpMN bacteriocins by the *S. pneumoniae* type 6A strain contributes to the ability of this strain to colonize and compete in the mouse nasopharynx (14). In this study, a non-BlpMN-producing mutant failed to compete with its bacteriocin-producing parent strain when the strains were administered in equivalent numbers. Cocolonization with a non-isogenic, non-BlpMN-producing strain, *S. pneumoniae* TIGR4, yielded similar results, thereby confirming that the production of the BlpMN bacteriocins contributes to the competitiveness of the associated strain within the complex microbial environment of the nasopharynx (14).

As one might expect, a number of GI-related studies have also been performed. A five-strain probiotic mixture composed of *Lactobacillus murinus* DPC6002 and DPC6003, *Lactobacullus pentosus* DPC6004, *Lactobacillus salivarius* DPC6005, and *Pediococcus pentosaceus* DPC6006 has been shown to improve the clinical and microbiological outcome of *Salmonella* infection in pigs (5). It was subsequently established that the only bacteriocin producer, *L. salivarius* DPC6005, dominated over strains coadministered with it in both the ileum digesta and mucosa of weaned pigs (57). Although an isogenic nonproducing mutant of *L. salivarius* DPC6005 was not employed, the authors suggested that the superior ileal survival of this strain could be attributed to bacteriocin production, indicating that this antimicrobial confers a competitive advantage over the other coadministered probiotics (57).

Bacteriocin producers may also modulate insensitive species within the GI tract. A recent study demonstrated that the bacteriocin-producing strain *Enterococcus faecium* KH24 significantly affected the fecal microbiota of mice (3). In this study, mice received 10^8 CFU/day of bacteriocinogenic *E. faecium* KH24 (Bac^+) and a nonbacteriocinogenic variant (Bac^-) for a period of 12 days. It was established that *Lactobacillus* populations were significantly greater in mice fed bacteriocinogenic *E. faecium* than those in the nonproducer. The authors concluded that *E. faecium* KH24 could be exploited as a probiotic and hypothesized that bacteriocinogenic enterococci may help to control the indigenous microbiota in a beneficial manner.

Evidence that bacteriocin production can contribute to microbial survival in the human GI tract has also been reported. One such study stemmed from functional genomic analyses of the intestinal isolate *Bifidobacterium longum* subsp. *longum* DJO10A which indicated that bacteriocin production might be an important adaptation for GI survival. Competitive growth rate experiments in a model fecal environment revealed that *B. longum* DJO10A had a significantly greater ability to compete against the intestinal isolates *Clostridium difficile* DJOcd1 and *E. coli* DJOec1 than did the nonproducing isogenic variant *B. longum* DJO10-JH1 (36). Although additional *in vivo* studies are necessary, these results provide a further indication that bacteriocin production is an important trait with regard to microbial competition in the human intestine.

Bacteriocins as killing peptides. The ability of bacteriocin-producing microorganisms to inhibit pathogens *in vitro* has been well documented (23, 35, 52). However, studies involving direct correlations between *in vitro* efficacy and *in vivo* protection are somewhat scarce. For instance, it has recently been shown that lactococci producing the broad-spectrum antimicrobial peptide lacticin 3147 fail to confer protection against *Listeria monocytogenes* infection in a mouse model, despite the efficacy of the bacteriocin against this pathogen *in vitro* (18, 50). However, it should be noted that, in this case, the producing strain is not a GI-associated microorganism. Likewise, it has also been revealed that although pediocin PA-1 production by *Pediococcus acidilactici* UL5 reduces *L. monocytogenes* viability by approximately 3 logs

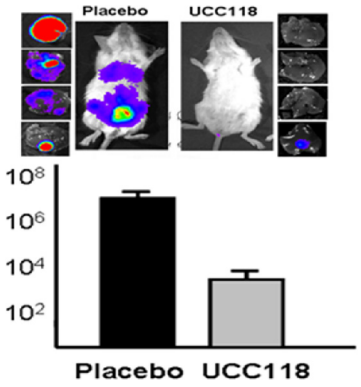

FIG 2 Bacteriocin-mediated anti-infective activity of *L. salivarius* UCC118. Survival of luminescent *L. monocytogenes* EGDe in the livers of mice administered a placebo (no bacterium; black bar) or 10^9 CFU *L. salivarius* UCC118 (gray bar) for 6 days prior to *Listeria* infection.

in vitro, a corresponding effect was not observed *in vivo* (13). In this instance, the intragastric administration of 10^{10} CFU/animal of *P. acidilactici* UL5 failed to provide protection against *L. monocytogenes* infection in mice, despite the fact that the administration of purified pediocin PA-1 to mice resulted in a ca. 2-log reduction of fecal listerial counts. Indeed, an increase in *L. monocytogenes* invasion was observed in the intestines, livers, and spleens of *P. acidilactici*-treated mice compared to those of control mice. These findings are in agreement with an earlier study by Bernbom et al. (2) that investigated the ability of the pediocin AcH producer *Lactobacillus plantarum* DDEN 11007 to prevent *L. monocytogenes* EP2 infection in germfree rats. In this case, the introduction of *L. plantarum* DDEN 1007 prior to *L. monocytogenes* inoculation resulted in a subsequent relative increase in *L. monocytogenes* numbers in the livers and spleens of gnotobiotic animals over those of control animals. The authors of both studies attributed the increase in pathogen numbers to a lowering of the intestinal pH, suggesting that the production of lactic acid by *Pediococcus* spp. and *Lactobacillus* spp. induced virulence gene production in the pathogen. This theory remains quite speculative, although it has been noted that acid-treated *L. monocytogenes* has been shown to be more invasive than its non-acid-adapted counterparts (43). There are some studies which demonstrated the ability of bacteriocin producers to inhibit pathogens in the GI tract. Most notably, Corr et al. (9) found that *L. salivarius* UCC118 provides protection against *L. monocytogenes* infection in mice (Fig. 2). The inhibition of the pathogen was shown to be the direct result of the production of the two-peptide bacteriocin Abp118, as it was demonstrated that a non-bacteriocin-producing isogenic derivative failed to protect mice from infection. Similarly, the bacteriocin-producing human isolates *P. acidilactici* MM33 and *L. lactis* MM19 were shown to reduce vancomycin-resistant enterococci (VRE) populations *in vivo* (41). *P. acidilactici* MM33 produces the bacteriocin pediocin PA-1/AcH, while *L. lactis* MM19 produces the bacteriocin nisin Z. In these studies, mice received daily intragastric doses of *L. lactis* MM19, *P. acidilactici* MM33, or *P. acidilactici* MM33A (a non-pediocin-producing mutant) for a total of 16 days. Within the first 6 days of administration, levels of VRE in the groups of animals administered the bacteriocin-producing strains were below the detection threshold whereas VRE levels in mice fed the non-pediocin-producing strain were similar to those of control mice.

As bacteriocins produced by Gram-positive bacteria usually possess little or no activity against Gram-negative pathogens, Gram-negative bacteriocin producers seem to have greater potential with respect to controlling such pathogens (28). One strain of particular note is *E. coli* H22. H22 produces several bacteriocins, including microcin C7 and colicins 1b and E1, and inhibits a number of pathogenic enterobacteria *in vitro*, including *Klebsiella pneumoniae* and *Salmonella* spp. (11). Studies involving a germfree mouse model demonstrated that *E. coli* H22 reduced fecal populations of *Shigella flexneri* 4 to undetectable levels within 6 days of administration. Additionally, *in vitro* inhibition assays confirmed that *E. coli* H22 lacked activity against members of the normal human microbiota such as members of the phylum "*Bacteroidetes*" and *Bifidobacterium* species. As a result, the authors concluded that *E. coli* H22 is a promising probiotic with respect to preventing intestinal infections in humans and livestock (11). Similarly, a mixture of eight colicin E7-producing *E. coli* strains was recently found to exhibit anti-*E. coli* O157:H7 activity in cattle (51). A daily dose of a mixture of colicinogenic strains to calves (10^8 CFU/g of feed) resulted in a 2-log reduction in fecal shedding of *E. coli* O157:H7 compared to that of a control group. Furthermore, tissue analysis revealed that the colicin E7-producing *E. coli* strains significantly reduced the extent of pathogenic colonization. Although colicin E7 production was not directly implicated, the authors suggested that the inclusion of colicin E7-producing bacteria in feed may be an effective means of controlling *E. coli* O157:H7 (51). Likewise, Stern and colleagues (53) investigated the ability of bacteriocin-producing *L. salivarius* or *Paenibacillus polymyxa* to perturb *Campylobacter jejuni* colonization in broiler chicks. Despite successfully inhibiting the pathogen *in vitro*, treatments with the bacteriocin-producing strains did not effectively reduce *C. jejuni* levels in chickens. However, complete elimination of the pathogen was achieved when chickens were administered 250 mg of the encapsulated bacteriocins. Therefore, the authors hypothesized that the bacteriocins in question may not be produced in sufficient quantities *in vivo* to elicit a positive effect in the intestinal environment (53).

Bacteriocins as signaling peptides. Bacterial communication via extracellular diffusible signaling molecules (quorum sensing) allows populations of bacteria to synchronize group behavior and can facilitate coordinated multicellular functionality (22). In Gram-negative bacteria, (*N*-acyl) homoserine lactone typically serves as a signal molecule, while in Gram-positive bacteria, peptides, including some bacteriocins, frequently serve as signaling agents (54). Thus, it has been suggested that at least some bacteriocins have a dual role, acting as inhibitors at high concentrations and as signaling compounds at lower concentrations (19). Therefore, bacteriocins produced by probiotic strains may also act as quorum-sensing molecules or autoinducing peptides in the intestinal environment.

In general, peptide-based quorum sensing in Gram-positive bacteria involves a two-component regulatory signal transduction system composed of a histidine protein kinase (HPK) located on the cell membrane and an intracellularly located response regulator (RR) (32). These are responsible for sensing of the signaling peptide and inducing an appropriate cellular response. In the case of autoinducing systems, it is thought that the signaling peptide is produced at a low level during normal growth but when present above a certain concentration threshold, the autoinducing peptide binds to the N-terminal domain of the HPK, resulting in auto-

phosphorylation and activation. The HPK then transfers a phosphoryl group to the RR, which ultimately provokes a response, often at the level of transcription. The autoinducing peptide normally has no function other than its signaling role, but it is known that some autoinducing peptides also function as antimicrobials. A classic example of this dual functionality relates to the bacteriocin nisin. Nisin acts both as a killing molecule and as a signal molecule, inducing its own biosynthesis in a cell density-dependent manner (32). This phenomenon has also been associated with other bacteriocins, including subtilin, produced by some *Bacillus subtilis* strains, and salivaricin Abp118 and plantaricin A, produced by *L. salivarius* UCC118 and *L. plantarum* C11, respectively (20, 24, 31).

Recent evidence has suggested that, in addition to regulating their own synthesis, bacteriocins may also engage in interspecies communication or bacterial cross talk. Cocultivation of the plantaricin A producer *L. plantarum* DC400 with several species of sourdough LAB revealed that bacteriocin production was induced in DC400 to various extents, depending on the microbial partner (15). Production of plantaricin A was induced most strongly by *L. sanfranciscensis* DPPMA174, a plantaricin A-sensitive strain. The presence of the plantaricin A peptide, in turn, induced a response in *L. sanfranciscensis* leading to the overexpression of proteins involved in the stress response, as well as amino acid and energy metabolism. It thus seems that plantaricin A production serves as a means via which the bacteria communicate, shaping the phenotypic traits of the starter LAB population and their subsequent contribution to fermentation (16). This phenomenon has also been associated with other bacteriocin systems, including plantaricin NC8 and lactacin B, produced by *L. plantarum* NC9 and *L. acidophilus* La-5, respectively (39, 55). Since sourdough fermentation represents a complex ecosystem in which different species of LAB interact, it is conceivable that similar interactions also occur between closely related bacteria within the GI tract.

Evidence has recently emerged regarding the impact of bacteriocins on the immune system. More specifically, studies by Meijerink et al. (40) and van Hemert et al. (56) identified a number of *L. plantarum* genes that may influence the immune response of dendritic and peripheral blood mononuclear cells, respectively. Deletion of these genes from the *L. plantarum* WCFSI genome resulted in substantial changes in cytokine profiles. Notably, the majority of the candidate genes identified were involved in bacteriocin production and/or secretion. The authors of both studies speculated that the bacteriocin produced by *L. plantarum* may modulate immune responses in a manner similar to that of human antimicrobial peptides secreted in the GI tract. It is important to note that previous results demonstrate that *L. plantarum* WCFS1 plantaricin genes were indeed induced in the GI tracts of mice, and thus, plantaricin production does indeed occur in the intestine (4, 56). Future investigations with different bacteriocinogenic strains are necessary to determine if the impact that this plantaricin has on immune functionality is simply an isolated case or a more common feature of bacteriocin peptides.

APPLICATIONS OF BACTERIOCINS IN HUMAN HEALTH AND FUTURE DIRECTIONS

Bacteriocins in human health. In addition to bacteriocinogenic probiotics, purified or partially purified bacteriocins also hold great promise with respect to the treatment of target pathogenic bacteria and may ultimately be employed as pharmabiotics and/or novel alternatives to existing antibiotics (22). Recent studies using a mouse model of *Salmonella* Newport infection have shown that treatment with microcin J25 resulted in a 2- to 3-log reduction in viable numbers of the pathogen in both the spleen and the liver compared to those of control mice (37). Mersacidin, produced by *Bacillus* sp. strain HIL Y85, was also active against methicillin-resistant *Staphylococcus aureus* (MRSA) in a hydrocortisone-treated mouse rhinitis model (34). This bacteriocin was able to completely eradicate MRSA from the nasal epithelium of the mouse, independent of the colonization time and number of inoculations. It has also been shown that a single dose of mutacin B-Ny266, produced by *Streptococcus mutans*, was 100% protective when administered intraperitoneally to mice previously infected with methicillin-susceptible *S. aureus* Smith (42). Finally, it is noteworthy that both lacticin 3147 and thuricin CD, produced by *Lactococcus lactis* DPC3147 and *Bacillus thuringiensis* DPC6431, respectively, exhibited inhibitory activity against *C. difficile* in an *ex vivo* model of the colon (46, 47). Thuricin CD is of particular interest, as this two-peptide bacteriocin was shown to be as effective as conventional antibiotics (e.g., metronidazole and vancomycin) in an *ex vivo* model of *C. difficile* infection. However, in contrast to conventional antibiotics, thuricin CD did not result in major alterations of GI populations, a contributing factor in recurrent *C. difficile* infection (49). Although further studies are required to fully determine the value of bacteriocins in clinical practice, these results highlight their potential in human health.

Future directions. Although extensive progress has been made with respect to our understanding of bacteriocin structure/function, regulation, and immunity, additional research is required to gain a full understanding of the factors which control bacteriocin production in the GI tract. For instance, a standardized method of assessing bacteriocin activity *in vivo* would be useful since variations in animal models, effective dosage, and quantification methods have made the direct comparison of data from different laboratories problematic. Future investigations in this regard may help to resolve the variability and inconsistencies historically associated with bacteriocin production in the mammalian host. Additionally, as functionality is likely to change, depending on the individual probiotic, the further use of *in vivo* models directly comparing bacteriocin-producing and -nonproducing isogenic strains will be important. This information may ultimately lead to human trials where the health implications of bacteriocin producers may be accurately assessed.

CONCLUSIONS

Collectively, the results presented in this review highlight the complexity associated with bacteriocin production in the mammalian GI tract. It is likely that mitigating factors including strain survival, the specific activity of the bacteriocin, the dosing regimen, the animal model, and the target organism all influence the ability of a bacteriocin to function *in vivo*. Additionally, bacteriocins actively produced *in vitro* may not necessarily be produced in sufficiently high quantities, or at all, within the GI tract (28). A thorough investigation of the factors influencing probiotic survival, bacteriocin production, and bacteriocin activity is required to bring about a better correlation between *in vitro* inhibition and *in vivo* results. Ultimately, a number of unanswered questions still remain regarding the efficacy of bacteriocin production *in vivo*. Further investigations will further unravel the role of bacteriocin-producing strains in the GI tract, possibly leading to the development of superior

probiotics with enhanced bacteriocin functionality. This information will ultimately lead to a greater understanding of bacteriocinogenic probiotics and their potential applications in human and veterinary health.

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