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Swapping the roles of bacteriocins and bacteriophages in food biotechnology

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To move towards a safer and more sustainable food production chain, natural antimicrobials have been traditionally applied to enhance safety. This is well exemplified by the use of bacteriocins, antimicrobial peptides synthesized by bacteria, as food biopreservatives. However, as knowledge on bacteriocin biology develops, novel functions beyond food preservation emerge and a shift towards health applications is positioning bacteriocins as anti-infectives and modulators of gut microbiota. On the other hand, bacteriophages, viruses infecting bacteria, have been long regarded as a threat for dairy fermentations. However, they may also become allies when specific phages infecting pathogenic or spoilage bacteria are intentionally used. This review summarizes the 'dark side' and rather unexplored roles of bacteriocins and phages that, certainly, have much to learn from each other.

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Introduction

Bacteriocins and bacteriophages (or phages) share a common biological outcome: both are endowed with potent and targeted antibacterial activity. Bacteriocins encompass a large structurally and functionally diverse group of gene-encoded antimicrobial peptides and proteins synthesized by bacteria. Bacteriocins from Gram positive bacteria commonly disrupt cell envelope functions by membrane permeabilization or inhibition of cell wall synthesis [1], while colicins and colicin-like bacteriocins synthesized by Gram negative bacteria mostly target intracellular processes [2]. Phages are viruses that specifically infect bacteria. When following a lytic cycle, phages replicate inside the cell and their progeny is released through lysis of the bacterial host. Thereby, phages have been commonly seen as a major threat in food fermentations driven by starter bacteria [3].

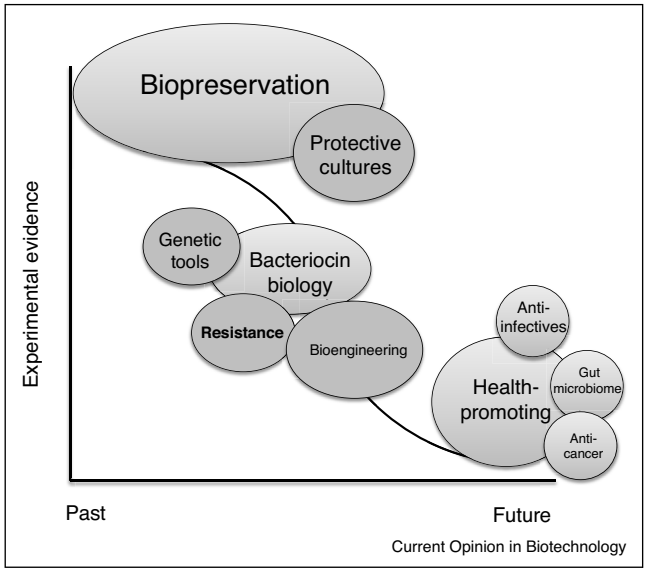
Bacteriocins and phages can be harnessed as promising biological tools to reduce the impact of food production on the environment, to enhance the role of the gut microbiota in human health and to mitigate the emergence and dissemination of multi-drug resistant (MDR) bacteria, whose origin is indisputably linked to agro-food settings as well [4,5••]. Besides their traditional role in food biopreservation to extent the shelf-life of food and reduce the use of chemical additives, bacteriocin research is witnessing a shift towards health-promoting activities. In turn, phages are gaining momentum as novel antimicrobials to reduce food-borne outbreaks as well as to stop the increase and spread of MDR zoonotic bacteria throughout the food chain. Recent examples, most pertaining to food biotechnology, are provided in this review.

Bacteriocins: new sources, new targets, other visions

In food biotechnology, bacteriocin research has mostly focused on bacteriocins produced by lactic acid bacteria and their applications as food biopreservatives against food-borne pathogens and food spoilage bacteria. These efforts have been justified by the relevance of this group of bacteria as food starter cultures, their long history of safe use in food and their intrinsic compatibility with food processing. Consequently, as shown in Figure 1, food biopreservation is by far the most extended application of bacteriocins, sustained by solid experimental evidences, and described in several comprehensive reviews on this topic [6,7]. More recently, there is a general trend towards research on bacteriocin applications related to their health-promoting activities, showcased by López-Cuellar *et al.* [8•] in their analysis of the current literature on bacteriocins and patent applications in the last decade. This trend is supported by the increasing number of reports on medical applications of bacteriocins expanding from their use as anti-infectives to putative anticancer drugs [9,10]. Others explore possible synergies between bacteriocins and clinical antibiotics [11]. New bacteriocin targets beyond bacteria are also being scrutinized with unforeseen results: the broad-spectrum enterocin AS-48 is able to kill the parasitic protozoan *Trypanosoma brucei* [12•], while EntV efficiently reduces *Candida albicans* virulence by inhibition of hyphal formation [13].

Moreover, the use of bacteriocins or bacteriocin-producing probiotics to modulate the gut microbiota is becoming

Figure 1



Bacteriocin innovations and supporting scientific evidence.

an exciting field in bacteriocin research [14]. Several diseases have been associated to an altered gut microbial composition and specific taxons have been correlated with human health and disease [15]. Bacteriocins, either provided through functional/fortified foods or by bacteriocinogenic probiotic bacteria, could potentially be harnessed to induce desirable shifts in the gut microbial populations. Although still under investigation, proof-of-concept studies have demonstrated the establishment of bacteriocin producers in the gut [16]. Umu *et al.* [17] showed that favorable changes in the gut microbiota may be induced in mice fed with bacteriocin producers. Interesting, population shifts depend on the inhibitory spectrum and physicochemical properties of the bacteriocins they produced.

The focus on food biopreservation has brought up excellent candidates such as the broad-spectrum lantibiotics nisin and lacticin3147, the anti-listeria pediocins and related bacteriocins and the circular bacteriocin AS-48, but it has limited the hunt for new baceriocins with distinct mode of action or active against other targets beyond harmful bacteria. Currently, this gap is filled in by less biased discovery tools through (meta)genome mining. Bioinformatics strategies have been developed for metadata integration to identify and prioritize antimicrobial biosynthetic gene clusters for further studies [18••]. Such systematic approach, for example, led to the discovery of lactocillin, a potent thiopeptide against Gram positive vaginal pathogens and revealed the wide distribution of this antibiotic family in genomes and metagenomes of the human microbiota [19]. Nevertheless, as gene-encoded entities, bacteriocins are amenable to bioengineering strategies. In this way, new variants have been created with enhanced antimicrobial activity, better physicochemical properties and extended inhibitory spectrum. In a latest bioengineering approach, recombinant nisin production and orthogonal translation in *E. coli* has been satisfactorily implemented to incorporate non-canonical amino acids into nisin, and variants with enhanced activity were recovered [20]. So far, yields of these 'new-to-nature' bacteriocins are low but alternative factories may be envisaged. Functional salmocins (*Salmonella* colicins) have been efficiently produced in green plants with up to 1.2–1.7 g product/kg of fresh leaf biomass [21].

There are also new visions pertaining to bacteriocin ecology in food. Bacteriocin production to kill or displace putative competitors in a specific environment is often regarded as a competitive advantage. However, as our knowledge on bacteriocin biology moves forward, other roles in intra-species and inter-species signaling, kin recognition, in promoting natural genetic transformation or even in bacterial virulence have been recently suggested for some bacteriocins [22]. While these functions have been mostly studied in pathogenic bacteria in the context of infection, the role of bacteriocins in signaling and/or interspecies competition within food-relevant bacterial communities is less understood and deserves further attention. One should keep in mind that a fermented product must be safe but also appealing and tasteful. Therefore, caution must be exercised when selecting bacteriocin producers as starters or protective cultures. Perin *et al.* [23] and Portilla-Vázquez *et al.* [24] have reported changes in the evolution of microbial consortia in raw milk cheese and in the production of metabolites, respectively, when bacteriocin producers are intentionally introduced. All together may lead to changes, desirable or not, in the organoleptic properties of the fermented product.

Bacteriocin resistance: a nuisance or an opportunity?

Resistance to bacteriocins can be readily selected under laboratory conditions but we lack sufficient surveillance to anticipate if bacteriocin resistance may become a burden for food applications or, even more worrying, if cross-resistance to clinical antibiotics may arise. So far, cross-resistance to clinical antibiotics is rare and most of the bacteriocin resistance mechanisms (including self-immunity) characterized to date seem to be rather specific, providing protection to closely related bacteriocins (see Draper *et al.* [25] for a recent review on lantibiotic resistance mechanisms). Nevertheless, exposure to bacteriocins does transiently induce multidrug efflux pumps and/or select for mutations leading to an altered cell surface which may impair antibiotic activity. Moreover, production of the epidermin-like bacteriocin Bsa by CA-MRSA has been shown to drive strain diversification and