



# Functions and emerging applications of bacteriocins

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Bacteriocins, defined as ribosomally synthesized antimicrobial peptides, have traditionally been used as food preservatives, either added or produced by starter cultures during fermentation. In-depth studies of a select few bacteriocins opened exiting new research fields and broadened the application of these antimicrobial peptides. The possibility of developing bacteriocins into next generation antibiotics, accompanied with the rapid development in genetics and nanotechnology, paves the way to even more fascinating applications such as novel carrier molecules (delivery systems) and the treatment of cancer. Also, some bacteriocins are found to regulate quorum sensing which suggests novel applications for this group of substances. While there is some interesting translational research on bacteriocins from Gram-negative bacteria, the majority of application-oriented studies are focused on bacteriocins from Gram-positive microorganisms, mostly lactic acid bacteria. The applications of bacteriocins are expanding from food to human health.

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## Introduction

All living organisms produce antimicrobial proteins (AMPs), many of which are referred to as antimicrobial peptides because of their relatively small size. Within the

eukaryotic immune system, AMPs are believed to serve as first line of defense in protecting the host against hostile intruders [1]. Bacteria produce two types of AMPs: those that are ribosomally synthesized (also known as bacteriocins), and non-ribosomally synthesized AMPs, with no structural genes coding for these AMPs, e.g. ε-poly-L-lysine [2].

## Definitions: current classifications can be confusing

Some investigators prefer separating ‘true’ bacteriocins such as colicins, first discovered by Gratia in 1925 [3], and colicin-like bacteriocins, from so-called bacteriocin-like inhibitory substances (BLIS) [4]. There is a continuing interest in bacteriocins from lactic acid bacteria (LAB), and some authors suggest a stand-alone classification for these AMPs [5]. Moreover, the broad variety of bacteriocins, their origins, complexities of production, and mechanisms of actions, justify the need for stand-alone classifications for several other groups of bacteriocins. It is appropriate to conclude that bacteriocins in general should be defined as ribosomally-produced multi-functional substances of a proteinaceous nature, with pronounced antimicrobial activity at certain concentrations. In addition, there is no need to define bacteriocins as having a net positive charge and amphipathic nature, since there are anionic bacteriocins such as subtilosin A reported in the literature [6].

## Bacteriocins: applications are determined by the functions

### ‘Primary’ and ‘secondary’ functions: signaling and protection of an ecological niche

Many, if not most of the presently known bacteriocins were first discovered and studied as antimicrobials. For more information, readers should be referred to various sources such as Fairweather’s book reviewing the involvement of bacteriocins in the regulation of various processes within microbial communities [7], and to more recent reviews (Hegarty *et al.* [8]). Synthesis of the bacteriocin nisin in *Lactococcus lactis* is elegantly controlled by a cascade of events in which nisin itself serves as a pheromone-like primary ‘trigger’ for its own production [9]. In streptococci, a signaling-involved membrane protein (ComM) regulates the production of a bacteriocin transporter, and triggers the cell’s immunity towards lytic enzymes [10]. Moreover, in *Streptococcus mutans*, an unmodified intracellularly-located bacteriocin, mutacin V, may work as a lytic agent against the producer cell when in the presence of a high concentration of a

competence-stimulating peptide. This may act as an evolutionary factor driving the exchange of genetic material with non-lysed competent cells [11]. There are also reports on bacteriocins inhibiting quorum sensing in various microorganisms at sub-MIC concentrations [12]. From an evolutionary point of view, it is logical for microorganisms to utilize quorum sensing inhibition as a means of defense, rather than killing cells that invade their ecological niche. Instead of producing large amounts of bacteriocins, the bacteriocin-producers prevent intruders from settling down by arresting biofilm formation via inhibition of quorum sensing with low-level production of bacteriocins [13]. In summary, there are many examples of bacteriocins exhibiting a variety of regulatory functions, including their own production [14]. Undoubtedly, they also play an essential role in kin recognition [15\*].

### Natural levels of production: enough for killing, or just to repel?

Data on the production and concentration of bacteriocins in the producer's usual ecological environment is scarce. Nevertheless, studies mimicking the natural environment will shed light on our assumptions of the primary function of bacteriocins. When analyzing microbial inactivation curves as a reflection of the bacterial response to the environmental stressor nisin at sub-MIC concentrations, a step-like response by the foodborne pathogen *Listeria monocytogenes* was observed [16]. While the aim of this study was to evaluate the pathogen's survival in the food environment with gradually decreasing concentrations of nisin, this can also be seen as an extrapolation of the natural condition where intruder cells are facing relatively low concentrations of the bacteriocin diffused throughout the environment. Based on the available literature, we speculate that the primary functions of bacteriocins are signaling and repelling rather than killing. Qualitatively different behavior is observed at concentrations far exceeding those in the microbial 'free-range' life.

When used in concentrations higher than in the natural environment of the producer microorganisms, some bacteriocins reveal a variety of additional functions, of which their antimicrobial activity is the most studied [17]. At MBC (minimal bactericidal concentration), they often act as membrane perturbors or as pore-forming substances [18]. Some bacteriocins can kill sensitive cells by interfering with the cell division process. Lipid II serves as a recognition 'anchor' for various AMPs (including nisin). However, some bacteriocins have the ability to segregate lipid II, thus preventing the targeted cell from normal cycling [19]. Interference with cell division, as well as other biological functions, may occur at substantially different concentrations for different bacteriocins, acting against different target microorganisms. For instance, micromolar concentrations of salivaricin B (a bacteriocin

first found in *Streptococcus salivarius*) are required to interfere with septum formation in *Micrococcus luteus* and *Streptococcus pyogenes*, as opposed to nanomolar concentrations of nisin A required for the same function [20]. Interference with bacterial septum formation may also result in bacteriostatic action for some bacteriocins [21]. Last but not least, there are numerous bacteriocins reported to cause lysis of sensitive cells [22].

### Bacteriocins' functions expanded: human health applications

Some bacteriocins, such as subtilisin A from *Bacillus subtilis*, were reported as having anti-viral [23] and spermicidal [24] activities. Subtilisin's antiviral activity is likely due to interference with the late stages of virus replication. Concentrations of subtilisin A that immobilize and de-activate human spermatozoa are inactive against lactobacilli isolated from the human gastrointestinal tract. In contrast, spermicidal concentrations of nisin were shown to inhibit LAB [25]. Moreover, several attempts have been undertaken to systematize bacteriocins' function in relation to their structure, and some systemic approaches have been reported to improve the functioning of a number of bacteriocins [26\*]. Taking a broad view of this and other critical reviews, we were able to map out an 'ecology of bacteriocins' based on presently available information (Figure 1).

While the primary application of bacteriocins has always been in food preservation [26\*], antimicrobial resistance to conventional antibiotics presents new opportunities for the exploration of bacteriocins' application in a variety of healthcare products where undesired and potentially resistant microorganisms must be controlled [27\*,28]. The National Institute of Health (NIH) recently encouraged a complementary approach in searching for novel drug formulations, where the activity of conventional antimicrobials can be enhanced when combined with novel and, often naturally derived, antimicrobials [29,30]. A multipronged approach utilizing synergistically acting antimicrobials with different targets in controlled bacteria has been studied for many years. Different bacteriocins were reported as acting synergistically with various food-grade substances [31] and with bacteriophages [32], although the latter study provided no FICs (fractional inhibitory concentrations) or isobolograms to validate the observed synergy. Potential areas of interest include oral and skin care, and respiratory, gastrointestinal, urogenital tract and other infections. In addition to anti-viral activity, bacteriocins could potentially be used in the post-surgical control of infectious bacteria [33]. Nisin, being the oldest discovered and most studied bacteriocin, is of particular interest in a variety of human health related applications due to its ability to control many Gram-positive pathogens and because of its enhanced range of action, including Gram-negative microorganisms, when used in combination with various

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