Overview of Colicins and Microcins

Subjects: Microbiology

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The family *Enterobacteriaceae* is a large, heterogeneous group of Gram-negative bacteria, which includes strains that naturally inhabit the gastrointestinal tract (GIT) of animals and humans. Being considered normal commensal members of the GIT microbiota, these microbes can also live and multiply in food environments. Additionally, *Enterobacteriaceae* are acknowledged as indicators of food production hygiene, preservation, and storage, often being used as indicators of food quality and safety. Additionally, *Salmonella* spp., *Yersinia enterocolitica*, pathogenic *Escherichia coli*, including *Escherichia coli* O157:H7, and *Shigella* spp., among others, are important foodborne pathogens. Moreover, some members of this group, namely *Citrobacter*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Kluyvera*, *Pantoea,* and *Serratia*, have been described both as harboring plant growth-promoting characteristics and attaining pathogenicity potential.

colicins microcins Enterobacteriaceae

1. Introduction

Bacterial resistance to available antibiotics is a huge problem, and that is why there is great interest in available natural alternatives, such as the use of bacteriocins. [1][2]. Bacteriocins produced by *Enterobacteriaceae* are ribosome-synthesized proteins, known as colicins and microcins [3]. Colicins are typically large proteins of high molecular mass, while microcins have low molecular weight [4][5] (**Figure 1**). *Enterobacteriaceae* often produce bacteriocins under stress conditions, such as the SOS response system [6]. Colicins and microcins can inhibit the growth of competing *E. coli* strains and other phylogenetically related bacteria [5]. A wide array of colicins and microcins use numerous cytotoxic mechanisms as mode of action, including pore formation, degradation of peptidoglycan precursors, phosphatase activity, RNAse activity (often targeting 16S rRNA and specific tRNAs), and DNAse activity [5]. Co-synthesizing specific immunity protein from producers protect producers from self-killing during bacteriocin antibacterial action [7][8].

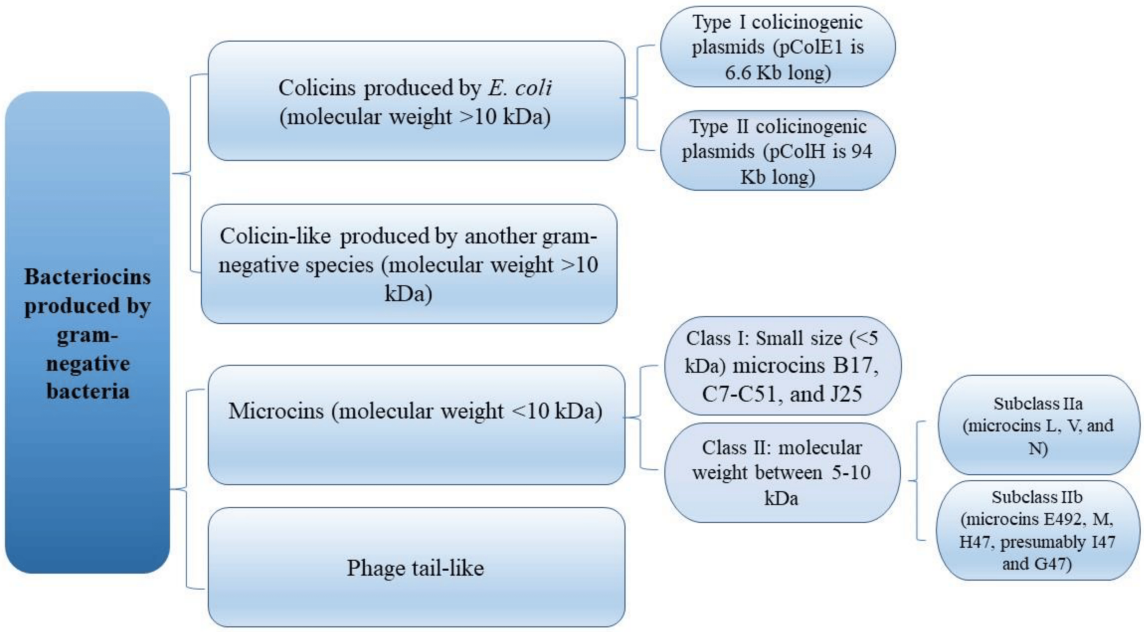

Figure 1. Classification of bacteriocins produced by Gram-negative bacteria.

2. Colicins—Short Overview of Genetic Organization, Classification, and Mechanisms of Action

Colicins are the most investigated group of bacteriocins. These molecules presenting a molecular mass 30–80 kDa are produced by specific *E. coli* strains and act against another *E. coli* strain and other *Enterobacteriaceae* [5][9][10][11][12][13]. Colicin-producing *E. coli* harbor colicinogenic plasmids, generically named pCol [9]. There are two types of colicinogenic plasmids, differentiated by size, number of copies in the cell, amplification ability, and aptitude to be transferred by conjugation. Type I colicinogenic plasmids are small (for example, pColE1 is 6.6 Kb), occur in a large number of copies in the cell, and encode group A colicins. Type II colicinogenic plasmids are large in size (e.g., pColH is 94 Kb), only one copy per cell, and are often capable of transfer by conjugation [14]. Large plasmids can contain either one or two colicin operons; therefore, the cells containing type II plasmids may be able to produce up to two distinct colicins. Various plasmids can encode similar colicin proteins [5][15][16]. Colicin's operons involve a gene cluster consisting of two to three genes: structural gene (*col* or *cxa*), the gene for immunity protein (*imm* or *cxi*), and the gene for the lytic protein (*kil* or *cxl*) [17]. The gene encoding the immunity protein is located downstream from the structural gene. Operons encoding ionophoric colicins do not include an immunity gene, but it is found on an opposite strand and has its own promoter. Genes encoding the lysis protein are always the last gene in the operon of group A colicins, while members of group B usually do not possess a lysis gene. The product of *cxl* is a lysis protein (also called colicin release protein or bacteriocin release protein), a small lipoprotein involved in the release of colicin into the medium and cell death after induction. Some functional regions of colicin genetic systems encode products associated with tissue adherence, serum resistance, and ability to conjugate [15].

Colicins are not produced in bacterial cells under normal conditions, but a limited number of colicin molecules are constantly present in the cell. Colicin amount drastically increases under the effect of various DNA-damaging

agents (e.g., UV light and antibiotic mitomycin C) and environmental factors, such as the lack of nutrients or increased bacterial population density [18]. Agents that cause DNA damage or stress lead to an “SOS response”, activating RecA proteinase, followed by auto-cleavage inactivation of LexA protein (repressor of colicin synthesis), hence allowing the transcription of the colicin operon [19]. In addition, alternative mechanisms of colicin synthesis activation, such as thymine starvation, catabolite repression, and mutation of *ompR* gene, have been described [20] [21]. Expressed colicins accumulate in the cytoplasm of the producing cell and need a significant amount of colicin lysis protein to be released to the extracellular medium. Colicin lysis proteins are small lipoproteins that show a high level of similarity in genetic sequence (*cxl* gene) and are co-expressed with colicin protein. The role of colicin lysis allows colicin release by provoking quasilysis, which causes structural changes and lysis of the cell envelope, activation of outer membrane phospholipase A, and death of the producing bacterial cell. Type II plasmids of group B colicin do not consist of a lysis gene (colicin D is an exception); therefore, their synthesis is not lethal for the producer cell [5][22].

Colicins show similar types of structural organization, including three distinct domains: one domain that is involved in the recognition of specific receptors, another domain with a role in translocation, and a third domain involved in the lethal activity. This organization is in coherency with the mechanism of action, in the sense that each phase of colicin action involves one domain of the colicin molecule [23]. The process of interaction between colicin and the cell of interest involves two or three steps. The first step includes binding to a specific receptor on the cell surface, followed by translocation of the colicin molecules across the cell envelope, followed by the action that causes bacterial death during the third step. The recognition step involves several receptors that are commonly involved in the uptake of essential nutrients (e.g., siderophore-bound iron, vitamin B12, or nucleosides). These receptors are parasitized by colicins, helping them enter more efficiently in the target bacteria [9]. The translocation step involves one of two distinct systems—Tol and Ton, on which the classification of colicins to groups A and B is based, respectively [24]. Colicins A, E1-E9, K, L, N, S4, U, and Y belong to group A. Colicins B, D, H, Ia, Ib, and M belong to group B. Tol system is formed by TolA, TolQ, TolR, and TolB, as well as Pal protein. Genes for proteins of translocation systems are found in clusters on *E. coli* chromosomes. The Ton system is formed by three inner membrane proteins (e.g., TonB, ExbB, and ExbD). Colicins of group A require all proteins from the Tol system or a subset of them, while all proteins from the Ton system are necessary for translocation of group B colicins [24][25][26].

Colicins from other close related bacteria (e.g., klebicins produced by *Klebsiella* spp. or S-pyocins produced by *P. aeruginosa*) have a similar size, structure, and function to *E. coli* bacteriocins. Similar to colicins, their antimicrobial activity can be due to pore formation or nuclease activity [27]. Inside each of the two groups, colicins and colicin-like bacteriocins may be differentiated according to their bactericidal mechanisms [11]. Colicins kill target cells through three different mechanisms: (a) by making voltage-dependent channels in the inner membrane of the target bacteria, (b) by a nuclease action in the cytoplasm (DNase, 16S rRNase, and tRNase activities), or (c) by inhibiting peptidoglycan synthesis [5][9][28][29]. In further detail, colicins undergo a series of conformational changes during the voyage from the extracellular space to the periplasmic membrane of the target cell. All channel-forming colicins act in a similar way. The receptor domain of the molecule mediates the first interaction with the host cell by recognizing membrane proteins, such as BtuB (B12 receptor) or iron transport proteins. The pore-forming domain of the colicin molecule (C-terminal domain) is made of a tightly packed group of 10 α-helices. Studies show that this process

involves initial fast absorption to the membrane of the target cell, followed by slow insertion of C8 and C9 helices into the membrane interior. Helices C8 and C9 form the hairpin structure, but these changes happen after interaction with the inner membrane [30]. The process of colicin insertion and pore formation does not involve target cell proteins [31]. Several models of a closed channel have been proposed [32][33]. The positive voltage applied to the closed channel leads to further insertion into the membrane pore. Furthermore, only several helices are necessary to form a viable pore [34]. All colicin channels are voltage-dependent and present high selectivity for protons over other cations, opening at the positive voltage and closing at the negative voltage. There are multiple open and closed states of the pores [35][36]. The cell-killing potential of pore-forming colicins is extremely high, as one colicin molecule is enough to destroy a target cell. Immunity proteins, encoded by the same plasmids as the colicin, are small polypeptides that act as a protection system against self-produced colicin and exogenous colicins secreted by neighboring bacterial cells [5].

Colicins with enzymatic activity may act as hydrolases or transferases that target phosphodiester bonds in the DNA (DNase) or RNA (rRNase or tRNase) of the host cell. Colicins begin their passage into the target cell via Ton or Tol systems, translocate through the inner membrane, and enter the cytoplasm, where they exert the lethal activity. DNase colicins degrade DNA by producing dents in dsDNA by repeated cleavage [5]. These colicins are metal-dependent but the nature of the metal ions required is still unknown, although research suggests that Zn^{2+} and Ni^{2+} are necessary as cofactors for enzyme activity [37][38]. RNase colicins may cause cell death by inhibiting protein synthesis and, for this activity, no cofactors are required. Target molecules of RNase colicins are 16S rRNA and anticodon loops of tRNA [5]. Nuclease colicins are produced and released from the cell in complex with its nuclease-specific immunity proteins, which protect the producing cell from the lethal activity [39].

Colicin M, firstly described in 1974, presents a distinct mode of action, since it is released without immunity protein and causes the death of the host cell by inhibiting peptidoglycan synthesis, specifically by degrading peptidoglycan precursors, and LPS O-antigen production. Colicin M activities can be inhibited by changing the osmolarity of the growth medium [13][40][41][42][43].

3. Microcins—Short Overview of Genetic Organization, Classification, and Mechanisms of Action

Microcins are low molecular mass bacteriocins (ranging from 1 to 10 kDa), produced by Gram-negative bacteria, often *E. coli*, under stress conditions [44][45], which respond very well to changes in pH, protease activity, or temperature alterations. Microcin's classification considers three criteria: (a) the presence, nature, and localization of post-translational modifications, (b) gene cluster organization, and (c) leader peptides sequences, therefore, separating microcins into two classes—class I and II [9].

Class I microcins are low molecular mass peptides (below 5 kDa), namely microcins B17, C7–C51, and J25. They are plasmid-encoded and go through post-translational modifications [46][47]. Class II includes peptides of higher molecular mass (in the range between 5 and 10 kDa), and is further divided into subclasses IIa and IIb. Class IIa contains plasmid-encoded peptides that do not undergo post-translational modification and are possibly forming

disulfide bonds (e.g., microcins L, V, and N). Class IIb includes chromosome-encoded linear microcins, which may carry a C-terminal siderophore post-translational modification (e.g., microcins E492, M, H47, and, presumably, I47 and G47) [48][49][50].

Hence, microcins are encoded by gene clusters located either in plasmids or by the bacterial chromosome. Gene clusters involved in microcin production include a variable number of determinants [9], with minimal structure organization, consisting of a structural gene, the self-immunity gene, and genes encoding the export system. For class I microcins, the self-immunity gene is not located near the structural gene, while genes involved in the post-translational modification are adjacent to the structural gene. In addition, at least one gene is involved in both secretion and self-immunity. A gene cluster of class I microcin B17 is located on single-copy plasmids found in *E. coli* and consists in seven genes forming an operon: *mcbA* encodes the B17 precursor, *mcbB*, *mcbC*, and *mcbD* encode components for post-translational modifications of McbA, while *mcbE* and *mcbF* have roles in secretion and self-immunity, and *mcbG* is required for full self-immunity. Microcin C (C7–C51) is the smallest microcin, characterized in *E. coli* strains and also located on a single-copy plasmid. The corresponding gene cluster is composed by *mccA*, *mccB*, *mccC*, *mccD*, *mccE*, and *mccF*, found only on the C51 genetic system. Structural gene *mccA* is only 24 bp in length, making it one of the shortest genes known. The last gene *mccF*, transcribed from the opposite strand, has a role in self-immunity towards C7, but not in self-immunity towards C51. Maturation of microcin C does not take place in the producing cell but in target cells after entrance through OmpF and Yej channels. Microcin J25 is found on low-copy-number pTUC100 plasmid in *E. coli* strains and its genetic structure consists in four genes (*mcjA*, *mcjB*, *mcjC*, and *mcjD*), organized in two operons. Gene *mcfA* encodes a precursor that must undergo modification by proteins encoded by *mcjB* and *mcjC* to form the distinct lasso structure [51][52][53][54].

As previously mentioned, class II microcins are divided into two subclasses, IIa and Iib. A set of genes that have a role in peptide export (at least two) are homologous between subclasses and require *tolC* to be functional. Class Iia microcins possess four genes organized in a similar way, all of them located on a plasmid. Genetic organization of microcin L, produced by *E. coli* LR05 strain involves genes *mclC*, *mclI*, *mclA*, and *mclB*. Gene *mclC* encodes peptide precursor, *mclI* is involved in self-immunity, while *mclA* and *mclB* have a role in peptide export [55]. Subclass IIb microcin genes are chromosomally encoded and show a complex transcriptional organization. Microcin E492 is the most well-studied, being secreted by *Klebsiella pneumoniae* RYC492, and its gene cluster is composed of 10 genes (*mceA* to *mceJ*) organized in six transcriptional units that are crucial for production, export, and self-immunity [45][54].

Microcin gene clusters have lower G + C content in comparison to their bacterial host genomes and are flanked by direct repeats, which could suggest that producing bacteria are not their original host and highlights the possibility of horizontal gene transfer events. As an example, the G + C content of microcins C7 and C51 gene clusters is 34%, which is significantly lower than 51%, found in the host *E. coli* chromosome [56].

Microcins production is up-regulated when bacteria are exposed to stress conditions, such as the lack of nutrients, oxygen or nitrogen starvation, iron availability in the culture media, and mild air limitations, among others. In many

cases, variation in pH values and cell density does not affect microcin production. These molecules are produced as inactive precursor peptides with a core structural sequence and an N-terminal leader peptide (microcin C is an exception, as it does not possess a leader peptide). Leader peptides have various functions in different microcins, and previous data suggest their role in the protection of the precursor against degradation, keeping the precursor inactive inside the producing cell, and that cleavage of the leader peptide at a specific cleavage site allows maturation and secretion of the microcin molecule [45][46]. Microcin maturation requires proteolytic enzymes that cleave the leader peptides and enzymes that ensure post-translational modifications. Class I microcins use a variety of different mechanisms for export, which includes efflux pumps or systems similar to ABC transporters. The processing and maturation of microcin MB17 are carried out by chromosomally encoded enzymes, mostly by metalloprotease PmbA, while export of microcin out of the cell is carried out by an ABC-type transporter McbEF. Experiments showed that the export machinery for B17 is not involved in the cleavage of the leader peptide [57]. Proteolytic cleavage of class II microcin leader peptide occurs during export. Secretion and maturation of class II microcins from the producing cell usually involve the machinery that includes the ABC transporter, its accessory proteins, and TolC protein [49]. Some microcins enter the bacteria as harmless molecules and become toxic after the maturation process occurs inside the target cell [47]. A large range of different post-translational modifications of microcin molecules involve enzymes encoded on the microcin gene clusters. At least three genes are involved in post-translational modifications of B17 microcin [45]. Microcins have receptor-mediated mechanisms of antimicrobial activity, as they overtake receptors that have an important role in nutrient uptake. Receptor types range from siderophore receptors (for microcins J25, L, M, V, and others) or porin OmpF (in the case of microcin B17). Translocation of the microcin protein requires protein complexes of the inner membrane, such as TonB or different ABC transporters [58][59].

Once inside the target cell, microcins present distinct and complex mechanisms of action. Some mechanisms of action have been studied in detail, while others remain to be confirmed [28]. Some microcins act by forming pores in the bacterial membrane, inhibiting aspartyl-tRNA synthetase and DNA gyrase GyrB. Other mechanisms include inhibition of secondary RNA polymerase channel, preventing transcription and inhibiting cellular respiration (J25), impairing the cellular proton channel (e.g., H47 and probably M and I), or the ATP synthase (H47) [28]. Class I microcins inhibit the activity of essential enzymes, such as DNA gyrase necessary for DNA supercoiling. B17 inhibits DNA supercoiling and induces the accumulation of complexes of DNA gyrase and cleaved DNA, leading to the formation of breaks in dsDNA and inhibition of DNA replication [60]. Other microcins, such as J25, target RNA polymerase, obstructing it in the active site and blocking the transcription process [61]. Microcin J25 also influences mitochondria and the respiratory chain [45]. Class II microcins target the inner membrane of the cell of interest and require proteins of the inner membrane for their activity. For example, microcin H47 targets the F_0 proton channel of ATP synthase [62]. Microcin V needs protein involved in serine uptake to permeabilize the inner membrane [47].

Certain high-molecular-weight peptides present cylindrical structures, which are highly similar to phage tail structure, can perforate the bacterial cell membrane and lead to cell death [63]. These antimicrobial peptides are named phage tail-like bacteriocins, derived from the domestication of phage tail genes (i.e., genes for peptide release and regulatory genes). The most well-studied bacteriocins from this group are R-pyrocuns and F-pyocins,

produced by *Pseudomonas aeruginosa*. Their mechanism of action is the disruption of the membrane potential leading to pore formation on the bacterial membrane [27][64].

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