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Fighting Hospital Infections with Bacteriocins

Since the late 1980s, starting with Professor Ingolf Nes and coworkers, scientists at Ås have focused on research involving bacteriocin purification, genetics, gene expression and mode of action studies. Increasingly, bacteriocin projects at Ås are now being directed at practical goals such as developing them as drugs to inhibit antibiotic resistant pathogens.

Bacteriocins are small antimicrobial peptides (30-60 amino acids) produced by bacteria that are usually active against related bacterial species but not against eukaryotic cells. First discovered in E. coli, bacteriocins occur among both Gram-negative (for example, E. coli and Pseudomonas aeruginosa) and Gram-positive bacteria (for example, Lactobacillus and Lactococcus spp.).

Although different bacteriocins have different specificities, all of them apparently act by targeting specific membrane receptors at pico- to nanomolar concentrations, causing membrane-disruption and pore formation which leads to cell death. An advantage of this killing mechanism is that it is fundamentally different from the mechanism of action of most antibiotics which inhibit key metabolic pathways. Therefore, bacteriocins do not discriminate between antibiotic-resistant and antibiotic-sensitive bacteria.

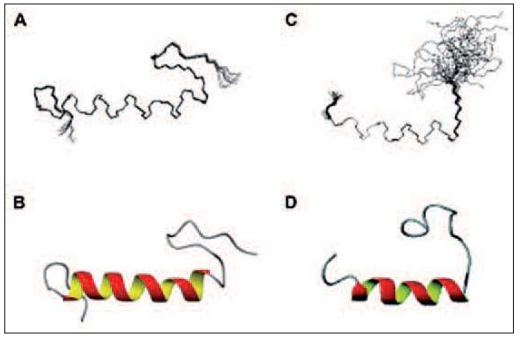

Fig. 1. NMR structures of EntK1 (A,B) LsbB (C,D). The structure ensembles of the 20 lowest energy structures superimposed are shown in (A,C) and cartoon representations of the lowest energy structures are shown in (B,D). Figure is publically available through Creative Commons from reference 2.

Current research at Ås is focused on the bacteriocin EntK1 which has 37 amino acid residues and is produced by Enterococcus faecium. EntK1's receptor is a Zn-dependent metallopeptidase (RseP) to which it binds via its C-terminal (1).

Prof. Dzung Diep (right) and his coworkers PhD student Ingvild Reinseth and postdoc Kirill Ovchinnikov.

A recent article in Frontiers in Microbiology (2), co-authored by the Ås group as well as partners at UiO and in Poland, used circular dichroism (CD) and NMR to determine structures of EntK1 as well as other bacteriocins with different bacteriocidal specificities. Fig. 1 shows NMR structures of EntK1 and a related bacteriocin, LsbB, as ensembles of the lowest energy structures. In antimicrobial tests, LsbB had a much narrower spectrum of activity compared to EntK1 which is especially toxic for Enterococcus faecium. Both bacteriocins have an N-terminal -helical motif, probably involved in pore formation, and an unstructured C-terminal half involved in receptor binding, and they apply the same mode of action. They attack the receptor RseP on target cells to cause leakage of cellular solutes across the membrane that eventually leads to cell death. In E. faecium, RseP is a virulent factor required for infection establishment in mammals. Hence this protein has a great potential as drug target.

E. faecium is an opportunistic bacterium, being a common gut bacterium in humans but also a serious pathogen in hospitals worldwide due to its increasing resistance to many antibiotics including vancomycin. In developing EntK1 for hospital use, Professor Dzung Diep and his coworkers at NMBU and UiO are taking the advantage of EntK1's extreme specificity to E. faecium to explore the therapeutic potential of the bacteriocin, initially in mouse models followed by human trials.

References

1. Ovchinnikov et al.: Defining the structure and receptor binding domain of the leaderless bacteriocin LsbB. J. Biol. Chem. 289 (2014) 23838.
2. Ovchinnikov et al.: The Leaderless Bacteriocin Enterocin K1 Is Highly Potent against Enterococcus faecium: A Study on Structure, Target Spectrum and Receptor. Front. Microbiol. 8 (2017) 774.