Mechanistic and functional aspects of the Ruminococcin C sactipeptide isoforms

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Résumé :

In a scenario where the discovery of new molecules to fight antibiotic resistance is a major public health concern, ribosomally synthesized and post-translationally modified peptides (RiPPs) offer a promising alternative. In this context, the Gram-positive human gut symbiont *Ruminococcus gnavus* E1 produces five sactipeptides, Ruminococcins C1 to C5 (RumC1-5), co-expressed with two modifying enzymes, which belong to the radical-SAM family. RumC1 has been shown to be effective against various multidrug resistant Gram-positive clinical isolates. The presentation reports the biosynthesis of the four mature RumC2-5 and their antibacterial activities. Establishing that both maturases exhibit substrate tolerance, we observed a variation in the antibacterial efficacy between the five isoforms. Using a structure/function approach, we have identified the critical residues within RumC sequences that are essential for an optimal antibacterial activity. In addition, our investigations into the mode of action of RumC peptides revealed that, unlike known sactipeptides, they do not form pores. While no synergies were observed for the five RumCs, we found a synergistic action with conventional antibiotics targeting the cell wall.

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