Biosynthesis of the Antimicrobial Peptide Epilancin 15X

Juan E. Velásquez and Wilfred van der Donk

Lantibiotics are antimicrobial peptides that are ribosomally synthesized and posttranslationally modified to their biologically active forms. The recently discovered lantibiotic epilancin 15X produced by *Staphylococcus epidermidis* 15X154 is active against several pathogenic bacteria, including methicillin-resistant *S. aureus* and vancomycin-resistant Enterococci. Epilancin 15X contains an unusual N-terminal lactate group (Lac) that could be important for its bioactivity. To understand its biosynthesis, the epilancin 15X gene cluster was sequenced. The lactate group is introduced by dehydration of a Ser residue at the first position of the core peptide by a dehydratase (ElxB), followed by cleavage of the leader peptide by a lantibiotic protease (ElxP), and hydrolysis of the resulting N-terminal dehydroalanine (Dha) residue. The pyruvate (Pyr) group thus formed is finally reduced to lactate by a novel NADPH dependent oxidoreductase (ElxO). Using substrate analogs synthesized by solid-phase peptide synthesis, the enzymatic activity of ElxO was reconstituted *in vitro* and a reaction mechanism was proposed. The enzyme is highly promiscuous and allowed for the production of novel peptides with enhanced bioactivity. Biological activity and enzymatic assays suggested that the N-terminal lactate group is not essential, but plays a protective role against proteolytic degradation.