Engineering of Lantibiotic Peptides through the Incorporation of Nonproteinogenic Amino Acids

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Lacticin 481 is a member of the class of ribosomally-synthesized peptide antimicrobial agents known as lantibiotics. Lacticin 481 contains several post-translational modifications, including characteristic thioether bridged amino acids lanthionine (Lan) and methyl-lanthionine (MeLan) as well as a dehydrated amino acid (Z)-2,3-dehydrobutyrine (Dhb). These modifications are introduced through enzyme-catalyzed dehydration and cyclization of the prepeptide substrate, LctA. Our laboratory has recently reconstituted the activity, *in vitro*, of the bifunctional enzyme LctM responsible for these modifications. Expressed protein ligation (EPL) and the [3+2] dipolar cycloaddition between an azide and alkyne have been utilized as synthetic or semi-synthetic routes for the preparation of truncated LctA analogs containing nonproteinogenic amino acids. These analogs have been used to provide insights into the substrate specificity and mechanism of LctM. These methodologies are being investigated as a means to engineer lantibiotic structures and dehydrated peptides.