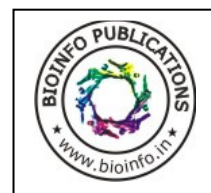


Phylogenetic signatures of functional conservedness in lantibiotics- an *in-silico* regulomics study

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Abstract- The name Lantibiotics was introduced in 1988 as an abbreviation for "Lanthionine-containing peptide antibiotics". In spite of this naming, Lantibiotics are not classed as antibiotics. The first structures of these antimicrobial agents were produced by pioneering work by Gross and Morell in the late sixties and early seventies, thus marking the formal introduction of Lantibiotics. Since then Lantibiotics such as Nisin have been for food preservation and have yet to encounter significant bacterial resistance. These attributes of lantibiotics have led to more detailed research into them.

Introduction

A comprehensive structural analysis of the lantibiotics was performed. Phosphorylation sites were detected for the sequences. Conserved domains were also analyzed for phylogenetic signatures (PHYLIP) and molecular modeling of representative members of the major groups of the lantibiotics were performed using Modeler 9.2. Several plant homologues were detected sharing sequence identity of over 85% with the lantibiotics mostly belonging to the bacteriocin superfamily. Most of the plant homologues identified were transcription factors induced by phytohormones. Phosphorylation sites detected in the sequences show a bias for serine phosphorylation in most of the conserved regions. Phylogenetic analysis revealed that blocks of lantibiotics are phylogenetically related to certain members of the mammalian immune response pathways as they share a stretch of conserved region in them. Apart from them certain sequences had metallothionein sequences as their sister groups indicative of a stress related functional conservedness.

Background

Lantibiotics are highly modified peptides from Gram-positive bacteria. They contain alpha, beta-unsaturated amino acids (dehydroalanine and dehydrobutyrine) and lanthionine or 3-methylanthionine rings. There are 2 types of lantibiotics:

Type A are strongly cationic and bactericidal - nisin, subtilin and Pep5 inhibit the growth of Gram-positive bacteria, probably by voltage-dependent pore formation in the cytoplasmic membrane, resulting in cellular efflux of electrolytes, amino acids and ATP.

Type B lantibiotics possess at most one positive charge and are not bactericidal.

Ribosomally synthesized peptide bacteriocins from Gram-positive bacteria can be subdivided into two major classes. Bacteriocins of class I are characterized by having modified amino acid residues (e.g., lantibiotics) and bacteriocins of

class II are characterized by not possessing modified amino acid residues (e.g., small heat stable non-lantibiotics). These two classes are the most studied due to their abundance and their potential use for industrial applications.

They are similar in size (approx 20-60 amino acids), mostly cationic, and possess a hydrophobic domain and/or amphiphilic region, which may relate to their action on membranes. The defining characteristic of lantibiotics is that they contain the unusual amino acid lanthionine (or β -methylanthionine). Generally, type A lantibiotics are characterized by being strongly cationic (with 2 to 7 net positive charge), having molecular masses more than 2 kDa, and having rigid ring conformations separated by areas of flexibility [2, 3]. It is currently believed that their primary bactericidal activity is mediated through the formation of voltage-dependent membrane channels.

Contrastingly, type B lantibiotics are characterized by being neutral or slightly anionic (with a 0 to -1 net charge), having molecular masses of less than 2 kDa, and having a more compact globular structure. Their primary function is mediated through the inhibition of essential enzymes. There is a unique group of lantibiotics called the two-peptide bacteriocins. In this system, two genes encoding each of the peptides are situated next to one another and both of the peptides are needed for bactericidal activity. Each peptide is either inactive or only slightly active when tested individually. The mode of bactericidal activity is believed to be the same as for type A lantibiotics. In some cases, they have been grouped along with type A lantibiotics [7, 9]. Lantibiotics are produced by a large number of Gram positive bacteria such as *Streptococcus* and *Streptomyces* to attack other gram positive bacteria and as such they are considered a member of the bacteriocins. Lantibiotics are well studied because of the commercial use of these bacteria in the food industry for making dairy products such as cheese [12, 14].