Posttranslational Peptide-Modification Enzymes in Action: Key Roles for Leaders and Glutamate

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In this issue of Cell Chemical Biology, Ortega et al. (2016) determine the structure of another lantibiotic dehydratase with a tRNA Glu-dependent mechanism of modification. Moreover, they identify a common recognition motif involved in leader peptide binding in a number of different peptide-modification enzymes. These findings open up new mining possibilities and allow novel approaches in peptide engineering.

Ribosomally produced and posttranslationally modified peptides (RiPPs) form a group of compounds that has gained increased attention over the last several years (Arnison et al., 2013). These peptides display a great chemical diversity and reflect Nature’s optimization strategy that separates substrate recognition (based on leader peptide binding) from catalysis to produce a large variety of bioactive molecules employing a modest number of promiscuous enzymes. Understanding the mechanism and substrate requirement of these enzymes is of particular interest not only because they are of fundamental biochemical interest as they display an array of unique activities, but because the knowledge gained from them can open possible uses in host/substrate combinations different from the natural one, thus increasing the diversity of the RiPPs we have available to us.

Lantibiotics are RiPPs that exhibit antimicrobial activity (Knerr and van der Donk, 2012). They contain several lanthionine rings that originate from the addition of a thiol group from a cysteine to a dehydroamino acid. Both the dehydratation and cyclization steps are performed by either one or two different enzymes. In type II lantibiotics, a single multifunctional enzyme (LanM) can first activate the serine and threonine residues via phosphorylation and then dehydrate and finally catalyze the formation of thioether bridges. Conversely, in type I lantibiotics the modifications are carried out by two separate enzymes.

Figure 1. Schematic Representation of the Modification Extent of Microbisporicin
Schematic representation of the modification extent of microbisporicin in Escherichia coli (A) inducing the structural gene (mibA) and the dehydratase (mibB), (B) including the tRNA Glu and tRNA-synthetase, and (C) adding the cyclase gene (mibC).
enzymes, i.e., a dehydratase, LanB, which has no significant homology to LanM, and a cyclase generally termed LanC that shares some homology with the type II enzymes. Recently, the structure of the lantibiotic dehydratase NisB was reported (Ortega et al., 2015). NisB has a domain responsible for the glutamyl-tRNA for complete dehydration. This motif identified in NisB is also present in other RiPP PTM enzymes in various combinations. However, it still remains a challenge to elucidate how the PTM enzymes dynamically interact with each other and with the substrate during modification in the bacterial cell, where strict compartmentalization is not possible. Will the leader be bound at the same cleft during the whole processive modification of the pre-peptide or will it slide, possibly by a pulling force? Is there a hopping or scooting mode of the modification enzymes during the sequential modifications? The information discussed here paves the way to a better understanding of these intriguing processive enzymes and will enable the development of even more highly valuable bioactive compounds.

REFERENCES


