Understanding the Complex Orchestration of Enzymatic Processing of Thiazole/Oxazole-Modified Microcins

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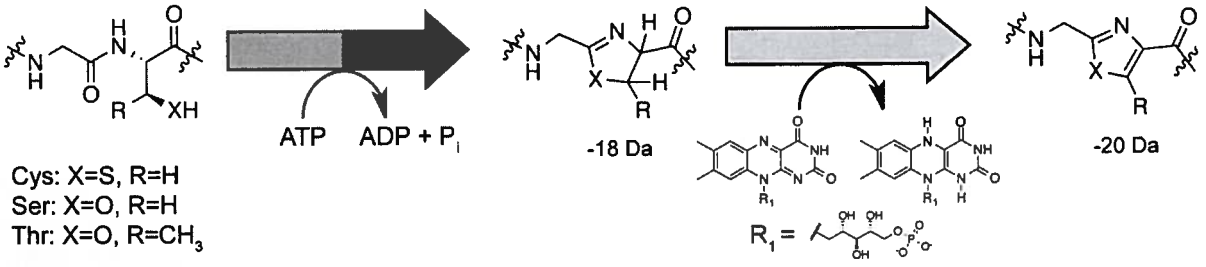
The modular nature of ribosomally synthesized and post-translationally modified peptide natural products enables their total biosynthesis through heterologous expression and purification of the substrates and enzymes. A deeper understanding of the selectivity and promiscuity for each step along the biosynthetic pathway will enable the generation of natural product derivatives or chemical libraries. The thiazole/oxazole-modified microcins (TOMMs) represent a burgeoning class of ribosomal natural products decorated with thiazoles and oxazoles originating from cysteines, serines, and threonines. The discovery and investigation of the TOMM cluster from *Bacillus* sp. Al Hakam (Balh) has provided insight into the mechanism of thiazole and oxazole biosynthesis and the finer details of substrate handling. Using substrate analogs and tandem mass spectrometry, the Balh TOMM biosynthetic enzymes were shown to be both chemoselective and site-selective in terms of substrate processing, yet promiscuous with regard to precursor peptide acceptance. These properties of the Balh TOMM biosynthetic enzymes may provide an avenue for the generation of a large-scale library of heterocyclic peptides.

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