Regio- and Chemoselectivity of Thiazole/Oxazole Biosynthesis

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The thiazole/oxazole-modified microcins (TOMMs) represent a burgeoning class of ribosomally produced natural products decorated with thiazole and oxazole heterocycles derived from cysteine, serine and threonine residues. The discovery of a novel biosynthetic cluster from Bacillus sp. Al Hakam has provided an opportunity for a thorough investigation of what governs the site-specific installation of thiazole and oxazole heterocycles. Using Fourier transform tandem mass spectrometry, the biosynthetic machinery was shown to process both of its substrates in a regio- and chemoselective fashion. Moreover, cognate and non-cognate precursor peptides are modified in an overall C- to N-terminal directionality, which is unique among characterized ribosomally synthesized natural products. Further studies elucidated, through a mutational analysis of residues adjacent to a cyclizable site, a bias for glycine at the preceding (-1) position. In contrast, these studies elucidated a remarkable flexibility in the following (+1) position, even allowing for the incorporation of charged amino acids.