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Bio-inspired engineering of thiopeptide antibiotics advances the expansion of molecular diversity and utility

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Thiopeptide antibiotics, which are a class of sulfur-rich and highly modified peptide natural products, exhibit a wide variety of important biological properties. These antibiotics are ribosomally synthesized and arise from post-translational modifications, exemplifying a process through which nature develops the structural complexity from Ser/Thr and Cys-rich precursor peptides. Following a brief review of the knowledge gained from nature in terms of the formation of a common thiopeptide scaffold and its specialization to individual members, we highlight the significance of bio-inspired engineering, which has greatly expanded the molecular diversity and utility of thiopeptide antibiotics regarding the search for clinically useful agents, investigation into new mechanisms of action and access to typically 'inaccessible' biosynthetic processes over the past two years.

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Introduction

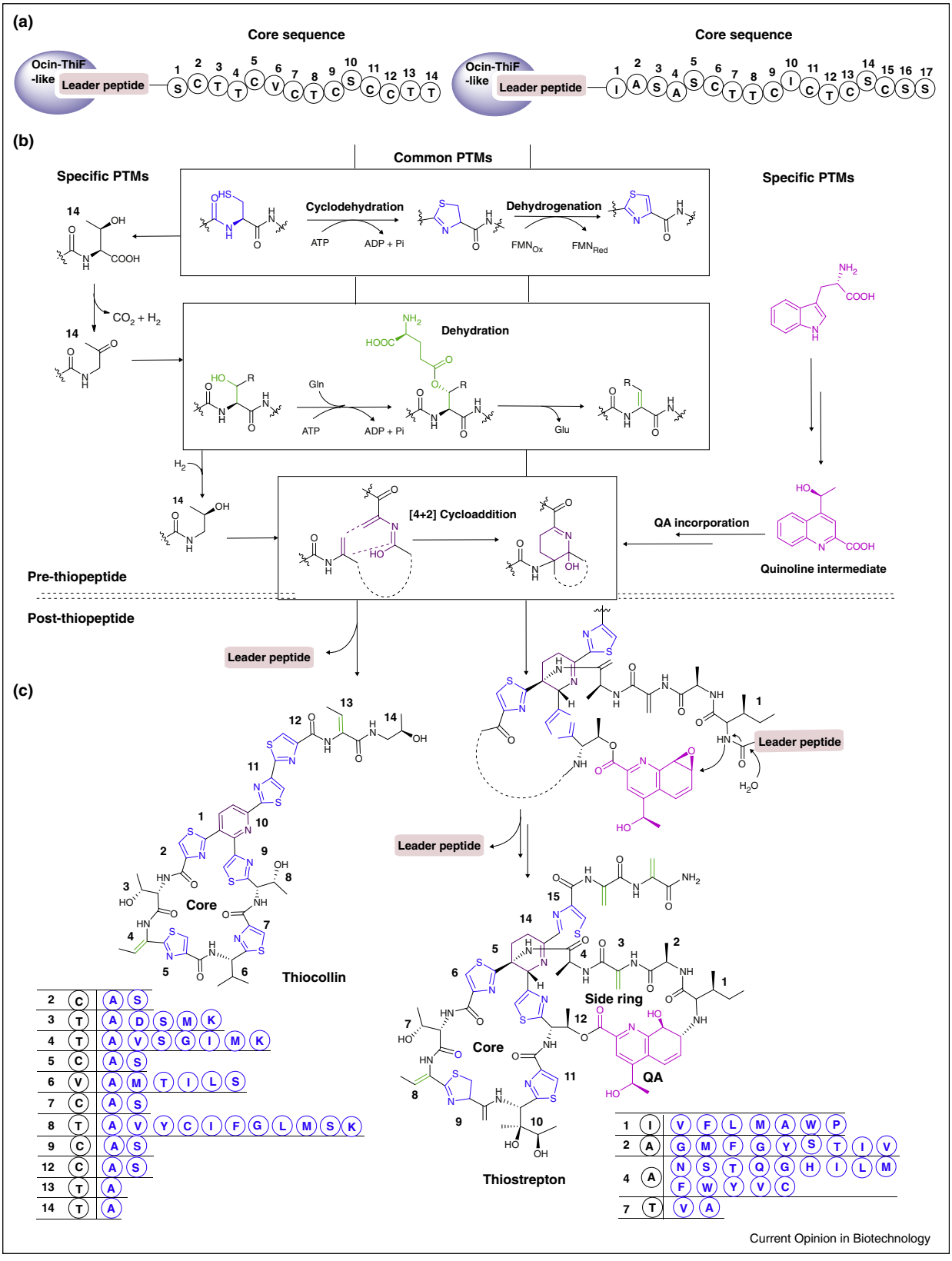
Over the past decades, peptide natural products (NPs) with ribosomal origin have been a focus in the discovery of new biosynthetic mechanisms [1]. Increasing evidence indicates that post-translational modifications (PTMs) of ribosomally synthesized precursor peptides are comparable to non-ribosomal peptide synthetases in terms of the creation of structurally complex molecules [2–4]. A precursor peptide typically consists of an N-terminal leader sequence and a C-terminal core sequence (Figure 1a). A myriad of PTMs can be applied, in a manner either dependent or independent of the former sequence, to transform the latter sequence into mature product(s) (Figure 1b). Although the building blocks are limited to 20 proteinogenic amino acids, in contrast to a much wider array of substrates found in the biosynthesis of non-ribosomal peptide NPs [5], the sequences of precursor peptides and the associated enzyme-processing strategies have been shown to be highly variable and evolvable in the formation of various ribosomal peptide NPs [6].

One example comes from thiopeptide antibiotics [7–10], a growing family of sulfur-rich peptide NPs that are ribosomally synthesized and post-translationally modified (Figure 1c). These antibiotics possess a wide variety of biological properties, e.g., anti-infection, anticancer and immunosuppression, and are beneficial to humans largely because of their highly functionalized unusual architectures, which share a macrocyclic peptidyl core that contains a six-membered heterocycle domain central to multiple azoles and dehydroamino acids [11]. Recent studies revealed a wide distribution of thiopeptide-encoding sequences in the genomes of human microbiota [12], generating interest in the roles played by related products in microbe-host interactions. Derivatization efforts has attracted considerable attention of molecular engineering to further expand the chemical spaces of thiopeptide antibiotics, improve their biological activities and overcome physical disadvantages [13]; however, the accessibility and efficiency of chemical synthesis are often impeded by the structural complexity of these compounds. The ribosomal origin of thiopeptide antibiotics was established in 2009 [14–18], garnering appreciation for the mechanisms that nature employs to develop various PTM strategies and obtain individual thiopeptide members from Cys and Ser/Thr residue-rich precursor peptides. This appreciation has recently motivated rational applications of various technologies for structural diversification (as discussed below), resulting in a number of thiopeptide analogs, either expected or unexpected.

Formation of a common thiopeptide framework and its specialization in nature

Thiopeptide antibiotics structurally appear to be the macrocyclic variants of goadsporin-like NPs, each of which derives a six-membered central heterocycle domain from a linear peptide possessing both azol(in)es and dehydroamino acid residues [19]. The in vitro biosynthesis of the thiopeptide member thiomuracin was successful [20••], benefiting from the recent knowledge regarding

Figure 1


(a)
Core sequence
Ocin-ThiF -like
Leader peptide
Core sequence
Ocin-ThiF -like
Leader peptide
(b)
Common PTMs
Specific PTMs
Cyclodehydration
ATP
ADP + Pi
Dehydrogenation
FMNOx
FMNRed
Specific PTMs
Dehydration
Gln
ATP
ADP + Pi
Glu
[4+2] Cycloaddition
QA incorporation
Quinoline intermediate
Pre-thiopeptide
Post-thiopeptide
Leader peptide
Leader peptide
Leader peptide
(c)
Core
Thiocollin
Side ring
Core
QA
Thiostrepton
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