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Opportunities and challenges from current investigations into the biosynthetic logic of nosiheptide-represented thiopeptide antibiotics

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Nosiheptide is an archetypal thiopeptide antibiotic, possessing a characteristic macrocyclic core that contains a 6-membered heterocycle central to multiple azol(in)es and dehydroamino acids. The discovery of the ribosomal origin of thiopeptides revealed a unifying theme, showing that the structural complexity arises from post-translational modifications (PTMs) of precursor peptides. Thiopeptide framework formation proceeds via cyclodehydration/dehydrogenation (for azol(in)es), dehydration (for dehydroamino acids), and cycloaddition (for the central heterocycle domain). This common process has not been reproduced in vitro, partly due to the poorly understood logic of thiopeptide biosynthetic pathways. Utilizing nosiheptide biosynthesis as a model system, we herein consider how nature coordinates a number of highly interwined, common and specific PTMs to accomplish the complexity of ribosomally synthesized and post-translationally modified peptides.

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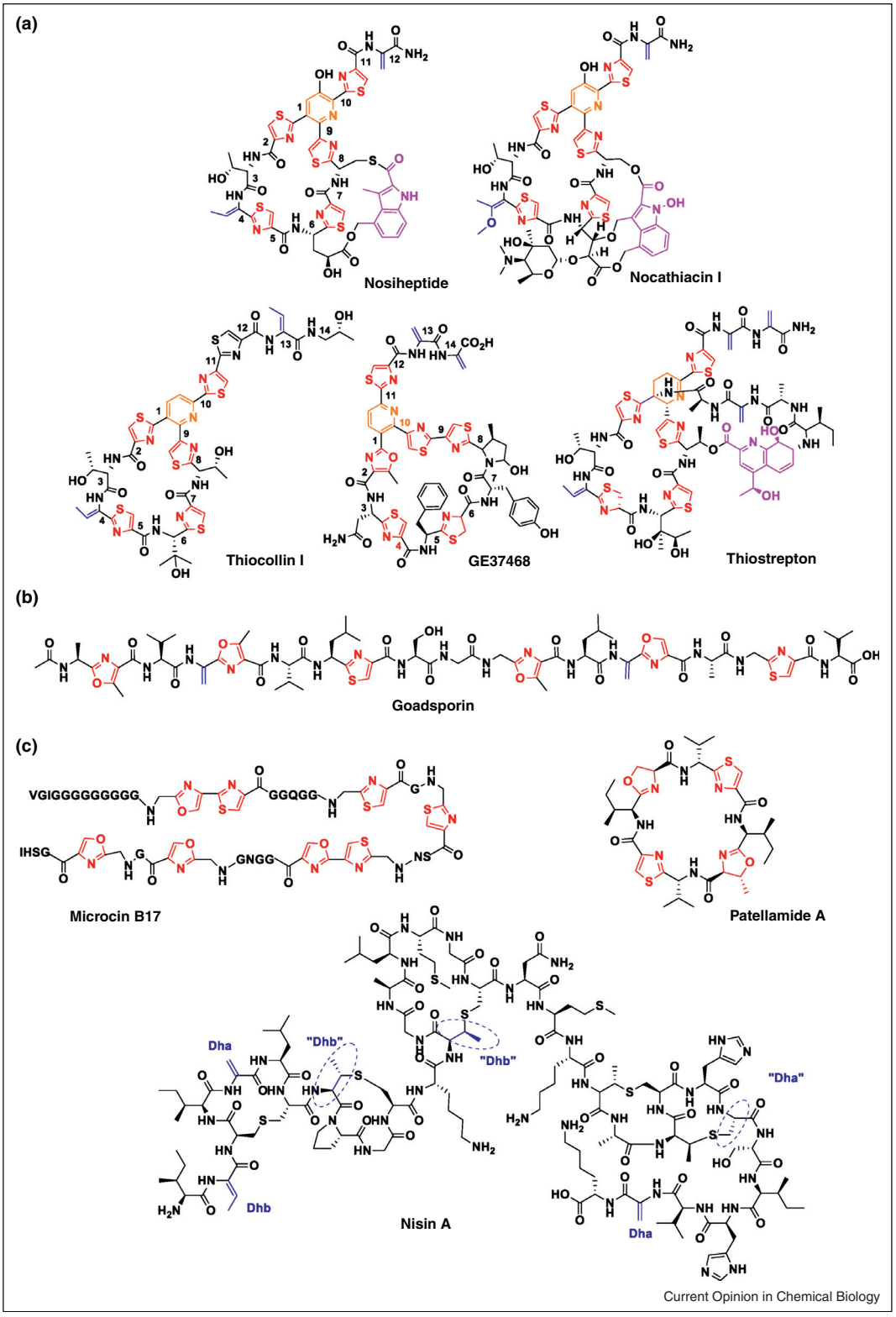
Introduction

Thiopeptide antibiotics form a growing class of sulfur-rich, highly modified peptide natural products [1–3]. Among the nearly 100 entities for which structures are known, nosiheptide (NOS) is one of the archetypical parent members (Figure 1a) [4,5]. NOS contains a macrocycle that is characteristic of all thiopeptides, with a pyridine domain central to multiple thiazoles and dehydroamino acids. It has a side ring system featuring an indolic acid (IA) moiety and is distinct from mono-macrocyclic (e.g., thiocillin, TCL) thiopeptides and other bis-macrocyclic members (e.g., thiostrepton, TSR) that possess a quinaldic acid (QA) moiety. The complex architecture of NOS, combined with its remarkable antibacterial activity [4,6] and unusual mode of action on ribosome [7–9], have attracted significant interest in analog development to fight progressively emerging bacterial resistance against traditional antibiotic therapies [10–13]. Early in the 1980–1990s, Floss *et al.* performed extensive isotopic feeding experiments [14–17] and established that the peptidyl backbone of NOS is derived exclusively from proteinogenic amino acids. However, whether thiopeptides, including NOS, are produced ribosomally or non-ribosomally had been a subject of intense dispute until very recently [18–20]. In 2009, we cloned and characterized the NOS biosynthetic gene cluster, and ultimately validated the ribosomal origin of NOS production [21••]. The identification of the NOS genetic basis now lays the foundation to answer lingering question, regarding how nature decorates a ribosomally synthesized linear precursor peptide to produce this complex molecule, which has not been accessible to chemical synthesis thus far. NOS biosynthesis has both commonalities and specificities for thiopeptides [22] and other types of structurally relevant, ribosomally synthesized and post-translationally modified peptides (RiPPs) [23••]. The elucidation of its biosynthetic logic would provide insights into how nature integrates multiple strategies to produce complex RiPPs and into potential applications for creating their diversity.

Model system for thiopeptide biosynthesis

Similar for other thiopeptides that have been biosynthetically characterized during the past four years (i.e., nocathiacin (NOC), TCL, TSR, siomycin, thiomuracin, GE2270A, cyclothiazomycin, TP-1161, GE37468, and berninamycin) [24,25,26,27,28,29,30,31••,32], NOS biosynthesis requires a set of post-translational modifications (PTMs), encoded by a conserved gene cassette, *nosGFDEOH*, to convert the precursor peptide NosM into a highly constrained, defining macrocyclic core (Figure 2a) [21••]. NosM contains a 37-aa leader peptide fused to a 13-aa core peptide, which is fully consistent with the amino acid sequence of the NOS backbone (Figure 2b). According to this correlation, five of the six cysteine residues within the core peptide are relevant to thiazole production. Furthermore, five of the six serine and threonine residues can be dehydrated to generate dehydroamino acids, in which two distant serine derivatives are assumed to participate in the formation of the central heterocycle to generate the 26-membered macrocyclic system. Because thiopeptides share a common genetic

Figure 1



Structures of representative thiopeptides and relevant ribosomally synthesized, post-translationally modified peptides (RiPPs). **(a)** Nosiheptide (NOS), nocathiacin I (NOC-I), thiocillin I (TCL-I) GE37468, and thiostrepton (TSR). **(b)** Goadsporin. **(c)** Microcin B17, patellamide A, and nisin A. The key structure features for each molecule are highlighted in color.