Biochimica et Biophysica Acta 1854 (2015) 1054–1070

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbapap

Review

Breaking a pathogen's iron will: Inhibiting siderophore production as an antimicrobial strategy

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ARTICLE INFO

Article history:
Received 3 April 2015
Received in revised form 29 April 2015
Accepted 6 May 2015
Available online 10 May 2015

Keywords:
Siderophore
Nonribosomal peptide synthetase
Polyketide synthase
NRPS-independent synthetase

ABSTRACT

The rise of antibiotic resistance is a growing public health crisis. Novel antimicrobials are sought, preferably developing nontraditional chemical scaffolds that do not inhibit standard targets such as cell wall synthesis or the ribosome. Iron scavenging has been proposed as a viable target, because bacterial and fungal pathogens must overcome the nutritional immunity of the host to be virulent. This review highlights the recent work toward exploiting the biosynthetic enzymes of siderophore production for the design of next generation antimicrobials.

1. Introduction

Antibiotic resistance is of major concern, and novel therapies are in urgent need to combat this growing health crisis. In response to the United States Presidential Executive Order to combat antibiotic resistant bacteria [1], the Centers for Disease Control and Prevention have announced the Antibiotic Resistance Solutions Initiative [2]. The World Health Organization is drafting a Global Action Plan on antimicrobial resistance [3]. These national and international proposals include plans for promoting awareness and education of the problem, directives for improved antibiotic stewardship, goals for prevention and response to outbreaks, and investment in the design of new antibiotics and diagnostics.

One viable mechanism for the development of novel antimicrobial agents is targeting bacterial pathways responsible for acquisition of essential nutrients [4]. Indeed, our defense systems against bacterial pathogens include "nutritional immunity" — withholding of nutrients [5]. Iron serves as an important cofactor for a variety of enzymes that perform crucial reactions, including roles in electron transfer, resistance to reactive oxygen intermediates, and RNA synthesis. Fe(III) is very insoluble and biologically inaccessible such that the concentration of free ferric iron available to pathogens in the human host ranges in estimation from 10^{-15} to 10^{-24} M [6,7], whereas a typical pathogenic bacterium requires ~1 μM iron for optimal growth [7]. In response, bacterial pathogens have developed a variety of systems to scavenge iron from the host, including methods to import hemoproteins and other iron binding proteins such as transferrin, and the use of hemophores, heme-scavenging molecules [5]. The focus of this review is the biosynthesis of low molecular weight iron chelators called siderophores. Bacteria synthesize, secrete, and then selectively take up the iron-loaded siderophore to colonize human tissues [8–10]. Siderophore biosynthetic enzymes frequently have no human homologues, making them attractive antimicrobial targets [11].

2. Siderophore biosynthesis

Compounds from primary metabolism serve as a source of building blocks to generate siderophore natural products with differing levels of complexity both chemically and biologically. Diagrams of the siderophores are included as they appear in the discussion, detailing their chemical simplicity (ex. pyochelin) or complexity (ex. pyoverdin). Siderophores sometimes do not only have roles in iron chelation, but can also have roles in other biological processes such as quorum sensing. To start our discussion, an overview of the biosynthetic process is provided. Bacterial pathogens synthesize siderophores using nonribosomal peptide synthetase (NRPS) enzymes, polyketide synthase (PKS) enzymes, and/or by NRPS independent siderophore (NIS) synthetase enzymes.

2.1. Nonribosomal peptide synthetase (NRPS) biosynthesis

Siderophores generated by NRPS enzymes are primarily composed of amino acids, including nonproteinogenic amino acids, linked by peptide bonds. Significant work in the field has detailed the mechanisms for peptide bond formation in NRPS enzymes, which are multidomain, multifunction assembly line enzymes (for excellent reviews, see [12,13]). In short, a module consists of a

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http://dx.doi.org/10.1016/j.bbapap.2015.05.001
1570-9639/

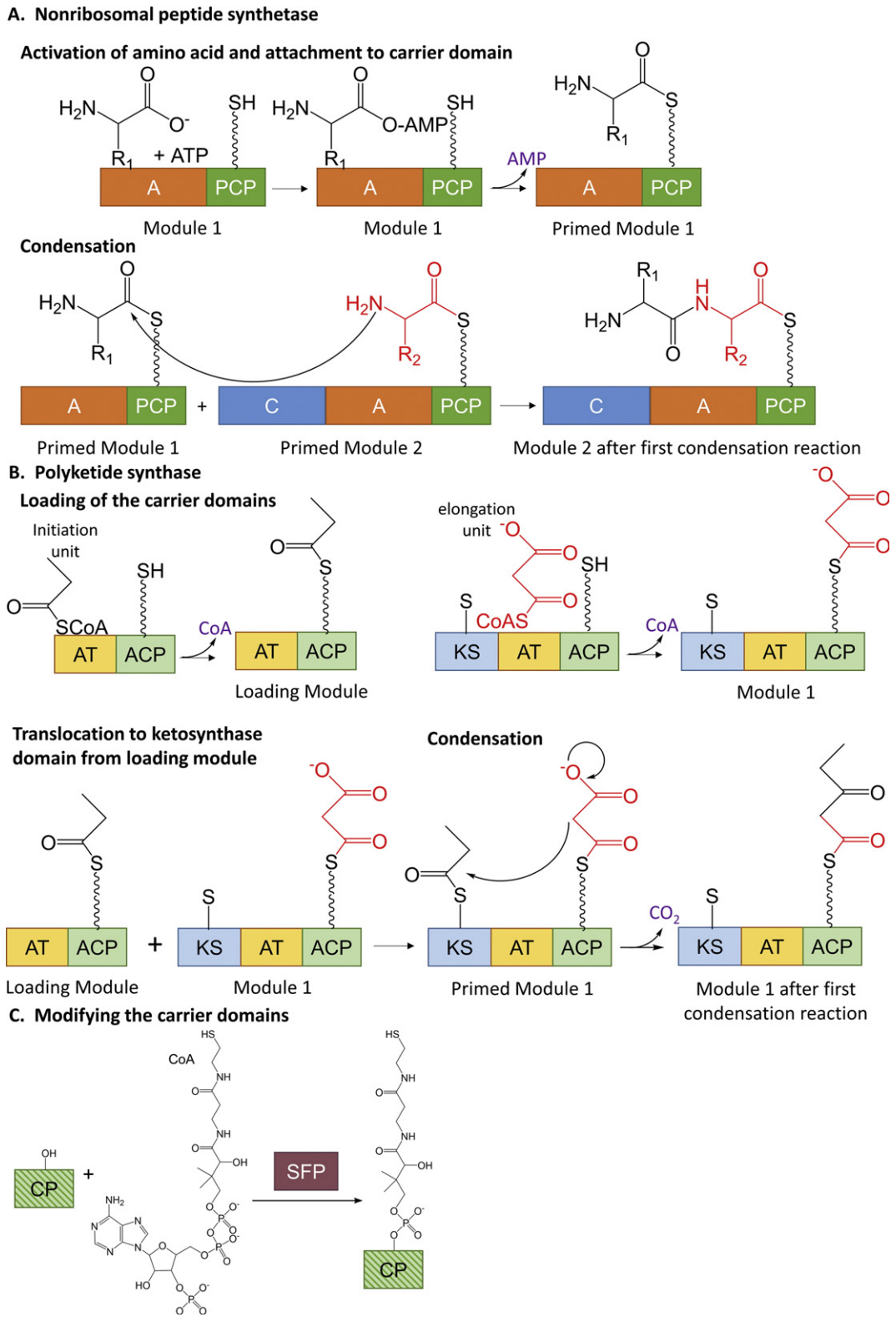

Fig. 1. Siderophore biosynthesis. A. Nonribosomal peptide synthetase chain elongation. The adenylation domain activates an amino acid and attaches it to the carrier domain, thereby priming the module (top line). The condensation domain forms a peptide bond between two primed modules (bottom line). The process continues with more modules in an assembly line fashion. A = adenylation, C = condensation and PCP = peptidyl carrier protein. The wavy line in the PCP domain denotes the phosphopantethienyl post-translational modification. B. Polyketide synthase bond formation. The acyl transferase domains load acyl groups onto the carrier domains of the loading module and module 1 (top). The acyl group from the loading module is transferred to the ketosynthase domain of module 1 thereby priming the module (bottom left). The ketosynthase domain performs the condensation reaction (bottom right). The growing chain is transferred to the ketosynthase domain of the next module for the assembly line to continue. AT = acyl transferase, ACP = acyl carrier protein and KS = ketosynthase. The wavy line in the ACP domain denotes the phosphopantethienyl post-translational modification. The short, straight line in the KS domain denotes an active site cysteine. C. Post translational modification of carrier domains to generate phosphopantetheinyl swinging arm. CP = carrier protein is striped in shades of green to represent that this is common to both NRPS (dark green) and PKS (light green) carrier domains. Sfp is a promiscuous PPTase from *Bacillus subtilis* commonly used to perform this reaction in vitro.