Different Effects of Acidic pH Shock on the Prodiginine Production in Streptomyces coelicolor M511 and SJM1 Mutants

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Prodiginines are a family of linear and cyclic oligopyrrole red-pigmented antibiotics that are produced by actinomycetes and other eubacteria [2]. Members of this class of antibiotics have been known for some time, as have their broad antifungal and antibacterial activities [17]. Recently, there has been a dramatic increase in interest in these natural products, as they have been reported to exhibit pronounced antimalarial, anticancer, and immunosuppressant activities [1, 4, 5]. A promising linear analog, PNU-156804, with improved immunosuppressant activity has been prepared [14], while another analog, GX15-070 (http://www.geminx.com), is currently undergoing phase II oncology trials [3]. Streptomyces coelicolor A3(2) has been known to generate the prodiginine antibiotics undecylprodiginine and a cyclized derivative, streptorubin B [2, 12, 13]. Over the last few years, research groups under the direction of Dr. Kevin Reynolds and Dr. Greg Challis have been studying prodiginine biosynthesis in S. coelicolor A3(2) [2, 12, 13]. This work has revealed that the 23 red genes in S. coelicolor A3(2) encode a fascinating and unusual pathway leading to the formation of undecylprodiginine and streptorubin B [2, 12, 13]. Two genes (redD and redZ) are known to encode the pathway-specific regulators in the cluster [18]. Prior to the initiation of this study, six genes (redX, redW, redU, redO, redN, and redM) were known to be required for the biosynthesis of 4-methoxy-2,2'-bipyrrrole-5-carboxaldehyde (MBC) [16], and four genes (redP, redQ, redR, and redL) were known to be involved in the biosynthesis of 2-undecylpyrrole (2-UP) [12, 13].

The biosynthesis of undecylprodiginine and streptorubin B is proposed as a bifurcated process involving the condensation of 2-UP and MBC (Fig. 1). Precursor incorporation experiments suggest that the 2-UP is generated by a decarboxylative casein-like condensation of glycine, with an acetate-
derived 3-ketomyristic acid derivative (Fig. 1). Initial analysis of the red gene cluster revealed redQ encoding an acyl carrier protein (ACP) and two genes, redP and redR, which encode homologs of the fatty acid biosynthetic enzymes FabH (3-ketoacyl-ACP synthase III) and FabF (3-ketoacyl-ACP synthase II), respectively [2, 12, 13]. It was proposed that RedP and RedR, in tandem with fatty acid biosynthetic enzymes that catalyze the conversion of 3-ketoacyl-ACP to acyl-ACP, were responsible for the formation of a RedQ-activated dodecanoic acid (Fig. 1) [12, 13]. The subsequent elaboration of dodecanoic acid to 2-UP was catalyzed by the RedK and RedL gene products [16]. The redH gene encoded a protein that was hypothesized to be responsible for the condensation of MBC and 2-UP to give undecylprodiginine [16], and the redG gene encoded a protein that was predicted to contain two domains, and has been shown to catalyze the oxidative carbocyclization of undecylprodiginine to streptorubin B (Fig. 1) [2]. In