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Aminoacyl-tRNA Synthetase (AaRS); a Promising target for antibiotic drugs

Abstract

Aminoacyl-tRNA synthetase (AaRs) enzymes are essentially critical in the biosynthesis of proteins. They catalyse the synthesis of the aminoacyl-tRNAs (aa-rRNA). There is a growing evidence that aminoacyl-tRNA synthetases could represent a broad target for antibiotics and antibacterial agents with the growing emergence of AaRs inhibitors like, Indolmycin (*which targets TrpRs*) Chuangxinmycin (*which targets ThrRs*) Granaticin (*which targets leuRs*) Furanomycin (*which targets IleRs*), Ochratoxin A (*which targets ProRS*), REP 8839 (*which targets metRS*) SB- 219383 (*which targets TyrRs*) and Mupirocin. Presently, mupirocin is the only commercially available antibiotic that inhibits bacterial AaRs, and it has proven to be a potent competitive inhibitor of Iso-Leucyl tRNA synthetase in *Staphylococcus aureus*. Despite the high potency, high and low level resistances have been reported in mupirocin clinical use as a result of acquired foreign gene (mupA) and point mutation respectively. The advent and structural modeling of mupirocin has served as a paradigm for the clinical development and deployment of some other AaRs. This work reviewed the prospect of AaRS inhibitors as a strong antibiotics.

Keywords: Aminoacyl-tRNA synthetase (AaRs), *Staphylococcus aureus* (*S. aureus*), aminoacyl-tRNAs (aa-rRNA)

Introduction

Aminoacyl-tRNA Synthetase (AaRS) enzymes have been a focus of recent research for antibacterial drug discovery. These enzymes play critical roles in protein biosynthesis by catalyzing the synthesis of aminoacyl-tRNAs (aa-rRNA). Once these enzymes are inhibited, protein biosynthesis is halted, which in turn results in attenuation of bacterial growth under both in vitro and infectious conditions. Consequently, these enzymes are interesting antibacterial drug targets. (Hurdle et al., 2005)

An important example of the clinical application of an AaRS inhibitor is provided by the antibiotic mupirocin (marketed as Bactroban). This selectively inactivates bacterial isoleucyl-tRNA Synthetase (IleRs). This product is currently the world's most widely used topical antibiotic for the control of MRSA methicillin resistance *staphylococcus aureus*. In recent years, compounds (both natural and synthetic) which inhibit AaRS have increased. While many of these new inhibitors also affect the counterpart human enzymes, there has been some success in identifying molecules that are specific for bacterial AaRS enzymes and that also exhibit antibacterial activities against several species in experimental infections (Gallant et al., 2000).