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Structures of Peptide Deformylase and Implication to Drug Development

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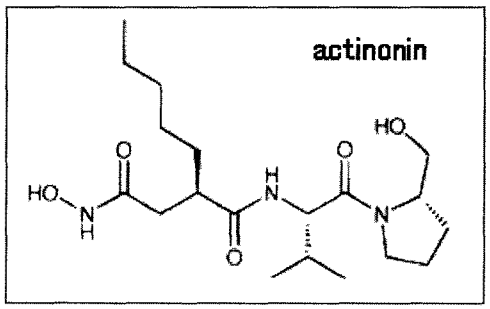
Introduction

Peptide deformylases (PDF, EC 3.5.1.88) are metalloproteases (Fe^{2+}) that cleave the N-terminal formyl groups from newly synthesized proteins, therefore important in protein processing. This activity has been proved to be essential for bacterial survival. There are some PDF homologues in animal and human, however, these are not functional on deformylation thus thought to be an ancestral remnant. For these reasons PDF has been receiving an increasing attention as a potential target in antimicrobial chemotherapy and several inhibitors have been reported. Number of these inhibitors mimic actinonin (see below), a naturally occurring hydroxamic acid pseudo-peptide that is known to be highly potent (K_i = 0.28 nM for *E. coli* PDF).



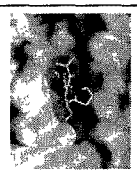
There have been several structural studies reported for PDFs from both Gram positive and Gram negative pathogens as well as the structures of PDF complexed with inhibitors providing a structural platform for the structure-based drug design of antibacterial agents. Despite the fact that PDFs exhibit rather low level of sequence similarity, they are classified into two types based on systematic search and analysis of bacterial genomes. We have examined a number of PDFs from major pathogens such as *Haemophilus influenzae, Bacillus cereus, Enterococcus faecalis, Streptococcus pyogens.*

Materials and Methods

Proteins were cloned, overexpressed, purified (>95% purity) and crystallized. The diffraction data on the apo and PDF-actinonin complex crystals were collected at 100 K using RAXIS IV++ image plate (Rigaku Corporation, Tokyo, Japan) mounted on a FR591 rotating anode operated at 50kV and 100mA with Confocal Maxflux Optics (MSC) and X-Tream^{TM} cryosystem (Rigaku Corporation, Tokyo, Japan), or using a Bruker Axs Proteum300 CCD detector (Madison, WI, USA) at the 6B beamline of Pohang Light Source, Pohang Korea. The raw data were processed and scaled using the program HKL 2000 (Otwinowski & Minor, 1997). All structures were using CNS and model building was carried out with the program O. All non-glycine residues are located within the allowed regions in Ramachandran plot in both structures.

Results and Discussion

The final structures are shown below and the details of the structures and the implication to drug development will be discussed.

	H. influenzae	*B. cereus*	*S. pyogenes*	*E. faecalis*
Native				
	2.6 Å	1.44 Å	2.5 Å	1.2 Å
Actinonin complex				
	2.5 Å	2.0 Å	1.8 Å	1.45 Å

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