

Sampling the conformational states involved in the slow tight-binding of a drug to a therapeutic target

Thierry Meinnel, Sonia Fieulaine & Carmela Giglione

¹ *Institut des Sciences du Végétal, UPR2355, Centre National de la Recherche Scientifique, Bâtiment 23, 1 avenue de la Terrasse, F-91198 Gif-sur-Yvette cedex, France.*

Peptide deformylase (PDF) is a well-recognized pharmaceutical target¹ with a large panel of applications in anti-infective and anticancer therapies. The past decade revealed the details of the catalytic mechanism thanks (i) to a number of data derived from 3D structure analysis and (ii) kinetic studies of site-directed variants¹. PDF uses a catalytic cation and the side-chains of the conserved residues of three short motifs to perform the reaction². Motif 3 includes the HEXXH motif of the metalloprotease family including collagenases and thermolysin. More recent analysis was aimed at selecting specific inhibitors. The data highlighted the various possible ways to inhibit the enzyme and for a compound to act as potent drug³. Compounds with peptide mimicry such as actinonin⁴ and heterocyclic compounds could be identified using a variety of screenings^{5,6}. The most potent compounds showed slow-tight binding^{7,8}. This mode-of-action is similar to many drugs already on the market inhibiting other targets. The structural basis of this effect – which increases the activity and promotes post-antibiotic effect - could not be established at the time. Peptide deformylases can be classified according two main types, Type-I and Type-II⁹. Recently, the three dimensional structure of a new Type-I PDF model could be solved. 1.3-2.0 Å resolution structures were obtained in complex with several specific inhibitors including actinonin. The structure of the free enzyme form turns out to be in an open conformation. Upon actinonin binding, the overall structure undergoes a considerable rearrangement with overall shrinkage resulting in trapping the inhibitor within the active site crevice. This conformational change makes other impossible interactions with the inhibitor through essentially one key residue of the enzyme. Using *Escherichia coli* PDF as an archetype of Type-1B PDF and NMR analysis, we could show that actinonin also induces overall conformational change of the enzyme with major effects occurring at the active site. The data provide the first insight into the slow, tight-binding mechanism of an inhibitor to PDF. The case of Type-II PDFs can be also discussed using new structural data. Finally, these data also provide valuable new information into the mechanism of action and enzymology of peptide deformylase.

References

1. Giglione, Pierre, & Meinnel, Mol. Microbiol., 2000. **36**: 1197-205.
2. Meinnel, et al., J. Mol. Biol., 1997. **267**: 749-61.
3. Boularot, et al., Curr. Opin. Investig. Drugs, 2004. **5**: 809-22.
4. Chen, et al., Biochemistry, 2000. **39**: 1256-62.
5. Apfel, et al., J. Med. Chem., 2001. **44**: 1847-52.
6. Hu, et al., J. Med. Chem., 2004. **47**: 4941-9.
7. Van Aller, et al., Biochemistry, 2005. **44**: 253-60.
8. Boularot, et al., J. Med. Chem., 2007. **50**: 10-20.
9. Giglione, Boularot, & Meinnel, Cell. Mol. Life Sci., 2004. **61**: 1455-74.