MS16.P56


Structural basis for inhibiting human tankyrases
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Poly (ADP-ribose) polymerases (PARPs) are enzymes that catalyze a covalent post-translational modification of proteins. PARPs attach ADP-ribose units from NAD+ to glutamate and lysine residues of the target molecule or to the growing chain of poly (ADP-ribose). These enzymes are involved in important cellular functions like DNA damage detection and repair, transcriptional regulation, intracellular trafficking, chromatin modification and cell death.

Tankyrases form a subfamily of human PARPs. They are also known as TRF1 (telomeric repeat binding factor)-interacting ankyrin related ADP ribose polymerases 1 & 2 [1]. Tankyrases are multidomain proteins having four distinct characteristics domains: HPS domain, ankyrin repeat domain with an unknown function, 24 ankyrin repeats involved in the protein-protein interactions, SAM (sterile-alpha motif) domain required for multimerization of tankyrase and a C-terminal PARP domain catalyzing poly(ADP-ribose) polymerization.

Tankyrases are potential drug targets for cancer and therefore efforts are ongoing within industry and academia to find potent inhibitors for it. The most evident benefits for inhibiting tankyrase are due to its functions Wnt signaling and in telomere homeostasis. Both of these are frequently misregulated in cancers leading to excessive Wnt signaling and subsequently accumulation of β-catenin, and elongated telomeres of cancer cells. Recently potent inhibitors for tankyrase were reported providing basis for development of drugs against tankyrases [2], [3].

We present a crystal structure of tankyrase 2 in complex with a highly potent and selective inhibitor. Most PARP inhibitors utilize the binding site of nicotinamide of NAD+. This is the first reported experimental complex structure of a PARP inhibitor not occupying that site. The structure reveals the plasticity of the NAD+ binding loop and it will create new strategies for inhibitor development for PARPs and especially for tankyrases.


Keywords: cancer, inhibitor, crystallography

MS16.P58


Structural studies of aspergillus fumigatus UDP-galactopyranosan mutase
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Drug resistant pathogens are a serious health problem, creating an urgent need for alternative antibiotics and antibiotic drug targets. One such target is UDP-galactopyranosan mutase (UGM). UGM is a flavoprotein that catalyzes the interconversion of UDP-galactopyranosan (UDP-Galp) to UDP-galactofuranosan (UDP-Galf); a precursor for the construction of Galf containing oligosaccharides. Galf is an essential component of the cell wall in bacteria, fungi and the cell surface matrix of protozoan parasites and appears to be essential for survival and virulence. Gene knock-out studies using Mycobacterium smegmatis (a model for M. tuberculosis) revealed that UGM is essential for the survival of the bacteria. A recent study in the protozoan parasite Leishmania major has shown that a UGM− strain is attenuated towards virulence [1]. The L.major knock-out strain is deficient in Galf-containing lipopolysaccharides (LPG) and expresses truncated glycosinolit-phospholipids (GIPLs). Furthermore, mice inoculated with the UGM- mutant didn’t develop lesion and are completely avirulent, indicating the importance of UGM for pathogenic survival and proliferation in mammals [1]. Work has also been done on A. niger and A. nidulans showing that Galf is important in Aspergillus. Deletion of the UGM gene dramatically attenuates virulence in Aspergillus. Since Galf is unique and UGM is not found in humans UGM is an interesting target for novel structure based drug design.

We are focusing on UGMs from eukaryotic pathogens from the fungus Aspergillus fumigatus (causes acute pneumonia and aspergillosis) and the protozoan parasite L. major (causes leishmaniasis). The eukaryotic enzymes share 51% sequence identity, but share only about 18% amino acid sequence identity to the prokaryotic UGMs [2]. We have solved the structure of L. major UGM (LmUGM) and used this structure to solve the Aspergillus fumigatus UGM (AuUGM) structure with and without substrate UDPGalp and inhibitor UDP. Despite low sequence identity with known prokaryotic UGMs the overall fold

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