Trapping conformational states of the SidA ornithine hydroxylase *in crystallo*

Aspergillus fumigatus is an opportunistic fungal pathogen which causes aspergillosis of the lungs. In order to grow, and cause disease, *A. fumigatus* produces siderophores to chelate and extract iron from the low iron environment in the lungs. SidA catalyzes the first step in the production of these siderophores, which is the N-hydroxylation of L-ornithine to form N5-hydroxy-L-ornithine. Inhibition of SidA results in significantly decreased levels of *A. fumigatus* growth.

Structural studies of SidA are being conducted to further understand the catalytic mechanism of SidA. SidA is a group B flavin dependent monooxygenase with a non-covalently bound FAD cofactor. FAD is reduced by NADPH before L-ornithine binding occurs. Molecular oxygen reacts with the reduced FAD to form a C4a-hydroperoxy flavin, which hydroxylates L-ornithine at its N5 position. $NADP^+$ remains bound throughout catalysis.

Information about the conformational changes involved upon cofactor and substrate binding and those throughout the catalytic cycle may be exploited to design potent inhibitors of SidA. A new crystal form of SidA in the $P2_1$ space group, shows a large rotation of the isoalloxazine group of FAD upon NADP(H) binding, which was unobserved in previous crystal forms. This rotation is independent of the oxidation state of FAD. Crystals in the oxidised state show weak ornithine density, whereas crystals in the reduced state show stronger ornithine density, suggesting inhibitors which are ornithine analogues may be observable in reduced crystals.

Further work is being conducted to observe the structure of SidA bound to the C4a-hydroperoxy flavin intermediate, and inhibitor bound structures.

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