Oxygen Diffusion Pathways in a Cofactor-Independent Oxygenase

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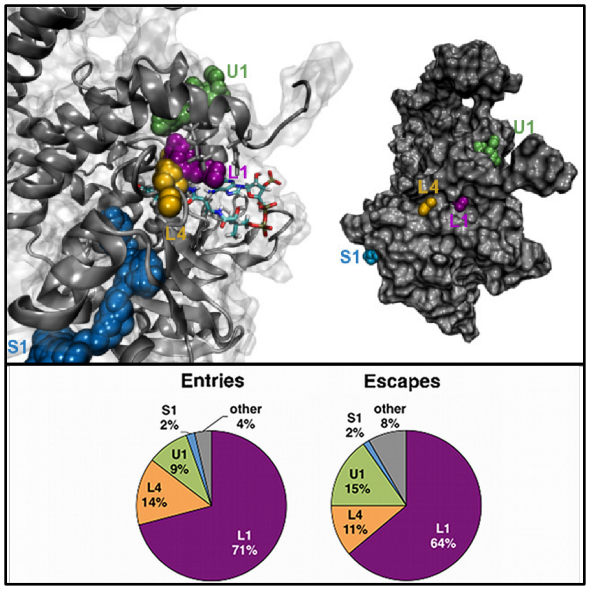

Learning how oxygen (O_2) reaches the active site of oxygen-using enzymes is critical to understanding how its reactivity is controlled.[1] Early studies suggested that O_2 diffused passively through proteins,[2] but this view conflicted with the known regio- and stereoselectivity of some reactions performed by oxygenases.[1] Recently, using a combination of computer simulations and experimental techniques, several studies suggested that O_2 diffuses through highly specific tunnels.[3] This work studies O_2 diffusion in DpgC, a cofactor-independent dioxygenase involved in the biosynthesis of vancomycin, a last-resort antibiotic.[4] Using Molecular Dynamics simulations we have found three main types of pathways, in agreement with xenon binding experiments. The pathway where O_2 enters between Phe432 and Lys428 (L1) accounts for the majority of the observed diffusion events, while the other pathways are observed with less frequency. We will validate these results by measuring the activity of different mutants expected to hinder or ease the diffusion of O_2.

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