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**Substrate-assisted in Oxygen Activation by Cytochrome P450 158A2: A New Mechanism of Proton Transfer.**

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CYP158A2 as well as other related P450s regarding CYP101A1 (Schlichting et al (2000) *Science* 287, 1615-1622, and Nagano et al (2005) *J. Biol. Chem.* 280, 31659-31663) and CYP107A1 (Nagano et al (2005) *J. Biol. Chem.* 280, 22101-22107) have solved the X-ray crystal structure of the ferrous-dioxygen bound P450s at high resolution, revealing the structural basis for proton transfer and dioxygen activation in P450s. The ferric substrate analog complex and the unique short-lived intermediate ferrous-dioxygen complex structures identify the role of active site water molecules that are critical for proton transfer during catalytic cycle, which are supported by biochemical studies. This has important implications not only for understanding the structural basis of a proton transfer pathway for oxygen activation via water molecules in CYP158A2 but also classifying two classes of P450s based on the pathway of proton transfer, one self-assisted enzyme involving the highly conserved threonine in the I-helix (CYP101A1) and the substrate-assisted enzyme requiring the substrate molecules either to directly transfer protons (CYP107A1) or to stabilize a water pathway for proton transfer (CYP158A2).