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Mechanistic studies of the role of a conserved histidine in a mammalian polyamine oxidase

Polyamine oxidases are peroxisomal flavoproteins that catalyze the oxidation of an *endo* carbon nitrogen bond of N1-acetylspermine in the catabolism of polyamines. While no structure has been reported for a mammalian polyamine oxidase, sequence alignments of polyamine oxidizing flavoproteins identify a conserved histidine residue. Based on the structure of a yeast polyamine oxidase, Saccharomyces cerevisiae Fms1, this residue has been proposed to hydrogen bond to the reactive nitrogen in the polyamine substrate. The corresponding histidine in mouse polyamine oxidase, His64, has been mutated to glutamine, asparagine, and alanine to determine if this residue plays a similar role in the mammalian enzymes. The kinetics of the mutant enzymes were examined with N1-acetylspermine and the slow substrates spermine and N,N'-dibenzyl-1,4-diaminobutane. On average the mutations result in a decrease of ~15- fold in the rate constant for amine oxidation. Rapid-reaction kinetic analyses established that amine oxidation is rate-limiting with spermine as substrate for the wild-type and mutant enzymes and for the H64N enzyme with N1-acetylspermine as substrate. The k_{cat}/K_{O2} value was unaffected by the mutations with N1-acetylspermine as substrate, but decreased ~55-fold with the two slower substrates. The results are consistent with this residue assisting in properly positioning the amine substrate for oxidation.

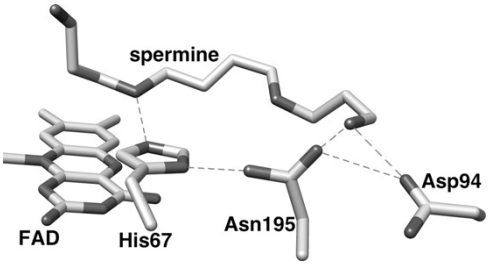

Figure 1: The active site of yeast Fms1 with spermine bound

Biography

José R Tormos has received a BS in Chemistry from the University of Sacred Heart in San Juan, Puerto Rico. He has earned his MS and PhD in Chemistry from the University of Iowa, where he worked on Cholinesterase Enzymes. As a Post-doctoral Research Fellow, he joined the Laboratory of Dr. Fitzpatrick in the Department of Biochemistry at the University of Texas Health Science Center at San Antonio, where he worked on flavoproteins nitroalkane oxidase and polyamine oxidase. After his post-doctoral appointment, he joined the Department of Chemistry and Biochemistry at St. Mary's University.

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