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Characterization of ferryl species in indoleamine 2,3-dioxygenase (IDO): Implications for catalysis

Ian M. Chrisman, Valeriy V. Smirnov

Indoleamine 2, 3-dioxygenase (IDO) is a type-*b* heme enzyme responsible for catalyzing the reaction of molecular oxygen and L-tryptophan to form N-formyl-L-kynurenine (NFK). The formation of NFK is the rate limiting step in the niacin pathway which is theorized to be the predominant metabolic pathway for L-tryptophan. Overexpression of this enzyme has been implicated heavily in cancer immune evasion and tumorigenesis. This effect occurs through multiple pathways, predominantly the depletion of L-tryptophan in naïve CD4⁺ immune cells which leads to apoptosis, and efflux of kynurenines which will cause differentiation of these cells into T_{reg} cells which deactivate the local immune system. Despite extensive research into the area the exact mechanism of IDO catalysis has yet to be elucidated. If this mechanism was to be fully elucidated it would be of great use in determining novel inhibitors which would be more efficacious than the currently used 1-methyl-L-tryptophan. The commonly accepted putative pathway of catalysis proposes that IDO utilizes a neutral ferryl complex as a reactive intermediate. This neutral ferryl complex commonly arises in heme enzymes through a single electron reduction of a ferryl radical cation. In this presentation we characterize these ferryl intermediates, through the use of stopped-flow spectrophotometry and electron paramagnetic resonance (EPR) spectrometry. In an *in vitro* assay with *meta*-chloroperoxybenzoic acid (mCPBA) this ferryl radical cation is observed to have a half-life of approximately seven milliseconds. This single electron transfer to the ferryl radical cation is highly favorable with an empirically determined electronic coupling factor of $1.63 \times 10^{11} \text{ s}^{-1}$. In contrast, the half-life of the neutral ferryl complex generated from ferrous IDO has a half-life of 506 milliseconds. Compared to a single turnover of 143 milliseconds, measured at similar pH, such disparate half-lives for the ferryl intermediates may indicate that the reaction pathway is likely to proceed through a different mechanism than the hypothesized computational two-step models.