Oxygen Activation by the α-Ketoglutarate-Dependent Dioxygenases

John C. Price,[a] Lee M. Hoffart,[a] Nina Svensen,[a] Eric W. Barr,[a] Jessica H. Brehm,[c] Pamela J. Riggs-Gelasco,[c] Michael T. Green,[b] J. Martin Bollinger, Jr.,[a,b] and Carsten Krebs[a,b]

[a]Department of Biochemistry and Molecular Biology and [b]Department of Chemistry, The Pennsylvania State University, University Park, PA 16802, [c]Department of Chemistry and Biochemistry, College of Charleston, Charleston, SC 29424

The Fe(II) and α-ketoglutarate-dependent dioxygenases couple the activation of dioxygen at a mononuclear non-heme Fe-center to the hydroxylation of their substrates and the decarboxylation of α-ketoglutarate. These enzymes catalyze many biologically important reactions. It is believed that these enzymes operate by a common molecular mechanism, and several intermediates have been proposed in their oxygen activation reactions. Although there is a wealth of experimental evidence for the validity of this mechanism, none of the postulated reaction intermediates was directly detected until 2003.

Recently, we began studying the oxygen activation reaction of one member of this enzyme family, taurine:α-ketoglutarate dioxygenase (TauD), using a combination of kinetic and spectroscopic methods, and identified a novel reaction intermediate, termed **J**. We demonstrated that **J** contains a formally Fe(IV) center in the high-spin configuration ($S = 2$). Moreover, the use of deuterated substrate revealed a large kinetic isotope effect ($k_H/k_D \approx 35$) on the decay of **J**, suggesting that **J** activates the aliphatic C-H bond by H-atom abstraction and that it is a Fe(IV)=O species. The presence of a Fe(IV)=O unit is corroborated by detection of a short, 1.62 Å interaction between the Fe and one of its ligands by EXAFS spectroscopy. DFT calculations suggest that **J** may have a trigonal bipyramidal geometry, with an axial oxo ligand.

In this lecture, new findings on the mechanism of oxygen activation by the α-ketoglutarate-dependent dioxygenases ongoing in our groups will be presented.