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Structural biology of redox partner binding: Simple and complicated

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Abstract

While the yeast cytochrome c peroxidase-cytc. system has been a paradigm for biological electron transfer (ET) reactions, a homologous system from Leishmania major (LmP-cytc) has proven to be somewhat simpler thus enabling more detailed enzymological and computational studies. The kinetic solvent isotope effect indicates that the rate limiting step involves proton transfer to the ferryl O atom in the reduction of Compound II. This information together with a neutron diffraction structure of Compound I (1) and computational studies on the pKa of active site groups (2) has provided deeper insights into the peroxidase mechanism. Since the association between LmP and cytc is relatively simple and does not involve major structural changes, it has been possible to use molecular dynamics to study the dissociation process. This, together with previous Brownian dynamics (3), supports the so-called “bind-and-crawl” mechanism wherein a very rapid non-specific complex forms which is followed by a rapid 2-dimensional search until the cytc settles on to the electron transfer active site on LmP. In sharp contrast, the interaction between P450s and their respective redox partners can, in some cases, require significant structural changes. In the P450cam system, the binding of its 2Fe2S redox partner (Pdx) results in structural changes that arms the catalytic machinery required for proton coupled electron transfer. Only Pdx can serve this function. A major challenge is to understand why there is such a level of selectivity, what the biological advantage of such selectivity might be, and whether or not other P450s exhibit a similar level of direct redox partner involvement on O2 activation.