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Investigating the Impact of Active Site Mutations on the Oxidoreductase Activity of Protein Disulfide Isomerase

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Protein disulfide isomerase (PDI) is a five-domain protein-thiol oxidoreductase part of the thioredoxin superfamily of enzymes. PDI is primarily localized in the endoplasmic reticulum of eukaryotic cells, but may be found to be secreted from cells as well as on cell surfaces. Physiologically, PDI plays important roles in proper protein folding as well as such processes as nitric oxide transport in vasculature. Its catalytic activities include redox state-dependent chaperone activity, disulfide isomerization, and thiol-disulfide redox. Of particular importance to this work is the oxidoreductase activity of PDI mediated by the *a* and *a'* domains, each of which contains a -CXXC- active site motif. Recently described is the potential catalytic role of a neighbouring lysine residue, extending this motif to be recognized as -CXXCK-. The current study is to investigate the impact of active site point mutations of these lysine residues of interest via substitutions to glutamic acid. Kinetic studies will be performed using the fluorogenic probe diosin glutathione disulfide, a pseudo-substrate for PDI. Deviations from wild type should give indications as to the catalytic role of a neighbouring lysine residue in its proposed ability to enhance the nucleophilicity of the respective cysteine. This may add to the mechanistic insight to both PDI's oxidoreductase activity as well as its potential regulation.