# A PDI-catalyzed thiol-disulfide switch regulates the production of hydrogen peroxide by human Ero1



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Oxidative folding in the endoplasmic reticulum (ER) involves ER oxidoreductin 1 (Ero1)-mediated disulfide formation in protein disulfide isomerase (PDI). In this process, Ero1 consumes oxygen ($O_2$) and releases hydrogen peroxide ($H_2O_2$), but none of the published Ero1 crystal structures reveal any potential pathway for entry and exit of these reactants. We report that additional mutation of the Cys(208)-Cys(241) disulfide in hyperactive Ero1$\alpha$ (Ero1$\alpha$-C104A/C131A) potentiates $H_2O_2$ production, ER oxidation, and cell toxicity. This disulfide clamps two helices that seal the flavin cofactor where $O_2$ is reduced to $H_2O_2$. Through its carboxyterminal active site, PDI unlocks this seal by forming a Cys(208)/Cys(241)-dependent mixed-disulfide complex with Ero1$\alpha$. The $H_2O_2$-detoxifying glutathione peroxidase 8 also binds to the Cys(208)/Cys(241) loop region. Supported by $O_2$ diffusion simulations, these data describe the first enzymatically controlled $O_2$ access into a flavoprotein active site, provide molecular-level understanding of Ero1$\alpha$ regulation and $H_2O_2$ production/detoxification, and establish the deleterious consequences of constitutive Ero1 activity.
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