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Novel structural observations in mammalian heme peroxidases

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Mammalian heme peroxidases including lactoperoxidase (LPO), myeloperoxidase (MPO), eosinophil peroxidase (EPO) and thyroid peroxidase (TPO) contain a covalently linked heme moiety. It has been generally believed that the heme group is fully cross-linked to protein molecule through at least two ester linkages involving conserved glutamate and aspartate residues with 1-methyl and 5-methyl groups of pyrrole rings A and C respectively. In MPO, an additional sulfonium ion linkage is present between 2-vinyl group of pyrrole ring A of the heme moiety and a methionine residue of the protein. There are additional interactions between protein molecule and prosthetic heme group which further stabilize the association. These linkages are formed through a self processing mechanism. Our recent structural studies have revealed that the covalent linkage involving glutamate and 1-methyl group of pyrrole ring of heme moiety is partially formed. When the glutamate is not covalently linked to heme moiety, its side chain occupies a position in the substrate binding site on the distal heme side thereby blocking the substrate binding site leading to the inactivation of LPO. Furthermore, the interaction of LPO with potassium salts results in placing a potassium ion in the distal heme cavity resulting in distortion of propionic group as a result of coordination with potassium ion. This blocks the binding of substrates in the distal heme cavity. These multiple ways indicate that natural conditions are present when LPO/TPO/MPO/EPO can be inactivated leading to the loss of physiological functions.