Myeloperoxidase-catalyzed Modification of Lipoproteins: The quest for the Active Species

Christian Obinger, Johanna Stampler, Markus Auer and Paul G. Furtmüller
Department of Chemistry, Division of Biochemistry, BOKU – University of Natural Resources and Applied Life Sciences, Muthgasse 18, A-1190 Vienna, Austria,
christian.obinger@boku.ac.at

Myeloperoxidase (MPO) is a member of the recently proposed peroxidasecyclooxygenase superfamily and is stored within the azurophilic granules of leukocytes. The heme enzyme is found within circulating neutrophils, monocytes and some tissue macrophage populations and is part of the innate immune defense system. The catalytic activity of MPO results in the generation of various reactive oxidants and diffusible radical species that play an important role in killing invading pathogens and parasites. However, these MPO-derived reactive oxidants can also promote host tissue injury via post-translational protein modifications and radical-mediated lipid peroxidation. Accumulating evidence suggests that MPO participates in a wide range of chronic inflammatory diseases and mediates the generation of proatherogenic low- and high density lipoproteins, apparently via modification of the lipid moiety of these particles.

Here, based on the known structure and peculiar enzymatic properties of MPO, we propose a mechanism of halide and nitrite oxidation and discuss the chemical nature of the resulting oxidants immediately after formation at the active site as well as after release from the protein. Typical MPO-mediated halogenation, nitration and/or oxidation reactions with biological targets (e.g. lipids or lipoproteins) are shown. Based on steadystate and presteady-state kinetic investigations, a mechanism of peroxidase mediated chlorination and oxidation with model target molecules of varying molar size is presented. Obtained data will be discussed with respect to the proposed role of MPO in the modification of lipids and lipoproteins *in vivo*.