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Review

Origin, structure, and biological activities of peroxidases in human saliva

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Abstract

Human whole saliva contains two peroxidases, salivary peroxidase (hSPO) and myeloperoxidase (hMPO), which are part of the innate host defence in oral cavity. Both hSPO as well as human milk lactoperoxidase (hLPO) are coded by the same gene, but to what extent the different producing glands, salivary and mammary glands, affect the final conformation of the enzymes is not known. In human saliva the major function of hSPO and hMPO is to catalyze the oxidation of thiocyanate (SCN^-) in the presence of hydrogen peroxide (H_2O_2) resulting in end products of wide antimicrobial potential. In addition cytotoxic H_2O_2 is degraded. Similar peroxidation reactions inactivate some mutagenic and carcinogenic compounds, which suggests another protective mechanism of peroxidases in human saliva. Although being target of an active antimicrobial research, the structure–function relationships of hSPO are poorly known. However, recently published method for recombinant hSPO production offers new tools for those investigations.
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Origin, ontogeny, and secretion of salivary peroxidases

Peroxidase activity is found in human exocrine secretions including tears, milk, and saliva as well as vaginal fluid [1]. Studies on peroxidase activity in human saliva have focused mainly on its antimicrobial activity and less interest has been paid on other possible protective mechanisms or structure–function relationship.

Human whole saliva is a mixed fluid comprising secretions from major and minor salivary glands, a serum-derived transudation from gingival crevices as well as components from oral microorganisms, leukocytes, and epithelial cells. In this complex milieu two main sources of peroxidase activity exist: major salivary glands and polymorphonuclear leukocytes (PMNs)[1] [2,3]. The "true" human salivary peroxidase (hSPO) is secreted from the acini of human parotid and submandibular glands [4] and therefore its daily output well reflects the total secretion of stimulated saliva. Salivary gland-derived hSPO is both structurally and catalytically rather similar, but not identical [5], to bovine milk lactoperoxidase (bLPO). In contrast, hSPO and human milk lactoperoxidase (hLPO) are coded by the same gene [6] and are likely to be identical. In this article, however, we call salivary enzyme as hSPO and milk peroxidase as hLPO since no data of their full identity, e.g., in catalytic properties exist, nor do we know how their biological activities are possibly modified by the producing glands and the fluid where they exist. However, due to many similarities particularly bLPO has served as a good model to study peroxidase-mediated reactions against oral microorganisms.

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[1] *Abbreviations used:* PMNs, polymorphonuclear leukocytes; hSPO, human salivary peroxidase; bLPO, bovine milk lactoperoxidase; hLPO, human milk lactoperoxidase; hMPO, human myeloperoxidase; NO_2^-, nitrite; NO_3^-, nitrate.

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A considerable proportion of total peroxidase activity in human mixed saliva is derived from PMNs and therefore represents human myeloperoxidase (hMPO) [3]. The proportion of hMPO varies as a consequence of gingival inflammation—the higher the inflammation rate, the higher the amount of blood-derived PMNs which in hypotonic saliva release their content of hMPO. In fact, specific hMPO assays have been used to mark the clinical status of human gingival health [7]. Among healthy adults the total concentration of hSPO and hMPO in stimulated whole saliva ranges 2–13 μg/ml [1], the major proportion often being hMPO [3].

Salivary peroxidase(s) are often referred as an important part of mucosal innate defence system [1]. This is supported by observations that hSPO is secreted already at early childhood, i.e., 2–6 months of age, at similar levels to adults [8,9]. In contrast, hMPO is present in whole saliva at very low levels before all teeth are fully erupted allowing leakage of PMNs into the oral milieu [9]. Adults tend to have more hMPO in whole saliva than fully dentate younger people since periodontal diseases with concomitant influx of PMNs (along with hMPO) into whole saliva [10] increase by age. No inborn deficiency of hSPO has yet been described, in contrast to hMPO.

Apart from aging, the only notable physiological factor to influence salivary peroxidase activities has been the variation in estrogen levels. Total peroxidase activity in human saliva fluctuates during menstrual cycles with peak values a few days before ovulation [11,12]. Also, salivary total peroxidase activity parallels the increase of estrogen during pregnancy [13]. These phenomena are most likely related to the increased secretion of female sex steroid hormones into whole saliva during menstruation and pregnancy [14] and to the occurrence of specific estrogen receptors in human salivary glands [15,16], as well as possible estrogen responsive element in the hLPO gene promoter [6]. To what extent these fluctuations are due to hSPO and/or hMPO is not known.

By incubating saliva with enamel powder, it has been detected that peroxidases are capable of binding irreversibly to human enamel in an enzymatically active conformation [17]. In vitro peroxidase-mediated reactions, assessed by consumption of H_2O_2, are even enhanced on enamel surfaces compared to human whole saliva [18]. Peroxidase activity has been detected also in dental plaque [19] and in salivary pellicles formed on denture based materials [20].

Structure and genetic polymorphism of salivary peroxidase

The gene coding for hSPO has been cloned and sequenced in 1996 [21] and a year later the cDNA sequence of hLPO was reported [6]. These two sequences are almost identical, and southern hybridization of human genomic DNA indicated the presence of only single LPO gene in human haploid genome [6]. Thus, the hSPO and hLPO were suggested to be coded by the same gene located in chromosome 17. The gene for hLPO is oriented tail-to-tail with the myeloperoxidase (hMPO) gene and they are separated with only 2.5 kb [6]. Together with the eosinophil peroxidase (hEPX) gene, these peroxidases form a gene cluster spanning a region of 90 kb. In addition, the three peroxidases have very similar intron–exon structure, suggesting that the genes are arised from the amplification of a common ancestor gene in the locus. No similarity, however, has been found in the promoter region of the hLPO and the other peroxidases, which is in accordance to the different expression patterns of these proteins. At the amino acid level, hLPO gene product shares 51% homology with the two other human peroxidases, hMPO and hEPX, while the homology with the thyroid peroxidase is only 41%. The highest similarity (83%) to hLPO is, however, found with bLPO [6].

All these peroxidases belong to the myeloperoxidase protein family. A comprehensive phylogenetic study of the myeloperoxidase family has recently been published [22], suggesting that in addition to mammalian peroxidases also enzymes from plants and bacteria can be grouped into this family. All these peroxidases are heme-containing enzymes with structurally similar catalytic domain, with conserved active site amino acids. The structure and mechanisms of the active site is discussed in detail by Furtmüller et al. in this issue.

While hMPO is a homodimer, each subunit being composed of one light and one heavy chain, the hSPO is a monomer. When purified from saliva, hSPO is found to have a molecular weight of approximately 80 kDa. Sometimes, however, up to three protein bands with different mobility in SDS–gels have been reported [5]. Experimental data show that, in accordance to the four putative N-glycosylation and one O-glycosylation sites found in the sequence, the protein is glycosylated [5], and the different mobilities of purified proteins may refer to different glycoforms or to differential proteolytic processing [23]. The reported protein polymorphism of hSPO contains six one amino acid changes (T105I, A244T, R414Q, V421M, R514Q, I614T, D700N; NIEHs-SNPs, egp.gs.washington.edu). Such single amino acid changes in hMPO may result in hMPO deficiency [24], but no such effects are yet described to hSPO. Four of the amino acid substitutions in hSPO are relatively conservative (T105I, A244T, V421M, and D700N) and can be classified as tolerated/benign when analyzed (egp.gs.washington.edu). Thus, apparently they do not cause major effects on the protein structure or activity. Three substitutions (R414Q, R514Q, and I614T), however, can be classified as probably/possibly damaging/intolerant. For example, both of the Arg (R) residues are located in the structurally conserved region of the human peroxidases (Fig. 1), and the Arg^{382} of hMPO,

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