



Overview of Selenoprotein P: A Biomarker in the Pathogenesis of Psoriasis

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5621

ABSTRACT

Background: Psoriasis is an autoimmune and inflammatory skin disease affecting 2–4% of the global population. The pathogenesis of psoriasis is far from being elucidated. Psoriasis comorbidities constantly lead researchers to look for their newer predictive markers. Selenoproteins are produced in the liver and involved in defense against oxidative stress by taking part in oxidation-reduction reactions neutralizing reactive oxygen species (ROS). It is worth mentioning here that oxidative stress closely related with inflammation participates in the development of pathological processes in psoriasis. Selenoproteins may improve immune response, thanks to their anti-inflammatory, chemo preventive and antiviral properties. Many disorders seem to be related to selenoprotein metabolism, such as cardiovascular, endocrine, immune and neurological diseases. Selenoproteins has recently become a particular object of studies on its potential use as a predictor or biomarker of different disease prognosis, pointing to the divergent actions of SeP or even promoting the development of some diseases. The elevated concentration of SeP was reported in various cardiometabolic disorders, such as obesity, DM, non-alcoholic fatty liver disease and CVD, all closely related to psoriasis.

Key words: Psoriasis, Selenoproteins, Pathogenesis; Clinical applications;

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Introduction

Selenoproteins are defined by the presence in the polypeptides of at least one selenocysteine (Sec) residue, the 21st codon-encoded amino acid, and can be found in many kinds of organisms, from bacteria to mammals. The human genome encodes at least 25 selenoproteins, including well characterized glutathione peroxidases (GPxs) and thioredoxinreductases (TrxRs). Consistent with the high nucleophilic reactivity of a selenol group (-SeH) in Sec, compared to a thiol group (-SH) in cysteine (Cys), many selenoproteins exhibit redox-related enzymatic activities, with Sec residues at their catalytic centers^[1].

Selenium exerts various biological functions mainly as part of the selenium-containing proteins, selenoproteins, like glutathione peroxidases (GPxs) or thioredoxinreductases (TrxRs). GPxs are antioxidant enzymes that reduce ROS, such as hydrogen peroxide and lipid hydroperoxides. TrxRs catalyze the reduction of a wide range of substrates, including thioredoxin and protein disulfide isomerase. Selenium and selenoproteins regulate inflammation by altering eicosanoid production^[2].

Indeed, some of these selenoenzymes play essential roles in cellular reactive oxygen species (ROS)-scavenging systems. Thus, a well acknowledged primary function of the



selenoprotein family is the efficient protection of the body from such stresses, suggesting indispensable roles in maintaining cellular/tissue homeostasis^[1].

Selenoprotein P is a unique selenoprotein, possessing a large number of Sec residues (10 Sec codons in frame in human cDNA), whereas other members typically bear one. This feature confers SeP a function as the predominant and highly efficient carrier that delivers Sec to the whole body, especially to the brain and testis, serving as a cellular Se resource for the *de novo* synthesis of other essential selenoproteins^[1].

Together with its phospholipid peroxidase activity, SeP is therefore thought to play central roles in selenoprotein-mediated redox homeostasis.

Thus, low plasma SeP would disturb such redox balances and, in fact, is reported to be related to several diseases. On the other hand, recent studies have revealed that increased plasma SeP is also associated with other human disorders. Elevated SeP is not merely a consequence of, but has profound causal and/or promoting effects on, the progression of some diseases^[3].

In humans, the maximum *SELENOP* mRNA was found in liver, but with lesser expression levels in the small intestine, spleen, colon, gall bladder and other tissues. The biological significance of non-liver derived SeP remains controversial, but, especially under pathophysiological conditions, SeP is also reportedly produced in tissues other than liver^[1].

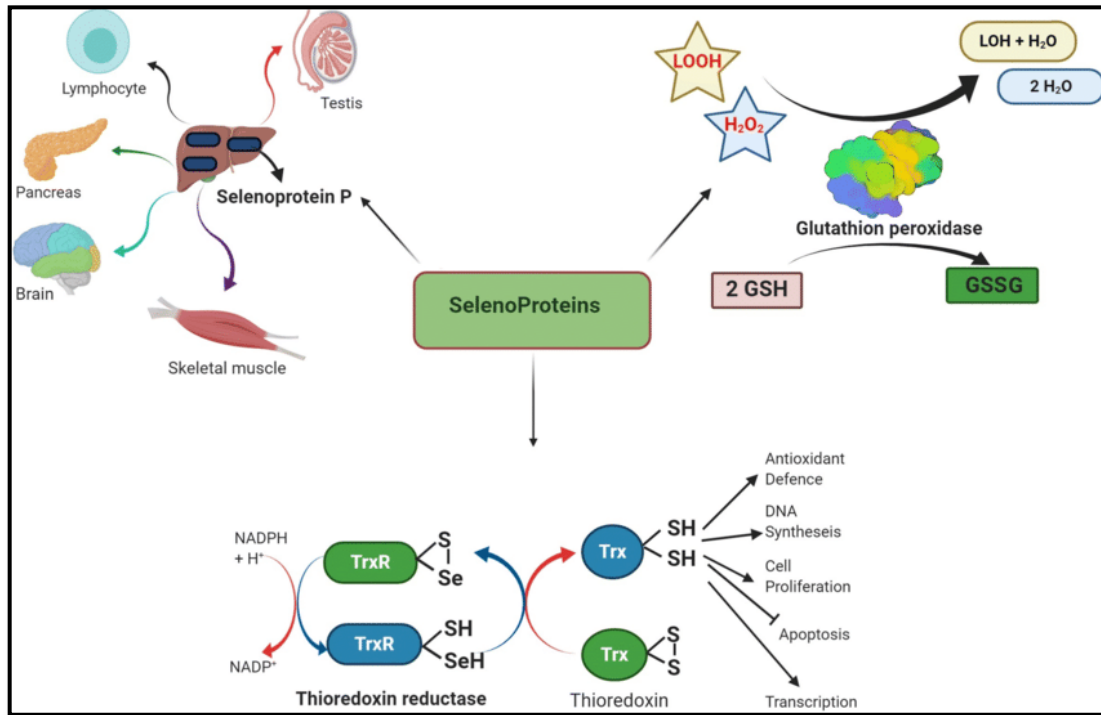
Pathophysiological functions of SeP:

From cell biological and biochemical points of view, there are still mysteries to be elucidated regarding the pathophysiological roles of SeP. One of these questions is why excess SeP causes such a variety of cellular reactions. In the context of T2DM, excess SeP results in insulin- or VEGF-resistance of hepatocytes and myocytes or of vascular endothelial cells, respectively, suppressing their mitogenic/survival signals such as the MAPK or AKT pathway^[4].

Contrarily, excess SeP promotes the proliferation and survival of smooth muscle cells in PAH, through aberrant activation of these pathways. Meanwhile, excess SeP induces pancreatic β cell death by an as yet unknown mechanism^[5].

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Figure(1): Examples of Selenoproteins and their functions in organisms. GSH: reduced glutathione, GSSG: oxidized glutathione, NADP: nicotinamide adenine dinucleotide phosphate^[6].

Clinical applications targeting SeP:

1. Selenoprotein P for prognoses of diseases:

Ooet al.^[7] have indicated that SeP is involved, sometimes causally, in diseases. Because of the relative ease in obtaining blood/plasma samples from human subjects, there are emerging attempts to utilize patients' plasma SeP level as one of the biomarkers for predictions or diagnoses/prognoses, possibly in combination with other markers. Plasma SeP concentration can predict a patient's insulin tolerance after 4 years, better than other indexes such as fasting blood glucose or HbA1c^[7].

For PAH patients, lower plasma SeP levels were significantly correlated with longer event-free survival. In addition, as noted above, given the association of lowered plasma SeP levels with human malignancies, SeP level could also be employed in early diagnoses and/or prognoses of cancer. A present technical obstacle, however, is that sensitivities and

accuracies of currently available assay methods/kits vary significantly. Therefore, a standardized method is needed to achieve the use of plasma SeP as a biomarker in clinical situations^[8].

Selenoprotein P expression was low in gastric adenocarcinoma tissues compared with control tissues and was related to the degree of gastric adenocarcinoma differentiation but not to TNM stage^[9].

2. Targeting SeP for prophylaxis and treatment:

Given that heterozygous deletion of the SeP allele in mice does not produce phenotypes with serious conditions, such as male infertility and neuronal deficiencies, which were seen in animals with homozygous deletion, the suppression of plasma SeP, even to half the basal level, could be a potential therapeutic strategy to ameliorate excess SeP-driven disorders without causing toxicity. Several approaches may be taken



to achieve the appropriate suppression of plasma SeP^[3].

High-throughput screening identified sanguinarine, a plant alkaloid, as a strong suppressor of *SELENOP* mRNA expression in PAH-PASMCs that has been shown to prevent hypoxia-induced pulmonary hypertension in model mice^[10].

Finally, Mita et al.^[5] reported a more direct approach, the injection of a SeP-neutralizing antibody to subjects, and indicated that this antibody-therapy ameliorated T2DM symptoms in model mice.

Selenium Deficiency and Psoriasis

The selenium concentration in psoriasis patients is lower than that of healthy individuals, but there are few studies on its role in the pathogenesis of the disease. An impaired antioxidant barrier in skin may result in a rise of free oxygen radicals in psoriatic plaques. Thionine may modulate immunologic mechanisms of the disease by increasing the number of CD4⁺ T cells in reticular dermis within psoriatic plaques^[11].

Previously published preliminary results of Serwin et al. showed that selenium concentration and selenium-dependent GSH-Px activity in erythrocytes are higher in males with psoriasis, lasting no longer than 10 years than in those with the disease lasting 3 years or more^[12].

Kadry and Rashed, using plasma and tissue samples from 20 patients with psoriasis and 10 healthy controls, investigated the levels of overexpression of osteopontin and selenium in psoriasis, and their relation to metabolic status in patients to identify a possible link between these markers and comorbidities observed. They observed that the plasma selenium levels were lower in patients with psoriasis than in controls and concluded that overexpression of

osteopontin and low plasma selenium levels are predictable factors for occurrence of psoriasis^[13].

reported low serum selenium levels in patients with psoriasis, and that treatment with thionine for 4 weeks failed to give a positive clinical response to topical treatment in these patients^[14].

Conclusion:

Selenoprotein P, particularly in cases of severe form or concurrent obesity, may be a potential predictor of inflammation and the development of metabolic problems in psoriatic patients. By suppressing SeP, conventional systemic medication helps lower the chance of comorbidities.

No conflict of interest.

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