Delineation of selenoproteins (GPx1 and GPx3) in immune response activity by protein-protein DOCKING

Nancy D1, P. Indra Arulesvi2*

1Research Scholar, Plant and Microbial Biotechnology Lab, Department of Biotechnology, School of Biosciences, Periyar University, Salem, Tamil Nadu, India
2Assistant Professor, Plant and Microbial Biotechnology Lab, Department of Biotechnology, School of Biosciences, Periyar University, Salem, Tamil Nadu, India
*Corresponding Author

Abstract

The desire of the mankind is to reside healthy in his lifetime. Nutritional research uncovers the secret to life-long health by good nutrition with optimum mineral concentrations. Among the micronutrients, interest in the biological impacts of selenium (Se) is escalating because of its essentiality for humans and animals, proved during the last decade researches. Selenium is required in a very narrow concentration and it varies based on the organism. Among the major 25 selenoproteins essential for human, assessment of GPx (Glutathione peroxidase) activity was done to emphasize its role in immune cell functioning. It measures the Se status of an individual indirectly. The interaction of GPx1 (2F8A) was studied with four different interacting proteins like 2XN9, 3CKK, 4NDM and 4MNH. The interaction of GPx3 (2R37) was studied with another four different interacting proteins like 2VLJ, 2VLR, 2X70 and 2XPG. The major interaction was obtained with MHC in T-cell activation, which enhances the immune responses for both the selenoproteins studied. The analysis of interaction activities of GPx1 and GPx3 by protein-protein DOCKING will aid a new way in treatment of various immune disorders and as immune booster, through selenium fortified products.

Keywords: Selenium, Selenoproteins, immune responses

INTRODUCTION

“The human wellness stems from eating nutritious, flavorful food”. The desire of the mankind is to reside healthy in his lifetime. For which, more than 22 mineral elements were required, which can be provided by the routine appropriate diet. Today’s most predominant; life threatening chronic diseases is linked with the nourishment. Five of the top ten issues facing humanity are specifically identified with diminishing nutrient supplement [1]. The simple truth may be that the susceptibility to disease is linked to either toxicity or nutritional deficiency. Nutritional research uncovers the secret to life-long health is good nutrition with optimum mineral concentrations. Among the micronutrients, interest in the biological impacts of selenium (Se) is escalating because of its essentiality for humans and animals, proved during the last decade researches. Selenium is required in a very narrow concentration and it varies based on the organism. In addition to its nutritional essentiality, Se has been implicated to reduce the incidence of debilitating disorders; such as male fertility, weakened immune function [2, 3], viral infection [4] and aging process [5]. There is evidence that less overt Se deficiency can lead to Keshan disease (fatal cardiomyopathy), kashin-beck disease, hypothyroidism, asthma and inflammatory conditions [6]. Normal level of Se in the foods is preferred even in pregnancy category and it is excreted in the breast milk [7]. Being a powerful natural antioxidant; it acts as immune-stimulator, cardioprotective and anti-carcinogenic [8]. The nutritional function of Se is fulfilled by the selenoenzymes/ selenoproteins such as glutathione peroxidase, thioredoxin reductase and iodothyronine 5'-deiodinase that are involved in various hormonal regulations [9]. Among the major 25 selenoproteins essential for human, assessment of GPx (Glutathione peroxidase) activity was done to
emphasize its role in immune cell functioning. It measures the Se status of an individual indirectly [10]. GPx3 and SeP selenoproteins are the commonly used markers, for assessment of Se status [11]. In which, glutathione peroxidase was reported to be mainly involved in T-cell activities. It has 8 isoforms, in which only 5 of them have SeCys residue and can catalyze \( \text{H}_2\text{O}_2 \) reduction. Based on Se incorporation, the relative biological importance was determined. It was denoted as GPx2 > GPx4 > GPx3 = GPx1. The analysis of interaction activities of GPx1 and GPx3 by protein-protein DOCKING will aid a new way in treatment of various immune disorders and as immune booster, through selenium fortified products. Among its family members, GPx1 is one of the most highly sensitive to changes in both Se status and oxidative stress conditions. But it appears that global protein synthesis is reduced under conditions of stress as a means of preserving cellular resources, and that GPx1 recovers rapidly compared to the other Se-proteins [12]. GPx2 is a secreted homotetrameric enzyme mainly expressed in the gastrointestinal system mucosa, including the squamous epithelium of the esophagus; and in humans, it is also detectable in the liver. GPx2 location and resistance suggest that this Se-protein may serve as a first line of defense in exposure to oxidative stress induced by ingested prooxidants or gut microbiota [13]. GPx3 is the only extracellular enzyme of the GPxs family. It is a glycosylated homotetrameric protein produced into the cells of the proximal tubular epithelium and in the parietal cells of Bowman’s capsule of the kidney. Part of GPx3 is then secreted into the plasma, where it constitutes approximately 15–20% of the total Se, but a major fraction remains bound to the basement membranes in kidneys [14]. Unlike GPx1, GPx3 presents more restricted hydroperoxide substrate specificity. Although its activity is 10 fold lower than the activity of GPx1. The binding of GPx3 to the basement membrane exposes the enzyme to higher levels of secreted GSH, thus increasing the activity of GPx3 at the basal extracellular aspect of epithelial cells [15]. As a whole, selenium participates in the immune response through several actions: it regulates the balance of activity in the eicosanoid synthesis pathways, leading to preferential synthesis of leukotrienes and prostacyclins over thromboxanes and prostaglandins, and down-regulates cytokine and adhesion molecule expression [14]. By up-regulation of the interleukin-2 receptor expression, it leads to enhanced activity of both T and B lymphocytes, natural killer and lymphokine activated killer cells [16].

**MATERIALS AND METHODS**

**Selenoproteins immune response analysis**

The selenoproteins that are mainly responsible for immune responses are GPx1 in erythrocytes and GPx3 in plasma. The protein ID for GPx1 and GPx3 were 2F8A and 2R37 respectively. The interaction of GPx1 (2F8A) was studied with four different interacting proteins like 2XN9, 3CCK, 4NDM and 4MNH. The interaction of GPx3 (2R37) was studied with another four different interacting proteins like 2VLJ, 2VLR, 2X70 and 2XPG. The details of the interacting proteins were given below (Table 1). The immune response was predicted by protein-protein docking by the software “Z DOCK in Accelrys Discovery Studio-3.5”. Based on the Z-score of the interactions, the major activities were explained for GPx1 and GPx3. Docking calculation was carried out on HP Intel® Xeon® processor E3-1200v2 family with 16Gb RAM, 1TB Hard disk, NVIDIA Quadro 2000 and windows 7 ultimate 64bit.

**RESULTS AND DISCUSSION**

The selenoproteins that are mainly responsible for immune responses are GPx1 in erythrocytes and GPx3 in plasma. The interaction of GPx1 (2F8A) was studied with 4 different proteins like 2XN9, 3CCK, 4NDM and 4MNH (Figure 1). The interaction of GPx3 (2R37) was studied with 4 different proteins like 2VLJ, 2VLR, 2X70 and 2XPG (Figure 2). Based on the Z-score of the interactions, GPx1 scored high with 2XN9 and GPx3 scored high with 2X70 (Table 2). It portrayed that the GPx1 protein activity is higher by complexion with MHC in T-cell activation. The GPx3 protein activity was higher with MHC class-I HLA bound T-cell activation. GPx1 mediated reactions are modulated by hydroperoxides, including cytokine signaling and apoptosis. Among its family members, GPx1 is highly sensitive to changes in both the Se status and the oxidative stress conditions [12].

Table 1: Protein details for DOCKING studies

<table>
<thead>
<tr>
<th>Protein</th>
<th>Interacting protein</th>
<th>Interacting/ Binding proteins details</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDB ID &amp; details</td>
<td>PDB ID</td>
<td></td>
</tr>
<tr>
<td>2F8A (GPx1- Glutathione peroxidase)</td>
<td>2XN9</td>
<td>Super antigenic complexed with MHC in T-cell activation.</td>
</tr>
<tr>
<td>In erythrocyte</td>
<td>3CCK</td>
<td>CD69 receptor- stimulates NK cell.</td>
</tr>
<tr>
<td></td>
<td>4NDM</td>
<td>MHC-like recognition for T-cell activation. Structure of AB18.1 TCR MHC - like recognition for T-cell activation. Structure of AB18.1 TCR</td>
</tr>
<tr>
<td></td>
<td>4MNH</td>
<td>MHC- like recognition of human γ- delta T-cells. Structure of DP10.7 TCR</td>
</tr>
<tr>
<td>2R37 (GPx3- Glutathione peroxidase)</td>
<td>2VLJ</td>
<td>Immunodominant T-cell receptor.</td>
</tr>
<tr>
<td>In plasma</td>
<td>2VLR</td>
<td>Immunodominant T-cell receptor.</td>
</tr>
<tr>
<td></td>
<td>2X70</td>
<td>MHC class- I HLA-A2 bound in T-cell activation.</td>
</tr>
<tr>
<td></td>
<td>2XPG</td>
<td>MHC class- I peptide complex in T-cell activation.</td>
</tr>
</tbody>
</table>

It rapidly recovers the protein synthesis under stress conditions. Unlike GPx1, GPx3 presents more restricted hydroperoxide substrate specificity [17]. Thus, glutathione peroxidase (GPx) and thioredoxin (TrxR) play complementary roles in the modulation of immune response. GPx limits the inflammatory response after TCR signaling [11].

Figure 1: Interaction analysis of GPx1-Glutathione peroxidase (2F8A)
**CONCLUSION**

The selenoproteins activity of GPx1 and GPx3 was elucidated by protein-protein DOCKING in particular to the immune responses. The interaction of GPx1 (2F8A) was studied with four different interacting proteins like 2XN9, 3CCK, 4NDM and 4MNH. The interaction of GPx3 (2R37) was studied with another four different interacting proteins like 2VLJ, 2VLR, 2X70 and 2XPG. The major interaction was obtained with MHC in T-cell activation, which enhances the immune responses for both the selenoproteins studied.

**ACKNOWLEDGEMENT**

We gratefully acknowledge the Periyar University, Tamil Nadu for the support rendered through the University Research Fellowship. We express our gratitude to the institutional incharges for providing space and the lab mates, for their immense help.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.
References


