Response of Selenium and Selenogenome in Immune Tissues to LPS-Induced Inflammatory Reactions in Pigs

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Abstract Circulating concentration of the essential trace element selenium (Se) was significantly lower in inflammatory disorders. Although Se plays physiological roles mainly through the function of 25 selenoproteins, the response of the selenogenome in immune tissues during inflammatory reactions remains unclear. The objective of this study was to determine the Se retention and selenogenome expression in immune tissues during the lipopolysaccharide (LPS)-induced inflammatory response in porcine. A total of 12 male pigs were randomly divided into two groups and injected with LPS or saline. After 4 h postinjection, blood samples were collected and pigs were euthanized. Pigs challenged with LPS had 36.8 and 16.6 % lower ($P < 0.05$) Se concentrations in the serum and spleen, respectively, than those injected with saline. Moreover, the activities of GPX decreased ($P < 0.05$) by 23.4, 26.6, and 30.4 % in the serum, thymus, and lymph node, respectively, in the pigs injected with LPS. Furthermore, the LPS challenge altered ($P < 0.05$) the mRNA expression of 14, 16, 10, and 6 selenoprotein genes in the liver, spleen, thymus, and lymph node, respectively. Along with 10 previously reported selenoprotein genes, the response of *Txnrd2*, *Txnrd3*, *Sep15*, *Selh*, *Seli*, *Seln*, *Selo*, *Selt*, *Selx*, and *Sephs2* to inflammatory reaction in immune tissues were newly illustrated in this study. In conclusion, the LPS-induced inflammatory response impaired Se metabolism and was associated with dysregulation of the selenogenome expression in immune tissues.

Keywords Selenium · Selenoprotein · LPS · Inflammatory reaction · Pigs

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Introduction

Selenium (Se) is an essential trace element for humans and animals. It plays pivotal roles in antioxidant defense, anticancer, detoxification, and improving immune function [1–5]. Numerous epidemiologic investigations and animal studies have shown inverse correlations between Se deficiency and inflammatory impairment, and lower serum Se status in inflammatory disorders with acute injury or trauma of tissues [6–10]. In contrast, supplementation of proper doses of Se can significantly alleviate and/or prevent the morbidity or mortality induced by inflammation in some clinical and animal studies [10–14]. In this regard, the retention and underlying molecular mechanism of Se in inflammatory response has recently gained increased attention.

A previous study has systematically investigated the retention of Se during the lipopolysaccharide (LPS)-induced acute phase response in rats, which found a significant decrease of Se content by 69.5 and 81.5 % in the plasma and liver, respectively [15]. While, the Se content was increased in the spleen, thymus, kidney, lung, heart, and muscle by LPS challenge, indicating that Se could play important roles in these tissues during an inflammatory response [15]. Since Se plays physiological roles mainly through the function of 25 selenoproteins that contain Se in the form of selenocysteine (Sec) [16, 17], understanding the response of selenogenome in

those immune tissues during the inflammatory response would be an important aspect. A recent study showed that the serum Se and selenoprotein P (Sepp1) concentrations declined in parallel by 50 and 61 % in mice after injection of LPS, which was associated with downregulation of the hepatic selenoprotein biosynthesis machinery [9]. Another in vitro experiment showed that the amount of TXNRD1 was substantially increased, whereas GPX1 was modestly decreased in LPS-treated macrophages [18]. Moreover, LPS treatment or Fcγ receptor stimulation of mouse macrophages increased expression of two endoplasmic reticulum (ER) selenoproteins, Selk and Sels [19, 20]. In general, many of these past studies were focused on a single or a few selenoproteins in the response of inflammation in cells or single immune tissue. However, little information is available on the responses of the whole selenogenome during the inflammatory response in human or higher animals. Since pigs are an excellent model for human nutrition and medicine [21], we selected pigs to determine the Se retention and whole selenogenome expression in immune tissues, including the liver, spleen, thymus, and lymph node, during the LPS challenge induced inflammatory response.

Materials and Methods

Piglets, Treatments, and Sample Collection

All procedures for this experiment were approved by the Animal Care and Use Committee of Hubei Province, China. A total of 12 male pigs (Duroc × Large White × Landrace; body weight at 18.4 ± 1.2 kg) were randomly allotted to two groups. Each group of pigs were treated with saline or LPS. The challenged group received an intraperitoneal injection with *E. coli* LPS (*E. coli* serotype 055:B5, Sigma Chemical) at 100 μg/kg BW, and the unchallenged group received an equivalent amount of sterile saline. The dose of LPS (100 μg/kg BW) was chosen according to our previous studies [22, 23], which showed increased expression of proinflammatory cytokines in the immune tissues of weaned pigs. Many studies have shown that, within 1~6 h postinjection, LPS activated the HPA axis and increased proinflammatory cytokine production in rats and pigs [22–25]. Thus, we used the time point of 4 h after LPS or saline treatment for experimental measurements in serum or tissues. Blood was collected from the anterior vena cava of pigs after 4 h of LPS injection. The serum was prepared by centrifugation at 3500×*g* for 10 min at 4 °C and stored at −80 °C until further analysis. After blood collection at 4 h, all pigs were humanely killed. The liver, spleen, thymus, and lymph node were collected, frozen immediately in liquid nitrogen, and then stored at −80 °C until analysis of mRNA abundance.

Se Concentrations and GPX Activity Analysis

The concentrations of Se in serum and tissues were measured by the hydride generation atomic fluorescence spectrometer (AF-610B, Beijing Rayleigh Analytical Instrument Corp., Beijing, China), against the standard reference of Se [GBW (E) 080441, National Research Center for Certified Reference Materials, Beijing, China] as previously described [14]. Total protein was extracted from 0.5 g liver tissue as previously described [26]. The activity of GPX was measured by a colorimetric method using specific assay kits (A005) from the Nanjing Jiancheng Bioengineering Institute of China. Protein concentrations were measured by the bicinchoninic acid assay [14].

Real-Time qPCR

Total RNA was prepared from the liver, spleen, thymus, and lymph node (20–50 mg tissue) using TRIzol (Invitrogen) and following the manufacturer's instructions. The quality and quantity of RNA were analyzed by an Agilent Bioanalyzer 2100 using an RNA 6000 Labchip kit (Agilent Technologies, Amstelveen, Netherlands). The cDNA was synthesized from 1 μg total RNA by using Super Script III reverse transcriptase (Invitrogen) and following the manufacturer's instructions. The mRNA levels of 25 selenoprotein genes were determined by qPCR (Bio-Rad CFX96 Touch) using the SYBRR Green PCR Master Mix (Bio-Rad, USA) and following the manufacturer's instructions. Primers (Supplemental Table 1) for the selenoprotein genes and reference gene *glyceraldehyde-3-phosphate dehydrogenase* (*GADPH*) were referenced from previous studies [27] and/or designed using Primer Express 3.0 (Applied Biosystems, Foster City, CA, USA). The 2^{-ddCt} method was used for the quantification with *GADPH* gene as a reference gene, and the relative abundance was normalized to the control (as 1).

Statistical Analysis

Data were analyzed using Student's *t* test by SPSS version 13 (Chicago, IL, USA). Data are presented as mean ± SE, and significance was set at $P < 0.05$.

Results

Se Concentrations and GPX Activities

After 4 h of treatment with LPS, the Se concentrations in the serum, liver, spleen, thymus, and lymph node was measured; the results are presented in Fig. 1. Compared to pigs treated with saline, the concentration of Se decreased ($P < 0.05$) by 36.8 and 16.6 % in the serum and spleen, respectively, in the
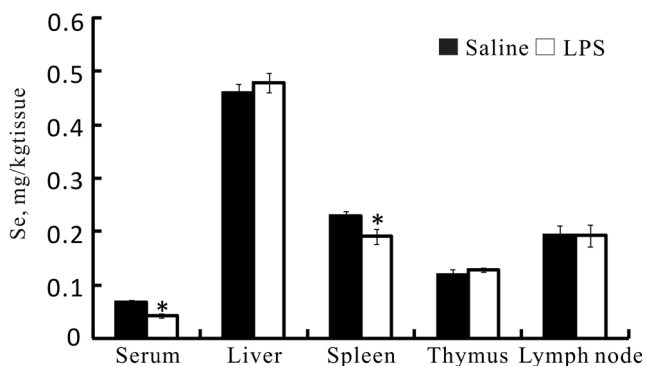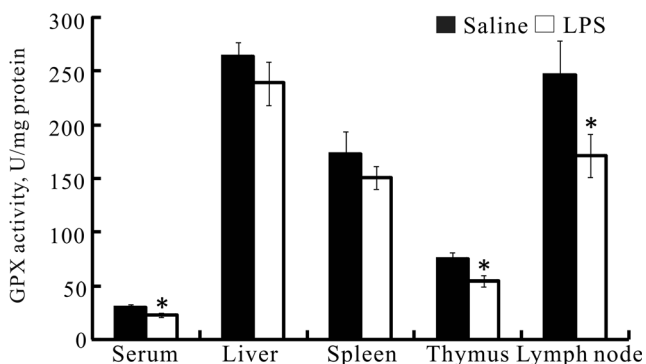
Fig. 1 Effects of LPS challenge on concentrations of Se in the serum, liver, spleen, thymus, and lymph node in pigs. Values are means ± SE, $n = 6$. *Labeled means with asterisk differ, $P < 0.05$*

pigs injected with LPS. However, the concentrations of Se in the liver, thymus, and lymph node of pigs were not significantly affected ($P > 0.05$) by the challenge of LPS (Fig. 1). Meanwhile, the results of activities of GPX in the serum, liver, spleen, thymus, and lymph node are displayed in Fig. 2. Relative to pigs treated with saline, the pigs injected with LPS led to decreased ($P < 0.05$) activities of GPX by 23.4, 26.6, and 30.4 % in the serum, thymus, and lymph node, respectively. However, no changes in GPX activity ($P > 0.05$) were seen in the liver and spleen after challenge with LPS (Fig. 2).

Liver mRNA Levels of Selenoprotein Genes

A total of 14 of the 25 assayed selenoprotein genes in the liver were affected by LPS challenge in pigs (Fig. 3). The results showed that the mRNA level of *Dio3* (599 %) was the greatest increased ($P < 0.05$), followed by *Dio2* (379 %), *Sels* (191 %), *Txnrd1* (122 %), *Seli* (88 %), and *Gpx1* (49 %) in the liver of pigs injected with LPS, when compared with those injected with saline. In contrast, pigs challenged with LPS had 45–77 % lower ($P < 0.05$) *Sepp1*, *Gpx2*, *Dio1*, *Txnrd2*, *Sephs*, *Selo*, *Selx*, and *Seln* mRNA abundance in the liver compared with those injected with saline.

Fig. 2 Effects of LPS challenge on activity of GPX in the serum, liver, spleen, thymus, and lymph node in pigs. Values are means ± SE, $n = 6$. *Labeled means with asterisk differ, $P < 0.05$*

Spleen mRNA Levels of Selenoprotein Genes

A total of 16 of the 25 assayed selenoprotein genes in the spleen were affected by LPS challenge in pigs (Fig. 4). The results showed that the mRNA level of *Dio2* (19.6 times) was the greatest increased ($P < 0.05$), followed by *Sels* (246 %), *Txnrd1* (183 %), *Gpx3* (138 %), and *Selt* (110 %), along with other selenoprtoein genes (*Selx*, *Dio1*, *Selk*, *Txnrd3*, *Seli*, and *Sep15*) from 23 to 63 % in the spleen of pigs injected with LPS, when compared with those injected with saline. In contrast, pigs challenged with LPS showed the decrease of ($P < 0.05$) mRNA abundance of *Sepp1*, *Gpx2*, *Dio3*, *Txnrd2*, and *Seln* from 30 to 81 % in the spleen compared with those injected with saline.

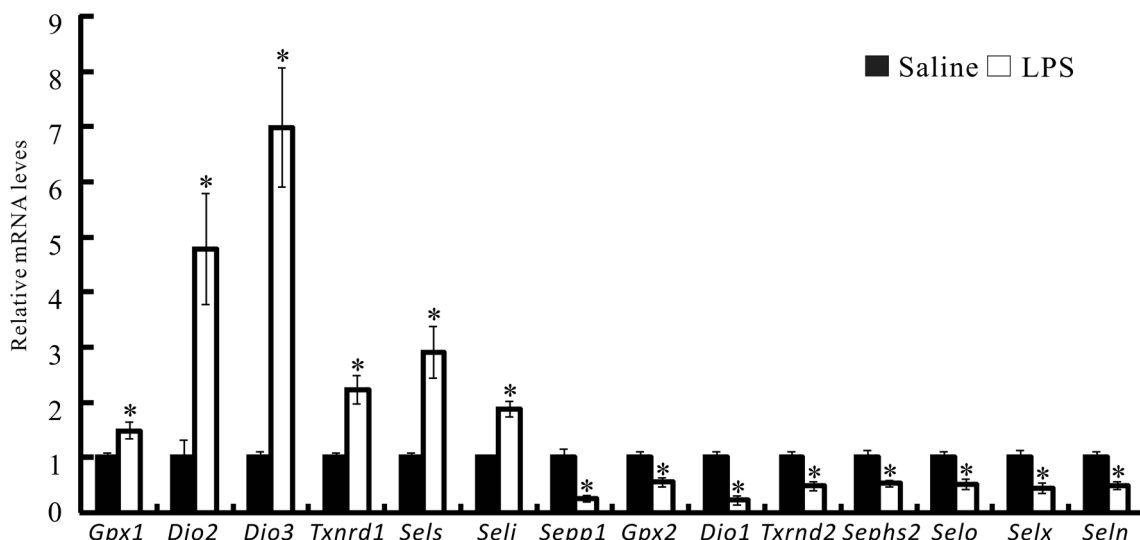## Lymph Node mRNA Levels of Selenoprotein Genes

Among the 25 selenoprotein genes assayed, 10 genes in the lymph node were affected by LPS challenge in pigs (Fig. 5). Specifically, relative to pigs treated with saline, the pigs injected with LPS had higher ($P < 0.05$) *Dio2* (140 %), *Sels* (135 %), *Gpx3* (98 %), *Dio1* (89 %), *Txnrd1* (52 %), *Selk* (52 %), *Selt* (29 %), and *Txnrd3* (28 %) mRNA abundance in lymph node. However, pigs challenged with LPS led to the increase of ($P < 0.05$) mRNA abundance of *Sepp1* (25 %) and *Txnrd2* (19 %) in the lymph node compared with those injected with saline.

Thymus mRNA Levels of Selenoprotein Genes

Among the 25 selenoprotein genes assayed, only 6 genes in the thymus were affected by LPS challenge in pigs (Fig. 6). Pigs challenged with LPS had higher ($P < 0.05$) *Dio2* (193 %), *Gpx3* (62 %), and *Sels* (52 %) mRNA abundance in the thymus compared with those injected with saline. However, pigs injected with LPS had lower ($P < 0.05$) *Selh* (36 %), *Txnrd2* (24 %), and *Selo* (15 %) mRNA abundance in the thymus compared with those injected with saline.

Discussion

The status of Se in body has been identified as an important regulator of disease [28]. Particularly, the immune system seems to depend on a well-maintained Se status to combat bacterial and viral infections, oxidative damage from environmental-, nutritional-, and age-related noxae, as well as other inflammatory challenges [9, 29–31]. Moreover, many previous studies demonstrated circulating Se concentrations were significantly lower in inflammatory disorders [6–9]. However, the retention of Se and the responses of whole selenogenome in the immune tissues during the inflammatory response are not well understood. In an attempt to answer these questions,
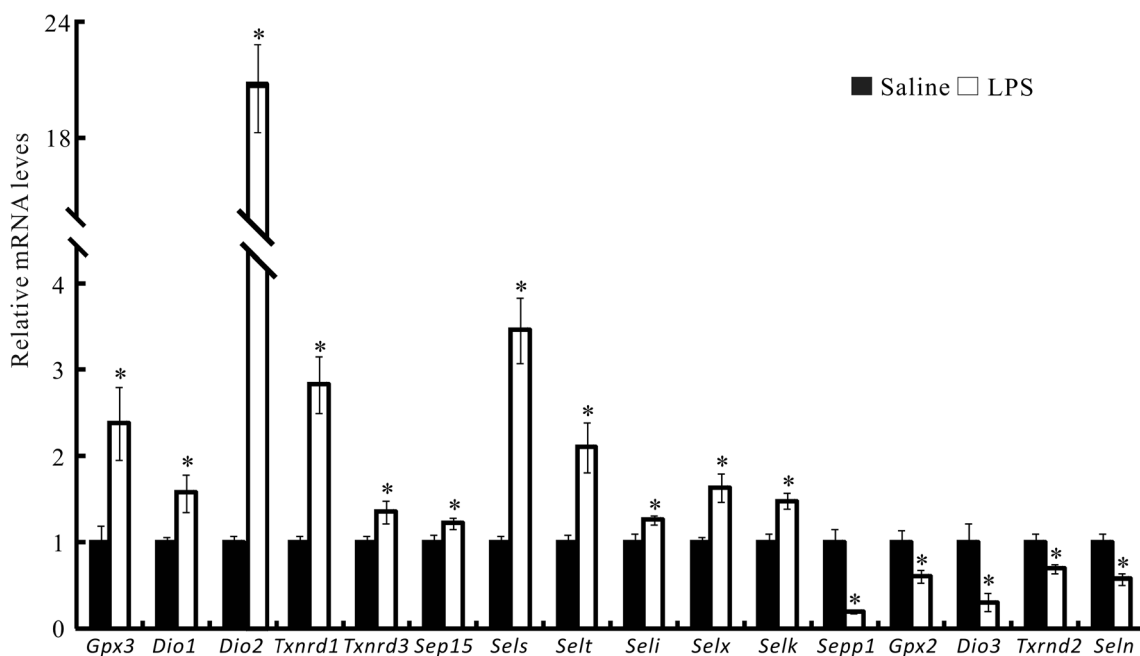
Fig. 3 Effects of LPS challenge on relative mRNA levels of selenoprotein genes in the liver in pigs. Values are means ± SE, $n = 6$. *Labeled means with asterisk* differ, $P < 0.05$

we have taken the advantage of the pig model of LPS-induced acute phase response that faithfully mimics some aspects of immune stress.

The concentration of Se was reduced in serum, while was not changed in the liver, thymus, and lymph node by LPS challenge in pigs, which are similar to those in previous studies [9, 15]. The Se concentration in spleen was decreased in our study, while Maehira et al. (2003) reported that the Se concentration in spleen was not affected by LPS challenge in rat [15]. These divergences could be due to the experimental condition, such as the LPS injection dose, animal species, and exposure times. Moreover, LPS challenge reduced GPX

activity in the serum, thymus, and lymph node in pigs. This finding is in agreement with previous studies, which reported that serum GPX activity was lower in LPS-induced rodents and human subjects with severe systemic inflammatory response syndrome, sepsis, and septic shock [12, 32]. Taken together, these results are similar to previous reports, which indicated that the metabolism of Se in immune tissues was impaired in acute phase response.

Another new dimension of the present study was the mRNA response profiles of 25 selenoprotein genes to the LPS challenge in the four immune tissues, including the liver, spleen, thymus, and lymph node. These profiles enabled us for

Fig. 4 Effects of LPS challenge on relative mRNA levels of selenoprotein genes in the spleen in pigs. Values are means ± SE, $n = 6$. *Labeled means with asterisk* differ, $P < 0.05$

Fig. 5 Effects of LPS challenge on relative mRNA levels of selenoprotein genes in the thymus in pigs. Values are means ± SE, *n* = 6. *Labeled means with asterisk* differ, *P* < 0.05
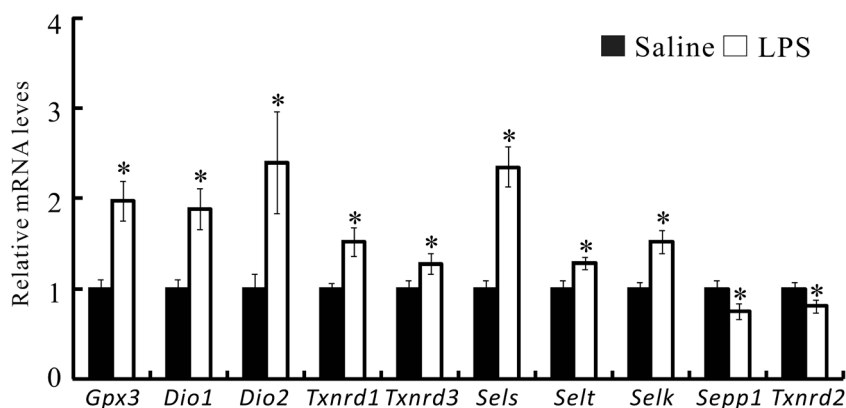
the first time to systematically explore the selenoprotein genes that might be involved in the inflammatory reaction induced by LPS challenge. Among all the genes assayed, LPS challenge affected mRNA levels of 14, 16, 10, and 6 selenoprotein genes in the liver, spleen, thymus, and lymph node, respectively. Specifically, LPS challenge consistently downregulated the mRNA levels of *Sepp1*, *Txnrd2*, *Gpx2*, *Seln*, *Selo*, *Selh*, and *Sephs2*, but upregulated those of *Sels*, *Dio2*, *Gpx3*, *Txnrd1*, *Txnrd3*, *Selk*, *Selt*, *Seli*, *Gpx1*, and *Sep15* in the liver, spleen, thymus, and/or lymph node. Whereas, there are three selenoprotein genes (*Dio1*, *Dio3*, and *Selx*) did not exhibit a common response to LPS challenge across the four tissues. Whereas *Sepp1* [9, 18], *Sels* [33], *Gpx1* [18], *Gpx2* [34], *Gpx3* [35], *Txnrd1* [18], *Selk* [20, 36], *Dio1* [37], *Dio2* [37–39], and *Dio3* [37] were shown to have protective functions against or involved in inflammation, the potential involvements of *Txnrd2*, *Txnrd3*, *Sep15*, *Selh*, *Seli*, *Seln*, *Selo*, *Selt*, *Selx*, and *Sephs2* in this regard are newly illustrated by us in the present study. Coincidently, eight of these ten genes (*Txnrd2*, *Txnrd3*, *Sep15*, *Selh*, *Seln*, *Selo*, *Selt*, and *Selx*) code for proteins, which possess antioxidant capacity [5, 16, 17, 40–42]. Although these selenoproteins might cope with the oxidative stress induced by LPS [43, 44], it is hard for us to explain why some of them (*Txnrd3*, *Sep15*, *Selt*, and *Selx*) were upregulated and others (*Txnrd2*, *Selh*, *Seln*, *Selo*, and *Selx*) were

downregulated in the immune tissues during the LPS challenge. Although the protein encoded by Seli possibly involved in phospholipid biosynthesis and Sephs2 plays a crucial role in synthesis of all selenoproteins [40], their exact role in inflammatory reaction remain to be determined.

Nevertheless, several seemingly conflicting or inconsistent scenarios were observed in the present study. Despite some selenoprtoein genes (*Sepp1*, *Sels*, *Gpx3*, *Dio2*, *Txnrd1*, and *Txnrd2*) exhibited a common response to LPS challenge across three to four immune tissues, other selenoprtoein genes (*Dio1*, *Dio3*, and *Selx*) even showed different responses to LPS challenge across immune tissues. Meanwhile, no single immune tissue showed any common response to LPS challenge across various selenoprotein genes. These divergences suggest that regulations of selenoprotein genes as well as Se metabolism by an LPS-induced inflammatory reaction may vary in various immune tissues. Meanwhile, the GPX activity in the thymus and lymph node were not in accordance with Gpx3 mRNA abundance. This paradoxic discrepancy may be interpreted by a complex feedback or posttranscriptional mechanism in regulating GPX3 synthesis [45, 46].

In conclusion, the present study indicated that a LPS-induced acute phase response impaired Se metabolism in immune tissues. This was demonstrated by decreasing Se concentrations and/or GPX activity in the serum, spleen, thymus, and/or lymph node. Moreover, the LPS-induced dysregulation of Se metabolism was associated with altered mRNA expression of 14, 16, 10, and 6 selenoprotein genes in the liver, spleen, thymus, and lymph node, respectively. These findings could help us to better understand the impairment of Se and selenogenome metabolism in immune tissues during an inflammatory reaction.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.
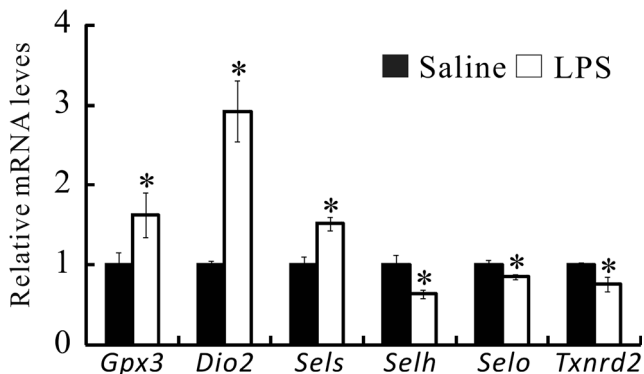
Fig. 6 Effects of LPS challenge on relative mRNA levels of selenoprotein genes in the lymph node in pigs. Values are means ± SE, *n* = 6. *Labeled means with asterisk* differ, *P* < 0.05.

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