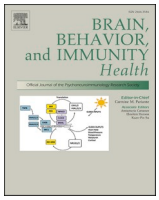
Brain, Behavior, & Immunity - Health 48 (2025) 101084

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



Progranulin modulates inflammatory responses to immune challenges by suppressing circulating cytokine levels☆

Takashi Matsuwaki *, Keitaro Yamanouchi, Masugi Nishihara

Laboratory of Veterinary Physiology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo, 113-8657, Japan

ARTICLE INFO

Keywords:
Progranulin
LPS
Infection
Fever

ABSTRACT

Progranulin (PGRN) is a multifunctional growth factor that is widely expressed throughout the body. It has recently been reported that PGRN haploinsufficiency is a major factor causing frontotemporal lobar dementia. Subsequently, many studies, including ours, have demonstrated the neuroprotective and neurotrophic functions of PGRN. We have also shown that PGRN is involved in voluntary exercise-induced neurogenesis and the suppression of neuroinflammation after traumatic brain injury. Because PGRN is expressed in immune cells in peripheral and central tissues, the main purpose of the present study was to elucidate the role of PGRN in inflammatory responses to immune challenges. Male C57BL/6J wild-type (WT) mice or PGRN-deficient (KO) mice of the same background were used in all experiments. We intraperitoneally injected lipopolysaccharide (LPS, 120 μg/kg) into the animals and measured their body temperature for 9 h during the day and their food intake for 24 h. Although LPS induced a fever response and anorexia in mice of both genotypes, the symptoms were much more severe in the KO mice. LPS is known to induce the secretion of inflammatory cytokines, which transmit immune signals from peripheral to central tissues. Thus, we subsequently determined the serum concentrations of the inflammatory cytokines IL-1β, IL-6, and TNF-α at 0, 1, and 3 h after LPS injection. KO mice showed a significantly stronger induction of IL-6 at 3 h and TNF-α at both 1 and 3 h after injection. IL-1β also tended to have stronger induction at 3 h in KO mice, although the difference was not statistically significant. In WT mice, LPS injection increased PGRN mRNA expression but did not enhance serum PGRN concentration. These results suggest that PGRN suppresses excessive inflammatory responses by moderating the secretion of inflammatory cytokines by functioning inside immune cells.

1. Introduction

Progranulin (PGRN) is a multifunctional glycoprotein containing 7.5 repeats of granulin peptide motifs (Baba et al., 1993; Muynck and Damme, 2011) expressed widely in the whole body, including the reproductive organs, gastrointestinal tract, endocrine organs and neural tissues (Bhandari et al., 1993; Daniel et al., 2000). The PGRN protein is processed into peptides of approximately 6 kDa, known as granulins (Bhandari et al., 1993; Bateman and Bennett, 1998; Matsuwaki et al., 2011), which are also referred to as epithelins (Shoyab et al., 1990). Our previous study revealed that PGRN is among the genes upregulated in the hypothalamus by sex steroids during the perinatal stage and contributes to sexual differentiation in rat brains. Furthermore, our findings indicate that PGRN plays a role in facilitates the mitogenic effects of estrogen in the hippocampus of adult rats. Subsequently, we developed a PGRN-deficient mouse strain (Kayasuga et al., 2007). These mice displayed increased anxiety and reduced male sexual behavior, providing evidence that PGRN is involved in masculinization in rodents.

In recent years, the involvement of PGRN in various diseases has been reported. Mutations in PGRN have been reported to be associated with the development of neurodegenerative diseases such as frontotemporal lobar degeneration (Baker et al., 2006; Cruts et al., 2006), Alzheimer's disease (Brouwers et al., 2008), amyotrophic lateral sclerosis (Sleegers et al., 2008), and neuronal ceroid lipofuscinosis, a lysosomal storage disease (Smith et al., 2012). In addition, PGRN influences the pathogenesis of glioblastoma multiforme (GBM), affecting both tumor cells and the surrounding immune cells (Poniatowski et al., 2024). These studies suggest that PGRN has multifaceted effects on the development of various diseases of the central nervous system. PGRN is systemically expressed and not limited to the central nervous system.

☆ This study was supported in part by JSPS KAKENHI Grants No. 23228004 to MN and 17H03931 and 22H00396 to TM.

* Corresponding author. Laboratory of Veterinary Physiology, Graduate School of Agricultural and Life Sciences, 1-1-1 Yayoi, Bunkyo-ku, Tokyo, 113-8657, Japan.
E-mail address: amwakit@g.ecc.u-tokyo.ac.jp (T. Matsuwaki).

https://doi.org/10.1016/j.bbih.2025.101084
Received 5 April 2025; Received in revised form 28 July 2025; Accepted 30 July 2025
Available online 31 July 2025

PGRN is also involved in serious diseases of peripheral tissues, including breast cancer (Purrahman et al., 2022), diabetes (Murakoshi et al., 2022), and rheumatoid arthritis (Lan et al., 2021). PGRN is expressed in immune cells in both the brain and peripheral tissues. We have previously demonstrated that PGRN, expressed in microglia, exerts anti-inflammatory effects in the brains of mice with traumatic brain injury (Tanaka et al., 2013a).

When the body is exposed to infectious stimuli, inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, are increased in the peripheral tissue to deliver information about inflammation into the central nervous system, which induces immune responses. Although these cytokines cannot penetrate the blood-brain barrier, they affect brain endothelial cells to produce prostaglandin E_2 (PGE_2). Subsequently, PGE_2 works in the hypothalamus to induce various infectious symptoms, among which fever and anorexia are typical responses to immune challenges observed in the early phase of infection (Nilsson et al., 2017; Matsuwaki et al., 2014, 2017).

We have previously demonstrated that PGRN KO mice showed excessive inflammation in the hippocampus (Ma et al., 2017) when intraperitoneally injected with lipopolysaccharide (LPS), a bacterial endotoxin. We hypothesized that, under infectious conditions, PGRN exerts its anti-inflammatory effects by suppressing cytokine production and/or secretion in the peripheral blood, which would affect the systemic responses controlled by the central nervous system. In the present study, we evaluated the immune responses of PGRN-deficient (KO) mice and compared them with those of WT animals. Serum concentrations of inflammatory cytokines and PGRN were measured before and after the LPS injection. Changes in the body temperature and food intake were also assessed.

2. Materials and methods

2.1. Animals

A PGRN knockout (KO) line was established from C57BL/6J mice (Kayasuga et al., 2007). Male littermates of KO and wild-type (WT) mice obtained by heterozygous breeding in our laboratory were used at 10–15 weeks of age. In the present study, 17 KO and 29 WT mice were used. Body weight ranged from 20 to 25 g. The animals were housed at one–four mice per cage on a 12-h light/dark cycle (lights on at 07.00 h) with water and food available *ad libitum* and at an ambient temperature of 22 ± 1C with a relative humidity of 50–70 %. All experimental procedures followed the Guidelines for the Care and Use of Laboratory Animals, Graduate School of Agriculture and Life Sciences, University of Tokyo and were approved by the Institutional Animal Care and Use Committee.

2.2. Measuring body temperature and food intake

One week before the experiment, the transmitter was implanted as previously reported (Matsuwaki et al., 2014). Briefly, mice (n = 10 for each genotype) were anesthetized with isoflurane (4 %) and placed in the supine position. Following skin incision, the linea alba of the abdominal muscle was incised. A transmitter (E-Mitter; Starr Life Science Corp., Oakmont, PA, USA) was implanted intraperitoneally, after which the muscle and skin were sutured. After the surgery, each animal was housed individually in a separate cage. A receiver connected by a wire to a computer was placed beneath each cage to collect transmitted signals. Temperature data were sampled every minute for 9 h. Lipopolysaccharide (LPS, serotype 0111:B4; 120 μg/kg, i.p.) or saline was injected 1 h after the start of recording at approximately 10 a.m. One week after the first injection, a second injection was administered, with the treatment reversed (i.e., saline was replaced with LPS or vice versa).

In a subset of animals (n = 6 for each genotype), the amount of food in each cage was measured immediately before and 24 h after injection. Food intake was calculated by subtracting the amount of food remaining 24 h after the injection from the pre-injection amount.

2.3. Blood sampling & assays for cytokines and PGRN

For cytokine assays, a group of animals (n = 7 for each genotype) was treated with LPS (120 μg/kg, i.p.) at approximately 10 a.m. Blood samples were collected from the vein behind the jawbone 0, 1, and 3 h after injection. To measure serum PGRN concentrations and mRNA expression levels in blood cells, 12 WT mice were treated with LPS, and blood was collected at 0, 1, 3, and 6 h after injection using the same method. ELISA kits from R&D Systems (Minneapolis, MN, USA) and Adipogen Life Sciences (San Diego, CA, USA) were used to determine serum levels of cytokines and PGRN, respectively.

2.4. Determination of mRNA expression level of PGRN in the blood cells

mRNA was extracted from the blood using a NucleoSpin RNA Blood kit (Macherey-Nagel, Düren, Germany) and used for qPCR of the PGRN gene. First-strand cDNA synthesis was performed as previously described (Komatsuda et al., 2024). qPCR was performed using cDNA as the template. PCR was performed using the Thunderbird SYBR qPCR MIX (TOYOBO, Osaka, Japan) and a LightCycler (Roche, Mannheim, Germany). The forward and reverse primers used for mouse PGRN were GGT TGA TGG TTC GTG GGG ATG TTG and AAG GCA AAG ACA CTG CCC TGT TGG, respectively. For normalization, the housekeeping gene hypoxanthine phosphoribosyltransferase (HPRT) was used as an internal control using the following forward and reverse primers: AGT CCC AGC GTC GTG ATT AGC GAT and CTT GAG CAC ACA GAG GGC CAC AAT, respectively.

2.5. Statistical analyses

The data were analyzed by Repeated Measures ANOVA for Result 1 and Two-way ANOVA for Results 2 and 3, followed by post-hoc comparison using Tukey-Kramer's test. For result 4, after performing One-way ANOVA, Dunnett's multiple comparison test was used to compare the values at each time point with the baseline (before LPS injection) to determine the time required to induce a possible change in PGRN expression. Differences were considered statistically significant at $P < 0.05$.

3. Results

1. PGRN-KO mice exhibited a stronger fever response to LPS.

To investigate the role of PGRN in controlling body temperature under infectious conditions, we injected LPS or saline into WT and PGRN KO mice and observed changes in their temperature. Both genotypes showed enhanced body temperature compared to the groups treated with saline. The LPS (120 μg/kg BW)-induced increase in body temperature was higher in KO mice than in WT mice (Fig. 1, Repeated Measures ANOVA followed by Tukey's multiple comparison test, effect of group: $F_{3,\ 36} = 22.12$, $P < 0.0001$; time: $F_{10.01,\ 360.2} = 14.65$, $P < 0.0001$; interaction: $F_{30.02,\ 360.2} = 3.47$: $P < 0.0001$). Although the fever levels were comparable after injection of 12 μg/kg BW LPS (Repeated Measures ANOVA followed by Tukey's multiple comparison test, effect of group: $F_{1,\ 10} = 0.025$, $P = 0.88$; time: $F_{5.64,\ 56.34} = 100.65$, $P < 0.0001$; interaction: $F_{5.64,\ 56.34} = 0.49$: $P = 0.80$), they were augmented in the 1200 μg/kg (Repeated Measures ANOVA followed by Tukey's multiple comparison test, effect of group: $F_{1,\ 10} = 2.34$, $P = 0.16$; time: $F_{2.21,\ 22.1} = 9.40$, $P < 0.001$; interaction: $F_{2.21,\ 22.1} = 4.49$, $P < 0.05$) injection group (Suppl. Fig. 1). These results suggest that PGRN suppresses infectious fever, particularly in severe infectious conditions.

2. LPS-induced anorexia was enhanced in PGRN KO mice.

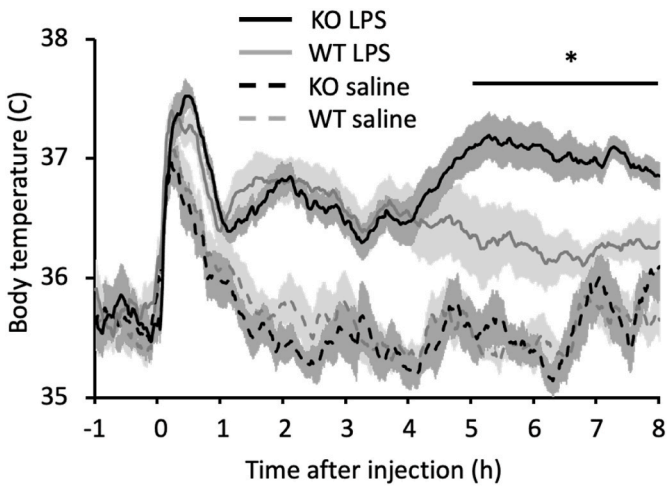


Fig. 1. Change of body temperature after LPS/saline injection in WT and PGRN KO mice
LPS (120 μg/kg, i. p.) or saline was injected at 0h (10 a.m.). Each line and vertical bar represents the mean and SEM (n = 10). *P < 0.05, Repeated Measures ANOVA followed by Tukey's multiple comparison test. Only differences between genotypes are indicated.

Second, to examine whether PGRN has any effect on infectious anorexia, we compared the volume of food intake before and after LPS injection (Fig. 2). Among the WT mice, LPS-injected animals tended to show a smaller volume of food intake, but the difference was not significant. In contrast, KO mice showed less food intake when they were injected with LPS compared to animals injected with saline, indicating that PGRN alleviates the development of anorexia against infectious stimuli (Mean ± SEM of the values at WT saline, WT LPS, KO saline, and KO LPS were 5.31 ± 0.12, 4.28 ± 0.48, 5.11 ± 0.37, and 3.16 ± 0.32, respectively. Two-way ANOVA followed by Tukey's multiple comparison test; effect of genotype: $F_{1,\ 20} = 2.61$, P = 0.07; treatment: $F_{1,\ 20} = 18.46$, P < 0.01; interaction: $F_{1,\ 20} = 11.40$, P = 0.20).

3. PGRN KO mice showed higher induction of inflammatory cytokines in response to LPS.

As infectious signals are known to be mediated by inflammatory cytokines delivered to the central nervous system, we measured the concentrations of three major inflammatory cytokines: IL-1. IL-6 and TNF-α levels 0, 1, and 3 h after LPS injection (Fig. 3). None of these cytokines was detected at 0 h. The concentrations of IL-1β and IL-6 were enhanced to detectable levels at 1 h and further increased 3 h after LPS injection in both WT and KO mice. Three hours after LPS injection, KO mice tended to have higher concentrations of IL-1β and significantly higher levels of IL-6. TNF-α concentrations were the highest at 1 h after injection and decreased to lower, but still detectable, levels at 3 h after LPS injection in both genotypes. At both time points, KO mice showed higher concentrations of TNF-α than WT mice did (Mean ± SEM of the values at WT 1 h, WT 3 h, KO 1 h, and KO 3 h, IL-1β: 30.25 ± 7.04, 70.03 ± 11.97, 23.91 ± 3.05 ng/ml, and the values at 107.49 ± 14.10; IL-6: 970.48 ± 95.25, 845.16 ± 224.19, 943.27 ± 163.58, and 2270.28 ± 341.01 ng/ml; TNF-α: 1648.45 ± 385.43, 269.17 ± 58.35, 3779.12 ± 484.38, and 438.64 ± 47.78 ng/ml, Two-way ANOVA followed by Tukey's multiple comparison test, IL-1β: effect of genotype: $F_{1,\ 20} = 1.83$, P = 0.19; time: $F_{1,\ 20} = 31.90$, P < 0.0001; IL-6: genotype: $F_{1,\ 18} = 8.76$, P < 0.01; time: $F_{1,\ 18} = 6.47$, P = 0.020; interaction: $F_{1,\ 18} = 9.45$, P < 0.01; TNF-α: genotype: $F_{1,\ 20} = 13.90$, P < 0.001; time: $F_{1,\ 20} = 56.68$, P < 0.0001; interaction: $F_{1,\ 20} = 9.64$, P < 0.01). Hence, PGRN appears to suppress the production and/or secretion of inflammatory cytokines under infectious conditions.

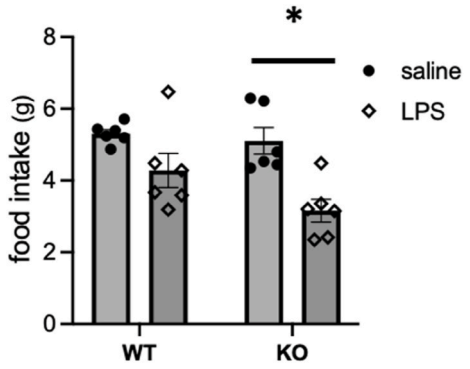


Fig. 2. Daily food intake after LPS/saline injection in WT and PGRN KO mice
LPS (120 μg/kg, i. p.) or saline was injected at 10:00 h. Each column and vertical bar represents the mean and SEM (n = 6). *P < 0.05, Two-way ANOVA followed by Tukey's multiple comparison test.

4. PGRN mRNA expression in blood cells was induced by LPS without an increase in the serum concentration.

One of the major sources of inflammatory cytokines that respond to immune challenges is the immune cells in the blood. Thus, to investigate the mechanism by which PGRN prevents the increase in cytokine concentrations, we investigated the serum concentrations and mRNA expression levels of PGRN at 0, 1, 3, and 6 h after LPS injection (Fig. 4). While the serum PGRN levels were comparable at all time points (mean ± SEM of the values at 0, 1, 3, and 6 h were 0.43 ± 0.032, 0.37 ± 0.023, 0.38 ± 0.030, and 0.52 ± 0.050 μg/ml, respectively. One-way ANOVA followed by Dunnett's multiple comparison test, $F_{3,35} = 3.84$, P = 0.018), the mRNA expression level of PGRN significantly increased in a time-dependent manner (mean ± SEM of the values at 0, 1, 3, and 6 h were 0.78 ± 0.14, 1.27 ± 0.41, 2.62 ± 0.28, and 3.96 ± 0.79/HPRT expression levels, respectively. One-way ANOVA followed by Dunnett's multiple comparison test, $F_{3,19} = 8.96$, P < 0.001), suggesting that PGRN synthesis in the blood cells is stimulated by the immune challenge and that the increased PGRN works inside the cells without secretion.

The results of all the experiments are summarized in Table 1.

4. Discussion

In the present study, we demonstrated that PGRN alleviates orchestrated symptoms in response to infectious stimuli, including fever and anorexia, under infectious conditions. The increase in inflammatory cytokines in the blood in response to LPS injection was enhanced in PGRN KO mice. Although the serum concentration of PGRN was not affected by LPS, the mRNA level of PGRN was increased after LPS injection in WT mice (Table 1).

4.1. PGRN suppresses excessive inflammatory responses by moderating the secretion of inflammatory cytokines in the peripheral blood

PGRN has been shown to play a crucial role in suppressing excessive inflammatory responses by moderating the secretion of inflammatory cytokines in the peripheral blood. We previously reported that PGRN, produced in CD68-positive microglia, suppresses excessive inflammatory responses related to activated microglia after traumatic brain injury (Tanaka et al., 2013a). Yan et al. (2016) further demonstrated that PGRN controls sepsis by reducing the levels of inflammatory cytokines and regulating IL-10 production with an anti-inflammatory effect, consistent with the results of the present study. Inflammatory cytokines are known to be delivered to the central nervous system and induce various immune responses, including fever and anorexia (Matsuwaki et al., 2017). The major cause of enhanced fever and anorexia in KO mice could be the increased levels of LPS-inducible inflammatory

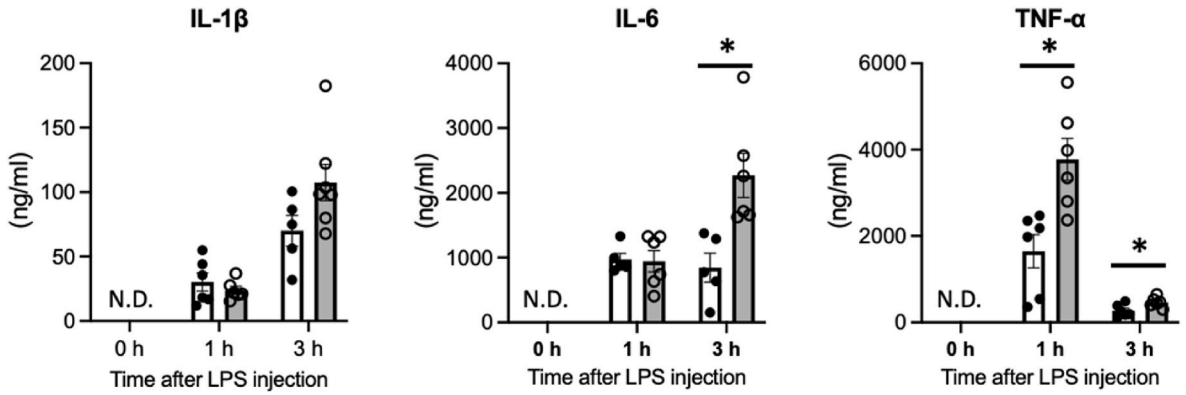


Fig. 3. Serum concentrations of inflammatory cytokines in WT and PGRN KO mice
LPS (120 μg/kg, i. p.) was injected at 0h (10 a.m.). Blood samples were collected from the vein behind the jawbone 0, 1, and 3 h after injection. Each column and vertical bar represents the mean and SEM (n = 6). *P < 0.05, Two-way ANOVA followed by Tukey's multiple comparison test. N.D.; not detectable.

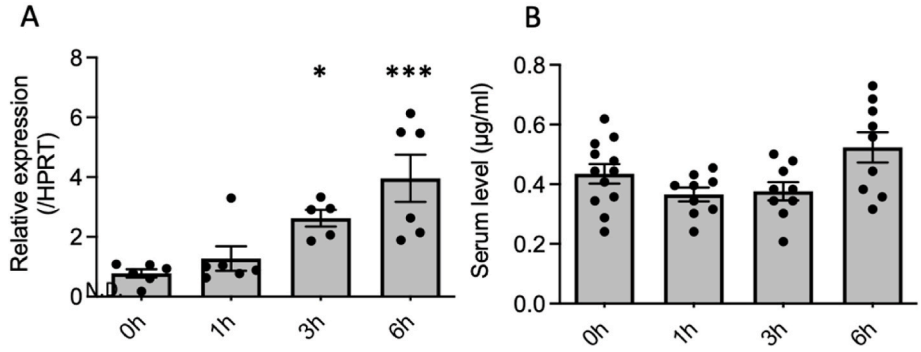


Fig. 4. mRNA expression levels (A) and peptide concentration (B) in the blood of WT mice
LPS (120 μg/kg, i. p.) was injected at 0h (10 a.m.). Blood samples were collected from the vein behind the jawbone 0, 1, and 3 h after injection. Each column and vertical bar represents the mean and SEM (n = 6). *; P < 0.05, ***; P < 0.001 vs 0h, One-way ANOVA followed by Dunnett's multiple comparison test.

Table 1
Summary of the changes after LPS injection.

	WT	PGRN KO
Body temperature	↑	↑↑
Food intake	↓	↓↓
Serum IL-1β concentration	↑	↑↑
Serum IL-6 concentration	↑	↑↑
Serum TNF-α concentration	↑	↑↑
Serum PGRN concentration	→	
PGRN mRNA expression in blood cells	↑	

Arrows represent the increase (↑), decrease (↓), or no alteration (→) of each value after LPS (120 μg/kg) injection.

cytokines. In addition, this effect of PGRN seems to last for a long period because KO mice maintained an enhanced fever until the end of the recording. Furthermore, as mice are nocturnal animals, the effects of LPS and PGRN on food intake suggest that their functions are exerted more than 9 h after injection (after light-off). Accordingly, it is indicated that PGRN works against the development of homeostasis-disrupting immune responses by suppressing the excessive production of inflammatory cytokines. To verify the possible role of PGRN, rescue experiments supplying KO mice with PGRN would be a promising option to be performed using methods similar to those used by Yan et al. in a higher dose (20 mg/kg) LPS-inducible sepsis model of PGRN KO mice.

4.2. PGRN synthesis is stimulated by immune challenges

In the present study, PGRN expression in the blood cells was significantly enhanced by LPS injection. Previous studies have demonstrated that PGRN synthesis is induced by various infectious challenges and plays a complex role in the immune response. In adipose tissue, an increase in PGRN expression has been reported under infectious conditions as well as during adipogenic differentiation (Schmid et al., 2020). Another research group demonstrated that Helicobacter pylori infection upregulates PGRN expression in gastric epithelial cells via the p38MAPK and MEK1/2 signaling pathways, potentially contributing to carcinogenesis (Wang et al., 2011). PGRN plays a crucial role in immune cell regulation and function. It is expressed in various immune cells, including microglia and peripheral immune cells (Daniel et al., 2000; Keating et al., 2020). These findings suggest that PGRN plays a significant role in infection-induced immune responses, with both protective and potentially harmful effects depending on the pathogen and context.

4.3. PGRN may function in immune cells without secretion

In the present study, the serum PGRN level was not affected by LPS, whereas its mRNA expression level was increased. One possible reason for this discrepancy between protein and mRNA expression levels is that there are some changes in mRNA translation, such as translation repression. Another possibility is that PGRN functions inside the immune cells without being secreted. Although PGRN has been detected as a secreted glycoprotein with neuroprotective and anti-inflammatory effects (Tanaka et al., 2013a, 2013b) and a possible link between the serum level of PGRN and the development of neurodegenerative diseases has been reported (Olczak et al., 2021), recent studies have demonstrated that PGRN protection against excitotoxicity is mediated by lysosomes rather than extracellular signaling, highlighting the

importance of its intracellular functions (Davis et al., 2021). Another study demonstrated that PGRN is secreted from synapses in an activity-dependent manner and can regulate synapse number and structure (Petoukhov et al., 2013). These findings suggest that, although PGRN is typically secreted, some of its effects may not always require extracellular action. PGRN is known to function both extracellularly and intracellularly in immune cells. While its role as a secreted protein interacting with receptors such as TNFR is well documented, PGRN also exerts intracellular effects, particularly within lysosomes. It regulates lysosomal function and enzyme activity, contributing to the degradation and recycling of cellular components, which is crucial for maintaining cellular homeostasis and modulating inflammatory responses (Tanaka et al., 2014, 2017). Furthermore, PGRN plays a role in the conversion and function of regulatory T cells, where it can act intracellularly to protect these cells from negative regulation by TNF-α, thus supporting immune tolerance and preventing excessive inflammation (Tang et al., 2011). These findings suggest that PGRN functions within immune cells without necessarily being secreted, highlighting its multifaceted role in both intracellular and extracellular immune regulation. As blood cells are not the only source of cytokines and PGRN, an *in vitro* study using cultured leukocytes (Zhang et al., 2024) is required to exclude the possibility of cytokine and PGRN secretion from other peripheral organs, including the spleen and liver.

4.4. Possible functions of PGRN in the brain

Another possible mechanism by which PGRN alleviates infectious fever is through its direct action in the brain. The hypothalamus is the thermoregulatory center in the brain that upregulates body temperature in response to various inflammatory stimuli (Matsuwaki et al., 2014, 2017). Previous studies have demonstrated that PGRN can influence the hypothalamic regulation of food intake and body weight by modulating the inflammatory responses and neural activity within this brain region. Thus, in addition to suppressing the increase in cytokines circulating in peripheral tissues, as mentioned above, PGRN may exert anti-inflammatory functions in the hypothalamus to ease immune-driven hyperthermia. However, our previous study revealed that the expression level of PGRN in the hippocampus increased 24 h but did not change until 18 h after LPS injection (Ma et al., 2017). Hence, we assumed that in the early phase of infection, PGRN exerts its anti-inflammatory effects mainly in the peripheral tissues. Evaluation of `PGRN expression within 6 h of LPS injection supports this hypothesis.

In conclusion, the present study suggests that in infectious conditions, PGRN plays an important role in alleviating excessive stress responses, including fever and anorexia. This effect of PGRN is mainly due to the moderating secretion of inflammatory cytokines in the peripheral blood via the existing immune cells. In addition, the direct effect of PGRN on the hypothalamus should be considered.

CRediT authorship contribution statement

Takashi Matsuwaki: Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Data curation. **Keitaro Yamanouchi:** Supervision. **Masugi Nishihara:** Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This study was supported in part by JSPS KAKENHI grant no. 23228004 to MN and no. 17H03931 and 22H00396 to TM.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.101084.

Data availability

Data will be made available on request.

References

Baba, T., Nemoto, H., Watanabe, K., Arai, Y., Gerton, G.L., 1993. Exon/Intron organization of the gene encoding the mouse epithelin/granulin precursor (Acrogranin). FEBS Lett. 322, 89–94. https://doi.org/10.1016/0014-5793(93)81544-a.

Baker, M., Mackenzie, I.R., Pickering-Brown, S.M., Gass, J., Rademakers, R., Lindholm, C., Snowden, J., Adamson, J., Sadovnick, A.D., Rollinson, S., Cannon, A., Dwosh, E., Neary, D., Melquist, S., Richardson, A., Dickson, D., Berger, Z., Eriksen, J., Robinson, T., Zehr, C., Dickey, C.A., Crook, R., McGowan, E., Mann, D., Boeve, B., Feldman, H., Hutton, M., 2006. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 442, 916–919. https://doi.org/10.1038/nature05016.

Bateman, A., Bennett, H., 1998. Granulins: the structure and function of an emerging family of growth factors. J. Endocrinol. 158, 145–151. https://doi.org/10.1677/joe.0.1580145.

Bhandari, V., Giaid, A., Bateman, A., 1993. The complementary deoxyribonucleic acid sequence, tissue distribution, and cellular localization of the rat granulin precursor. Endocrinology 133, 2682–2689. https://doi.org/10.1210/endo.133.6.8243292.

Brouwers, N., Sleegers, K., Engelborghs, S., Maurer-Stroh, S., Gijselinck, I., Zee, J. van der, Pickut, B.A., Broeck, M.V. den, Mattheijssens, M., Peeters, K., Schymkowitz, J., Rousseau, F., Martin, J.-J., Cruts, M., Deyn, P.P.D., Broeckhoven, C.V., 2008. Genetic variability in progranulin contributes to risk for clinically diagnosed alzheimer disease. Neurology 71, 656–664. https://doi.org/10.1212/01.wnl.0000319688.89790.7a.

Cruts, M., Gijselinck, I., Zee, J. van der, Engelborghs, S., Wils, H., Pirici, D., Rademakers, R., Vandenberghe, R., Dermaut, B., Martin, J.-J., Duijn, C. van, Peeters, K., Sciot, R., Santens, P., Pooter, T.D., Mattheijssens, M., Broeck, M.V. den, Cuijt, I., Vennekens, K., Deyn, P.P.D., Kumar-Singh, S., Broeckhoven, C.V., 2006. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 442, 920–924. https://doi.org/10.1038/nature05017.

Daniel, R., He, Z., Carmichael, K.P., Halper, J., Bateman, A., 2000. Cellular localization of gene expression for progranulin. J. Histochem. Cytochem. 48, 999–1009. https://doi.org/10.1177/002215540004800713.

Davis, S.E., Roth, J.R., Aljabi, Q., Hakim, A.R., Savell, K.E., Day, J.J., Arrant, A.E., 2021. Delivering progranulin to neuronal lysosomes protects against excitotoxicity. J. Biol. Chem. 297, 100993. https://doi.org/10.1016/j.jbc.2021.100993.

Kayasuga, Y., Chiba, S., Suzuki, M., Kikusui, T., Matsuwaki, T., Yamanouchi, K., Kotaki, H., Horai, R., Iwakura, Y., Nishihara, M., 2007. Alteration of behavioural phenotype in mice by targeted disruption of the progranulin gene. Behav. Brain Res. 185, 110–118. https://doi.org/10.1016/j.bbr.2007.07.020.

Keating, C.E., Houser, M.C., MacPherson, K.P., Herrick, M.K., Coomes, A., Joers, V.L., Oliver, D., Johnson, A.G., Chang, J., McEachin, Z., Varvel, N.H., Prokop, S., Tansey, M.G., 2020. Loss of progranulin leads to dysregulation of innate and adaptive immune cell populations, increased susceptibility to experimental colitis, and brain infiltration of peripheral immune cells. Alzheimer's Dement. 16. https://doi.org/10.1002/alz.042177.

Komatsuda, M., Ataka, K., Yamanouchi, K., Nishihara, M., Matsuwaki, T., 2024. Hypercorticosteronemia induces hyperphagia and obesity in human growth hormone transgenic rats. Neuroscience 560, 326–333. https://doi.org/10.1016/j.neuroscience.2024.10.012.

Lan, Y.J., Sam, N.B., Cheng, M.H., Pan, H.F., Gao, J., 2021. Progranulin as a potential therapeutic target in immune-mediated diseases. J. Inflamm. Res. 14, 6543–6556. https://doi.org/10.2147/JIR.S339254.

Ma, Y., Matsuwaki, T., Yamanouchi, K., Nishihara, M., 2017. Progranulin protects hippocampal neurogenesis via suppression of neuroinflammatory responses under acute immune stress. Mol. Neurobiol. 54, 3717–3728. https://doi.org/10.1007/s12035-016-9939-6.

Matsuwaki, T., Asakura, R., Suzuki, M., Yamanouchi, K., Nishihara, M., 2011. Age-dependent changes in progranulin expression in the mouse brain. J. Reprod. Dev. 57, 113. https://doi.org/10.1262/jrd.10-116s.

Matsuwaki, T., Eskilsson, A., Kugelberg, U., Jönsson, J.-I., Blomqvist, A., 2014. Interleukin-1β induced activation of the hypothalamus–pituitary–adrenal axis is dependent on interleukin-1 receptors on non-hematopoietic cells. Brain Behav. Immun. 40, 166–173. https://doi.org/10.1016/j.bbi.2014.03.015.

Matsuwaki, T., Shionoya, K., Ihnatko, R., Eskilsson, A., Kakuta, S., Dufour, S., Schwaninger, M., Waisman, A., Müller, W., Pinteaux, E., Engblom, D., Blomqvist, A., 2017. Involvement of interleukin-1 type 1 receptors in lipopolysaccharide-induced sickness responses. Brain Behav. Immun. 66, 165–176. https://doi.org/10.1016/j.bbi.2017.06.013.

Muynck, L.D., Damme, P.V., 2011. Cellular effects of progranulin in health and disease. J. Mol. Neurosci. 45, 549. https://doi.org/10.1007/s12031-011-9553-z.

Murakoshi, M., Gohda, T., Sakuma, H., Shibata, T., Adachi, E., Kishida, C., Ichikawa, S., Koshida, T., Kamei, N., Suzuki, Y., 2022. Progranulin and its receptor predict kidney function decline in patients with type 2 diabetes. Front. Endocrinol. 1, 849457, 0.3389/fendo.2022.849457.

Nilsson, A., Wilhelms, D.B., Mirrasekhian, E., Jaarola, M., Blomqvist, A., Engblom, D., 2017. Inflammation-induced anorexia and fever are elicited by distinct prostaglandin dependent mechanisms, whereas conditioned taste aversion is prostaglandin independent. Brain Behav. Immun. 61, 236–243. https://doi.org/10.1016/j.bbi.2016.12.007.

Olczak, M., Poniatowski, Ł.A., Siwińska, A., Kwiatkowska, M., Chutorański, D., Wierzba-Bobrowicz, T., 2021. Elevated serum and urine levels of progranulin (PGRN) as a predictor of microglia activation in the early phase of traumatic brain injury: a further link with the development of neurodegenerative diseases. Folia Neuropathol. 59, 81–90. https://doi.org/10.5114/fn.2021.105137.

Petoukhov, E., Fernando, S., Mills, F., Shivji, F., Hunter, D., Krieger, C., Silverman, M.A., Bamji, S.X., 2013. Activity-dependent secretion of progranulin from synapses. J. Cell Sci. 126, 5412–5421. https://doi.org/10.1242/jcs.132076.

Poniatowski, Ł.A., Woźnica, M., Wojdasiewicz, P., Mela-Kalicka, A., Romanowska-Próchnicka, K., Purrahman, D., Żurek, G., Krawczyk, M., Nameh Goshay Fard, N., Furtak-Niczyporuk, M., Jaroszyński, J., Mahmoudian-Sani, M.R., Joniec-Maciejak, I., 2024. The role of progranulin (PGRN) in the pathogenesis of glioblastoma multiforme. Cells 124. https://doi.org/10.3390/cells13020124.

Purrahman, D., Mahmoudian-Sani, M.R., Saki, N., Wojdasiewicz, P., Kurkowska-Jastrzębska, I., Poniatowski, Ł.A., 2022. Involvement of progranulin (PGRN) in the pathogenesis and prognosis of breast cancer. Cytokine, 155803. https://doi.org/10.1016/j.cyto.2022.155803.

Schmid, A., Hochberg, A., Kreiß, A.F., Gehl, J., Patz, M., Thomalla, M., Hanses, F., Karrasch, T., Schäffler, A., 2020. Role of progranulin in adipose tissue innate immunity. Cytokine 125, 154796. https://doi.org/10.1016/j.cyto.2019.154796.

Shoyab, M., McDonald, V.L., Byles, C., Todaro, G.J., Plowman, G.D., 1990. Epithelins 1 and 2: isolation and characterization of two cysteine-rich growth-modulating proteins. Proc. Natl. Acad. Sci. 87, 7912–7916. https://doi.org/10.1073/pnas.87.20.7912.

Sleegers, K., Brouwers, N., Maurer-Stroh, S., Es, M.A. van, Damme, P.V., Vught, P.W.J. van, Zee, J. van der, Serneels, S., Pooter, T.D., Broeck, M.V. den, Cruts, M., Schymkowitz, J., Jonghe, P.D., Rousseau, F., Berg, L.H. van den, Robberecht, W., Broeckhoven, C.V., 2008. Progranulin genetic variability contributes to amyotrophic lateral sclerosis. Neurology 71, 253–259. https://doi.org/10.1212/01.wnl.0000289191.54852.75.

Smith, K.R., Damiano, J., Franceschetti, S., Carpenter, S., Canafoglia, L., Morbin, M., Rossi, G., Pareyson, D., Mole, S.E., Staropoli, J.F., Sims, K.B., Lewis, J., Lin, W.-L., Dickson, D.W., Dahl, H.-H., Bahlo, M., Berkovic, S.F., 2012. Strikingly different clinicopathological phenotypes determined by progranulin-mutation dosage. Am. J. Hum. Genet. 90, 1102–1107. https://doi.org/10.1016/j.ajhg.2012.04.021.

Tanaka, Y., Chambers, J.K., Matsuwaki, T., Yamanouchi, K., Nishihara, M., 2014. Possible involvement of lysosomal dysfunction in pathological changes of the brain in aged progranulin-deficient mice. Acta Neuropathol. Commun 2, 78. https://doi.org/10.1186/preaccept-4589926441299369.

Tanaka, Y., Matsuwaki, T., Yamanouchi, K., Nishihara, M., 2013a. Exacerbated inflammatory responses related to activated microglia after traumatic brain injury in progranulin-deficient mice. Neuroscience 231, 49–60. https://doi.org/10.1016/j.neuroscience.2012.11.032.

Tanaka, Y., Matsuwaki, T., Yamanouchi, K., Nishihara, M., 2013b. Increased lysosomal biogenesis in activated microglia and exacerbated neuronal damage after traumatic brain injury in progranulin-deficient mice. Neuroscience 250, 8–19. https://doi.org/10.1016/j.neuroscience.2013.06.049.

Tanaka, Y., Suzuki, G., Matsuwaki, T., Hosokawa, M., Serrano, G., Beach, T.G., Yamanouchi, K., Hasegawa, M., Nishihara, M., 2017. Progranulin regulates lysosomal function and biogenesis through acidification of lysosomes. Hum. Mol. Genet. 26, ddx011. https://doi.org/10.1093/hmg/ddx011.

Tang, W., Lu, Y., Tian, Q.-Y., Zhang, Y., Guo, F.-J., Liu, G.-Y., Syed, N.M., Lai, Y., Lin, E. A., Kong, L., Su, J., Yin, F., Ding, A.-H., Zanin-Zhorov, A., Dustin, M.L., Tao, J., Craft, J., Yin, Z., Feng, J.Q., Abramson, S.B., Yu, X.-P., Liu, C., 2011. The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. Science 332, 478–484. https://doi.org/10.1126/science.1199214.

Wang, H., Sun, Y., Liu, S., Yu, H., Li, W., Zeng, J., Chen, C., Jia, J., 2011. Upregulation of progranulin by Helicobacter pylori in human gastric epithelial cells via p38MAPK and MEK1/2 signaling pathway: role in epithelial cell proliferation and migration. FEMS Immunol. Med. Microbiol. 63, 82–92. https://doi.org/10.1111/j.1574-695x.2011.00833.x.

Yan, W., Ding, A., Kim, H.-J., Zheng, H., Wei, F., Ma, X., 2016. Progranulin controls sepsis via C/EBPα-Regulated Il10 transcription and ubiquitin Ligase/proteasome-mediated protein degradation. J. Immunol. 197, 3393–3405. https://doi.org/10.4049/jimmunol.1600862.

Zhang, W., Qin, H., Wang, G., Zhang, J., He, W., Feng, C., Wan, H., Wang, F., Guo, Z., 2024. Deciphering the potential role of PGRN in regulating CD8(+) T cell antitumor immunity. Cell Death Discov. 14, 223. https://doi.org/10.1038/s41420-024-02001-7.