Minireview

The expression and function of growth hormone secretagogue receptor in immune cells: A current perspective

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Impact Statement

Emerging evidence shows that ghrelin and growth hormone secretagogue receptor (GHS-R) play significant roles in inflammation. Ghrelin in the circulation can reach all parts of the body, and it signals through its receptor GHS-R in tissues. To understand the role and mechanism of ghrelin signaling in inflammation, it is critical to identify the immune cells that express GHS-R, since the receptor expression predicts the site of action and specifies the effects. However, the current data on GHS-R expression in immune cells are sparse and confounding. In this review, we summarize the emerging findings in the literature regarding GHS-R expression in common immune cells, and discuss the current understanding of the effects of GHS-R in immune cells under different states. We believe that our perspective in this review will help to guide the future research of ghrelin signaling in immunity, thus to advance the understanding and application of ghrelin signaling in inflammatory diseases.

Abstract

The orexigenic hormone ghrelin and its receptor, growth hormone secretagogue receptor (GHS-R), have been extensively studied in the last two decades, revealing that ghrelin signaling has important implications in health and disease. Metabolic diseases, such as obesity and diabetes, are often accompanied by low-grade chronic inflammation, that has been coined as "meta-inflammation." Immune cells are key cellular mediators of meta-inflammation, controlling both initiation and resolution of inflammation. Immune cells exhibit dynamic changes in cellular characteristics and functional output in response to the stimuli/insults from their surrounding microenvironment. Emerging evidence shows that ghrelin has an important effect on inflammation, in addition to its well-known effects on metabolism. However, the cellular/molecular mechanism of ghrelin signaling in immunity is largely unknown because the knowledge in regard to the expression and function of GHS-R in immune cells is currently sparse. In this review, we have accumulated the recent findings related to the expression and functions of GHS-R in various immune cells under different physiological and pathological states. This review aims to inspire further investigation of the immunological roles of ghrelin signaling and advance the therapeutic applications of ghrelin signaling in meta-inflammation.

Keywords: Ghrelin, growth hormone secretagogue receptor (GHS-R), immune cells, immunometabolism, inflammaging, polarization, meta-inflammation, macrophages, neutrophils, dendritic cells, T lymphocytes, B lymphocytes

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Introduction

Ghrelin, aka orexigenic hormone or hunger hormone, classically is known for its roles in the regulation of appetite and adiposity.[1] Ghrelin is extensively studied by our group and others as an important regulator of glucose homeostasis[2] and energy homeostasis.[1–10] As we previously reviewed that ghrelin is a multifaced hormone and ghrelin signaling has a broad range of functions.[11] In addition to regulating metabolism, ghrelin signaling also regulates cardiac function,[12] muscle mass,[13] bone density,[14] and cancer.[15] Ghrelin gene produces three protein isoforms by alternative splicing or post-translational modification: acyl-ghrelin (aka active ghrelin, ghrelin), unacyl ghrelin (UAG, aka inactive ghrelin), and obestatin.[11,16,17] Acyl-ghrelin is active form of ghrelin, often simply referred as ghrelin; it binds specifically to growth hormone secretagogue receptor (GHS-R),[1,18] and acylation of ghrelin is required for its binding to GHS-R.[19,20] UAG is considered as inactive form due to low binding affinity to GHS-R.[21] The functional receptor for obestatin is

Table 1. Ghrelin and GHS-R expressing tissues in human, mouse, and rat.

Expression	Species	Tissue types	Detection method	References
Ghrelin	Human	Stomach, duodenum, jejunum, ileum, colon, esophagus, buccal, antrum, lung, pancreas, lymph node, spleen, liver, gallbladder, pituitary, somatotropinoma, breast, kidney, adrenal, ovary, fallopian tubes, testis, prostate, adipose tissue, placenta, muscle, bladder, thyroid, thymus, atrium, myocardium, skin	RT-PCR	40,41
	Mouse/rat	Stomach, duodenum, jejunum, ileum, cecum, colon, submaxillary gland, lung, pancreas, liver, hypothalamus, pituitary, kidney, adrenal, ovary, testis, thyroid, adipose tissue, muscle, thymus, atrium, ventricle, aorta, plasma	RT-PCR RIA	16,43–45,77
GHS-R	Human	Pituitary, hypothalamus, hippocampal formation, cerebral cortex, basal ganglia, small intestine, rectum, appendix, lung, pancreas, spleen, gallbladder, adrenal, bone marrow, testis, skin	RT-PCR	79
	Mouse/rat	Pituitary, hypothalamus, brain, small intestine, spleen, lung, pancreas, kidney, adrenal, heart, thymus, bone marrow, skeletal muscle, brown adipose tissue, white adipose tissue, testes	RT-PCR	42–44,77

GHS-R: growth hormone secretagogue receptor; RT-PCR: reverse transcription polymerase chain reaction; RIA: radioimmunoassay.
It is important to note that the GHS-R expression above does not pertain to specific cell types, but rather reflects the levels in the whole tissue that includes different types of cells, including immune cells.

still an ongoing debate, as multiple receptors have been proposed including GHS-R,[22] glucagon-like peptide 1 receptor,[23] and G-protein coupled receptor 39.[24] While ghrelin function as agonist for GHS-R, liver-expressed antimicrobial peptide 2 (LEAP-2) has now been identified as antagonist for GHS-R.[25] GHS-R has two isomers: GHS-R1a and GHS-R1b; GHS-R1a is considered as the functionally relevant receptor because it binds to ghrelin, whereas GHS-R1b does not.[26,27] It has been shown that GHS-R1b has an inhibitory effect on GHS-R1a signaling and can form heterodimeric complexes with other receptors.[28] In this current review, we focus on acyl-ghrelin (referring it as ghrelin), because it is the only confirmed endogenous agonist for GHS-R, and limit our discussion on the functionally relevant receptor GHS-R1a (referring as GHS-R).

Immune cells have critical roles in normal and disease conditions; in this review, we primarily focus on the role of ghrelin signaling in chronic inflammation, aka meta-inflammation, that is prevalent to obesity-associated diseases and aging.[29–32] Immune cells – such as macrophages, dendritic cells (DCs), neutrophils, T cells, and B cells – have been shown to play critical roles in the initiation and resolution of inflammation under diet-induced obesity (DIO).[33–36] In obesity, the infiltration of macrophages and DCs into adipose tissues is increased exponentially,[30,37,38] and macrophages shift toward a pro-inflammatory state and secrete pro-inflammatory cytokines.[30] In aging, immune dysfunction in the elderly is evident, showing reduced responsiveness to vaccination, decreased immune surveillance, reduced resistance to infections, but increased susceptibility to inflammation and autoimmune activation.[31,39] Another hallmark impairment of the immune system in aging is thymic atrophy. Thymic atrophy causes increased output of self-reactive T cells, reduced autoimmune suppression by regulatory T cells, and decreased naïve T cells; these pathological changes exacerbate inflammation and immunosenescence, promoting inflammaging.[32] Thus, immune cells have critical roles in the pathogenesis of diseases and aging. It is extremely important to understand the expression and roles of GHS-R in immune cells in order to further elucidate the immune regulation of ghrelin signaling in inflammatory diseases and aging.

Ghrelin and GHS-R expressing tissues and cells

Ghrelin is highly produced by X/A-like cells, a group of unique endocrine cells in gastric mucosa of the stomach, and it is also ubiquitously expressed throughout the body.[40,41] In contrast, GHS-R expression is much more restricted. In mice, the highest expression of GHS-R is detected in the pituitary gland and the hypothalamus,[42–44] and low levels of GHS-R expression are detected in selective peripheral tissues, such as heart, thymus, testes, lung, adrenal, small intestine, spleen, and kidney.[43,45] We reported that GHS-R is detected in mouse bone marrow, pancreas, skeletal muscle, brown adipose tissue, and white adipose tissue, whereas GHS-R expression level in those peripheral tissues is much lower compared to that in pituitary and brain.[42] The tissues expressing ghrelin and GHS-R in humans and rodents are, respectively, summarized in Table 1. While ghrelin, as a hormone, can reach all tissues through circulation, GHS-R is a cell-surface receptor that is expressed in specific cell types to mediate down-stream signaling events. It needs to be emphasized that the data of GHS-R expression are more limited compared to that of ghrelin, and the GHS-R expression data in Table 1 do not pertain to specific individual cell types, but rather to the whole tissue that includes different types of cells (including various immune cells). For example, in liver, while the predominant cell type is hepatocytes, it also contains immune cells, such as Kupffer cells, innate lymphoid cells (ILCs), DCs, natural killer (NK) cells, invariant NKT (iNKT) cells, mucosal-associated invariant T (MAIT) cells, and γδ T cells.[46,47] Therefore, caution need to be taken when interpreting the GHS-R expression data in tissue.

Expression of ghrelin and GHS-R under chronic inflammatory states

The notion that ghrelin signaling is relevant to metabolic diseases and aging is based on the evidences reported by our group and others on the tissue expression profile of ghrelin and GHS-R under obesity and aging, and the identified functions with loss or gain of function studies of ghrelin/GHS-R.[1,3,9,43,48–53] We showed that mouse plasma ghrelin levels

Table 2. Expression of ghrelin and GHS-R in various human/mouse tissues under inflammatory states.

Expression	Species	Disease state	Expression level change	Time of sample collection or length of diet	Tissue	Detection method	References
Ghrelin	Human	DIO	↓	30 ± 7 years 30.4 ± 4.1 years	Plasma	RIA, RT-PCR	50,57
		DIO	↓	44.3 ± 12.6 years	Serum	RT-PCR	58
		DIO	↑	44.3 ± 12.6 years	Gastric	RT-PCR	58
		CD	↑	30.5 ± 11 years	Sigmoid colon	RT-PCR	59
		UC	↑	39 ± 11.5 years	Sigmoid colon	RT-PCR	59
	Mouse	DIO	↓	HFD for 8–14 weeks	Plasma	RIA	51–53
		DIO	↑	HFD for 7 weeks	Corpus, duodenum	RIA	51
		Aging	↑	4–22 months	Plasma	RIA	48
		Aging	↑	2–24 months	Brain	RT-PCR	43
		Aging	↓	24–28 months	Brain	RT-PCR	43
		UC	↑	DSS for 7 days	Lymph node	RT-PCR	60
GHS-R	Human	CD	↑	30.5 ± 11 years	Sigmoid colon	RT-PCR	59
		CD	↑	39 ± 11.5 years	T cells from PBMC	Flow cytometry	59
	Mouse	DIO	↓	HFD for 11 weeks	Nodose ganglion, hypothalamus	RT-PCR	49
		Aging	Highest in 1–2 months	1–2 months	Pituitary	RT-PCR	43
		Aging	↑	13–16 months	Peritoneal fluid	RT-PCR	42
		UC	↑	DSS for 7 days	Colon, lymph node	RT-PCR	60,61

DIO: diet-induced obesity; CD: Crohn's disease; UC: ulcerative colitis; HFD: high-fat diet; GHS-R: growth hormone secretagogue receptor; PBMC: peripheral blood mononuclear cell; DSS: dextran sulfate sodium; RT-PCR: reverse transcription polymerase chain reaction; RIA: radioimmunoassay.
The arrows note the expression level changes of ghrelin or GHS-R: ↑ indicates increase and ↓ indicates decrease.

are increased with aging.[43,48] Counterintuitively, plasma ghrelin levels are reduced under DIO,[51,52] and the ghrelin-producing cells in the stomachs of mice are decreased under DIO.[53] Consistent with the mouse data, circulating ghrelin levels in obese humans are also reduced.[50] A recent report uncovered that decreased ghrelin levels in obesity are due to the fact that the insulin receptor in ghrelin-expressing cells inhibits ghrelin secretion under obesity.[54]

We showed that *GHS-R* gene expression in mouse pituitary glands is highly variable throughout aging: with the highest expression in one to two months old mice, an increasing trend with aging between 6 and 28 months of age, while the expression at 28 months of age is still lower than that of one to two months old young mice.[43] In addition, we reported that high-fat diet feeding significantly increased the expression of GHS-R in the arcuate nucleus and ventromedial hypothalamus in the mouse brain.[3] Interestingly, another study reported that the GHS-R mRNA levels in the nodose ganglion and hypothalamus of high-fat diet fed mice were lower compared to that of chow-fed mice.[49] Importantly, we demonstrated that GHS-R ablation protects against DIO, and ameliorates age-associated inflammation and insulin resistance.[3,42,55] These results collectively indicate that ghrelin/GHS-R signaling has important roles in diet- and aging-associated meta-inflammation and metabolic dysfunctions.

As mentioned above that hormone ghrelin is produced ubiquitously in almost all tissues, including immune cells, the highest expression of ghrelin is detected in stomach.[41] Regardless of the site of production, as a hormone, ghrelin can reach all target cells through circulation in the body. Ghrelin's function is mediated by its receptor GHS-R. In contrast to ghrelin, the expression of GHS-R is restricted to specific cell types; the highest expression of GHS-R is in the neurons of brain.[42,43] Among other selected cell types expressing GHS-R, immune cells, including macrophages[42] and T cells,[56] have the second highest expression. The site of GHS-R expression dictates where the ligand–receptor interaction takes place. Thus, ghrelin can regulate immune cells by endocrine and/or autocrine mechanism. It is essential to determine the sites and levels of GHS-R expression under physiological/pathological conditions in order to understand the regulatory roles of ghrelin signaling in pathogenesis and disease progression of various diseases, and facilitate the development of potential cell-specific therapeutic interventions. Table 2 summarizes the expression level changes of ghrelin and GHS-R under various chronic inflammatory conditions, such as DIO, aging, as well as acute inflammation, such as inflammatory bowel diseases of Crohn's disease and ulcerative colitis. Ghrelin expression in both humans and mice under DIO is highly variable. In obese humans, ghrelin levels are decreased in plasma and serum, but increased in gastric tissues.[50,57–59] In obese mice, ghrelin levels are decreased in plasma, but increased in corpus and duodenum.[51–53] Interestingly, ghrelin expression in humans and mice is overall increased, which is evident in plasma and brain in aging, and colon and lymph nodes in Crohn's disease and ulcerative colitis.[43,48,60] GHS-R expression is decreased in hypothalamus and nodose ganglion of DIO mice.[49] GHS-R expression is mostly increased in pituitary, peritoneal fluid, colon, lymph node, and peripheral blood mononuclear cell (PBMC) in aging, Crohn's disease, and ulcerative colitis.[42,59–61] The current knowledge of GHS-R expression in immune cells and its immune regulation is preliminary, which is the major reason that we write this review, hoping to inspire further investigation.

GHS-R expression in innate and adaptive immune cells

In general, immune cells can be divided into two major categories: innate immune cells, which include monocytes, macrophages, neutrophils, DCs, and NK cells, and adaptive immune cells, which include T and B cells.[62] Here, we have summarized the current literature regarding the expression of GHS-R in innate and adaptive immune cells, its expression under inflammatory conditions, as well as reported functions of GHS-R in these immune cells.

Monocytes

GHS-R is reported to express in human monocytes. One study reported that GHS-R expression in monocytes is similar between Crohn's disease patients and healthy controls.[59] Another study showed that 21% of CD14+ human monocytes in PBMC express GHS-R, and ghrelin administration reduces secretion of pro-inflammatory cytokines (interleukin [IL]-1b and IL-6) in lipopolysaccharide (LPS)-treated monocytes.[63]

Macrophages

Ellie Metchnikoff identified macrophages as phagocytes that function to clear cellular debris and bacterial products; macrophages also repair tissue injury. Macrophages are essential in retaining tissue homeostasis; macrophage dysfunction triggers systemic inflammation.[64] Responding to microenvironmental cues, macrophages rapidly react to stimuli to combat insults/injury.[65,66] Polarization is a hallmark phenotypical change of macrophages; the phenotypical change of macrophages directly affects their functional outcomes. Macrophages are often described as a dichotomy of M1-like and M2-like macrophages: M1-like macrophages being pro-inflammatory and M2-like macrophages being anti-inflammatory.[66–69] While the M1–M2 paradigm is widely used *in vitro*,[66] it is now recognized that in tissues, macrophages exist as a continuous spectrum instead of a distinctive M1–M2 population.[70,71] For the convenience of the discussion, we will continue to use the M1–M2 concept in this review.

We previously reported that GHS-R is highly expressed in mouse peritoneal macrophages (PMs), 60% of the highest-expressing tissue, the hypothalamus.[42] Moreover, we found that GHS-R expression is elevated in PM of aged mice, and that ablation of GHS-R shifts macrophages of peritoneal fluid and white adipose tissue toward an anti-inflammatory state in the aged mice.[42] We also found that M1-like macrophages are decreased, and pro-inflammatory cytokine expression of tumor necrosis factor (TNF)-a, IL-1b, and IL-6 is reduced in epididymal fat of GHS-R-ablated mice fed high fructose corn syrup (HFCS).[55] Similar to our findings, others also showed that adipose tissue in GHS-R-ablated mice under DIO had decreased pro-inflammatory macrophage marker expressions including monocyte chemoattractant protein (MCP)-1, TNF-a, and inducible nitric oxide synthase (iNOS), whereas the anti-inflammatory markers of arginase-1 (Arg-1) and macrophage galactose-type lectin-1 (Mgl-1) were increased.[72] In addition, we reported that the macrophage Raw264.7 cell line expresses GHS-R, and GHS-R antagonist or GHS-R siRNA knockdown resulted in significant reduction of pro-inflammatory marker expressions under LPS-induced inflammation.[55] Collectively, these results indicate that GHS-R has a cell-autonomous effect in macrophages and GHS-R is involved in the polarization and immune remodeling of macrophages. That is to note that GHS-R, as G protein-coupled receptor, has high ligand-independent constitutive activity, which is about 50% of the maximal activity.[73,74] The effect of GHS-R in immune cells could be mediated by both ligand-dependent and independent (constitutive) mechanisms. We observed that global deletion of GHS-R did not alter the serum ghrelin level compared to wild-type littermates under both fed and fast conditions.[18] While more studies are needed, we speculate that the effects of GHS-R in macrophages are mediated by both ghrelin-dependent and ghrelin-independent mechanisms. That is likely that even without endogenous ghrelin, GHS-R can modulate immune cells by altering its down-steam signaling pathways. Current studies reported by us and others on the effect of GHS-R on macrophage polarization are summarized in Table 3, showing that suppression of GHS-R promotes an anti-inflammatory polarization of macrophages both *in vivo* and *in vitro*.

DCs

While there are reports showing GHS-R expression in DCs,[63,75,76] the function of GHS-R in DCs is still debatable. Dixit *et al.* reported that GHS-R is detected in both immature and mature monocyte-derived DCs.[63] GHS-R expression has been reported in thymic stromal cells, which include DCs, macrophages, and epithelial cells.[77] The same group also reported that the number of $CD11c^+$ DCs in thymic medulla of aged mice is enhanced by ghrelin administration, and also showed co-localization of GHS-R and $CD11c^+$ DCs, which suggest that age-associated decline of thymic output may be linked to reduced expression of thymic ghrelin and GHS-R.[75] However, it needs to note that the cell-specific function of GHS-R in DCs has not been determined.

Neutrophils

Human neutrophils from the blood have previously been found to express both ghrelin and GHS-R.[56] Currently, only limited information is available regarding whether GHS-R in neutrophils affects the function of neutrophils in humans and rodents. A study using vertebrate rainbow trout (*Oncorhynchus mykiss*) reported that ghrelin treatment *in vitro* elevates production of superoxide in phagocytic leukocytes from trout head kidney.[78] In the same study, GHS-R antagonist treatment suppressed ghrelin-induced superoxide production in phagocytic leukocytes; this suggests that GHS-R might play a role in oxidative burst of the phagosome. The precise function of GHS-R in neutrophils in humans and rodents remains to be further elucidated.

NK cells

Although very limited, human NK cells have been found to express both ghrelin and GHS-R.[79] In both lean and obese mice, ghrelin treatment has been shown to increase NK cells in peritoneal fluid of surgically induced sepsis.[80] Similarly, another study reported that ghrelin-treated rats

Table 3. GHS-R-associated changes of macrophage cell-surface markers and cytokine expression in mice.

Inflammatory stimuli	Summary of results	Tissues/cells	Treatment or age	Detection method	References
HFD-induced obesity	Adipose tissue macrophages of GHS-R global knockout mice show reduced M1 pro-inflammatory markers (MCP-1, TNF-a, and iNOS) and increased M2 anti-inflammatory markers (Arg-1 and Mgl-1).	Epididymal adipose tissue	12-month feeding	RT-PCR	72
HFCS-induced inflammation	Ablation of GHS-R reduces pro-inflammatory cytokines of TNF-a, IL-1b, and IL-6, as well as chemokine MCP-1 in epididymal fat.	Epididymal adipose tissue	10-month feeding	RT-PCR, flow cytometry	55
	Ablation of GHS-R reduces mRNA expression of F4/80, MCP-1, CD11c, TNF-a, and IL-1b in peritoneal macrophages.	Peritoneal fluid	10-month feeding	RT-PCR	55
Aging	GHS-R ablation shifts the M1/M2 macrophage ratio toward anti-inflammatory and attenuates pro-inflammatory cytokines (F4/80, MCP-1, TNF-a, IL-1b, IL-6, CD11c) in epididymal white adipose tissue.	Epididymal adipose tissue	13- to 16-month old	RT-PCR	42
	GHS-R ablation attenuates age-associated expression of F4/80, MCP-1, TNF-a, IL-1b, and CD11c in brown adipose tissue.	Brown adipose tissue	13- to 16-month old	RT-PCR	42
	GHS-R ablation reduces the expression of MCP-1, TNF-a, IL-1b, and CD11c in the peritoneal macrophages, shifting peritoneal macrophages toward anti-inflammatory state.	Peritoneal fluid	13- to 16-month old	RT-PCR	42
LPS-induced inflammation	GHS-R siRNA knockdown in RAW 264.7 cells results in decreased expression of MCP-1, CD11c, TNF-a, IL-1b, and IL-6.	RAW264.7	18 h LPS (1 μg/mL)	RT-PCR	55
	GHS-R shRNA knockdown in RAW264.7 cells attenuates LPS-induced increases of MCP-1, TNF-a, IL-1b, and CD11c.	RAW264.7	16 h LPS (1 μg/mL)	RT-PCR	42
	GHS-R antagonist attenuates LPS-induced increase of TNF-a and IL-1b.	RAW264.7	16 h LPS (1 μg/mL)	RT-PCR	42

GHS-R: growth hormone secretagogue receptor; HFCS: high fructose corn syrup; HFD: high-fat diet; LPS: lipopolysaccharide; MCP-1: monocyte chemoattractant protein; TNF: tumor necrosis factor; iNOS: inducible nitric oxide synthase; IL: interleukin; RT-PCR: reverse transcription polymerase chain reaction; RIA: radioimmunoassay.

with *Trypanosoma cruzi* infection had elevated NK cells in spleen.[81] The same study revealed that about 10% of NK cells in spleen express GHS-R in steady state, and the GHS-R expression is increased in activated NK cells.[81] However, it is not known if GHS-R alters function of NK cells.

B lymphocytes

B lymphocytes from human blood were found to express both ghrelin and GHS-R, whereas the expression level varies among individuals.[56] It is also shown that human leukemic B cell lines, including Raji and Daudi, express GHS-R. Currently, functional relevance of GHS-R in B lymphocytes is unclear.

T lymphocytes

Similar to B cells, human T lymphocytes from blood also express ghrelin and GHS-R and show great variability among individuals.[56] It was reported that the percentage of GHS-R positive $CD3^+$ T cells from human blood is significantly elevated in Crohn's disease patients compared to healthy controls, while the percentage of GHS-R expressing T cells in ulcerative colitis patients did not differ from controls.[59] Dixit *et al.*[82] showed that the active form of ghrelin is represented in more than 70% of human T cells. Furthermore, approximately 30% of highly purified human resting T cells express GHS-R, and its expression is upregulated under T cell activation.[63] In the same study, ghrelin treatment inhibits pro-inflammatory cytokine production (IL-1β and IL-6) in primary human T cells upon anti-CD3 activation. Interestingly, this study revealed that GHS-R is co-localized with aggregated lipid rafts under cellular activation, suggesting GHS-R may affect T cell activation.

In line with human data, murine splenic T cells are also reported to express GHS-R and ghrelin. Ghrelin administration restores proliferation of $CD4^+$ T cells, showing a protective effect for surgically induced sepsis.[83] Similarly, it was reported that ghrelin treatment increases γδ T cells in peritoneal fluid of lean septic mice.[80] However, another study showed that ghrelin suppresses anti-CD3-induced proliferation of mouse splenic T cells in a dose-dependent manner.[84] Current literature in the area is confounding. One study showed that ghrelin does not affect proliferation of human T cells, nor their secretion of IL-2 and interferon gamma (IFN-γ).[63] However, another study reported that ghrelin treatment inhibits mRNA expression of Th1 cell-produced cytokines of IL-2 and IFN-γ, as well as Th2 cell-produced cytokines of IL-4 and IL-10 in the murine splenic T cells.[84] Thus, while there is evidence that ghrelin/GHS-R signaling has an important role in T cells, much more studies are needed to further define the precise function of GHS-R in T cells.

Conclusions

GHS-R is expressed in immune cells, and its expression changes dynamically depending on the microenvironment. GHS-R responds to various inflammatory cues, and is

altered under various disease conditions such as DIO, aging, and inflammatory diseases.

While the role of GHS-R in the immune system is not fully understood, the current available data clearly indicate that GHS-R has a role in both innate and adaptive immunity. There is strong evidence that GHS-R is expressed in macrophages and T cells, and GHS-R is associated with macrophage functional programming and T cell activation. The loss-of-function study indicates that ablation of GHS-R shifts the macrophage phenotype from pro-inflammatory to anti-inflammatory, which supports a role of GHS-R in macrophage polarization. In addition, there is also evidence that GHS-R expression is upregulated in activated T cells and co-localized with lipid rafts. Increased expression levels of GHS-R in macrophages and T cells are detected in inflammatory disease models; this suggests that ghrelin/GHS-R may be involved in the pathogenesis of inflammatory diseases. Blockage of the GHS-R signaling pathway may have a therapeutic potential in both metabolic and inflammatory disease states. Besides macrophages and T cells, the other immune cells such as DCs, neutrophils, NK cells, and B cells also express GHS-R, whereas the function of GHS-R in these immune cells remains to be elucidated.

Overall, ghrelin signaling has exciting implications in immune functions in health and great therapeutic potentials in disease. However, it is important to note that the ghrelin signaling in immunity is likely to be complex. There are differential immune phenotypes exhibited by ghrelin and GHS-R, notably both ghrelin and GHS-R deficiency show anti-inflammatory effects. This discrepancy suggests that GHS-R may activate both ghrelin-dependent and ghrelin-independent signaling pathways in immune cells, which underscores the critical need for further investigation. Single-cell RNA sequencing and cell-specific gene targeting would be advantageous for a better understanding of the cell-specific roles and regulatory mechanisms of ghrelin signaling in immunity.

AUTHORS' CONTRIBUTIONS

JYN and YS contributed to the conceptualization. JYN and MH contributed to the investigation. YS contributed to the resources. JYN and MH contributed to the writing—original draft preparation. JYN, XDT, BSP, GW, and YS contributed to the writing—review and editing. GW and YS contributed to the supervision. YS contributed to the project administration. YS and XDT contributed to the funding acquisition. All authors have read and agreed to the published version of the manuscript.

DECLARATION OF CONFLICTING INTERESTS

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