Review article

Animal lectins: potential receptors for ginseng polysaccharides

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ABSTRACT

Panax ginseng Meyer, belonging to the genus Panax of the family Araliaceae, is known for its human immune system-related effects, such as immune-boosting effects. Ginseng polysaccharides (GPs) are the responsible ingredient of ginseng in immunomodulation, and are classified as acidic and neutral GPs. Although GPs participate in various immune reactions including the stimulation of immune cells and production of cytokines, the precise function of GPs together with its potential receptor(s) and their signal transduction pathways have remained largely unknown. Animal lectins are carbohydrate-binding proteins that are highly specific for sugar moieties. Among many different biological functions *in vivo*, animal lectins especially play important roles in the immune system by recognizing carbohydrates that are found exclusively on pathogens or that are inaccessible on host cells. This review summarizes the immunological activities of GPs and the diverse roles of animal lectins in the immune system, suggesting the possibility of animal lectins as the potential receptor candidates of GPs and giving insights into the development of GPs as therapeutic biomaterials for many immunological diseases.

1. Introduction

1.1. Ginseng polysaccharides

1.1.1. Ginseng

Panax ginseng Meyer is a well-known medicinal plant in the world. The ginseng is a deciduous perennial belonging to the family Araliaceae and genus *Panax*. The genus name of ginseng, *Panax*, is derived from the Greek *pan* (all) *akos* (cure), meaning "cure-all" or "all healing," which describes the traditional belief that ginseng has properties to heal all aspects of the body. The name ginseng comes from the Chinese words "Jen Sheng," meaning "man-herb," because of the humanoid shape of the root or rhizome of the plant, which is the part of the plant most commonly used for extraction [1,2]. There are about 13 different species of ginseng which have being identified all over the world. Among them, the most commonly used species of ginseng are Asian ginseng (*P. ginseng* Meyer, *Renshen*) and American ginseng

(*Panax quinquefolius* L., *Xiyangshen*) which all belong to the *Panax* genus of the Araliaceae family [3]. Asian ginseng has been used for thousands of years as a tonic to improve overall health, restore the body to balance, help the body to heal itself, and reduce stress [4], and American ginseng has been used by Native Americans for at least hundreds of years [2,5]. Ginseng is prepared and used in several ways as fresh ginseng (sliced and eaten, or brewed in a tea), white ginseng (peeled and dried), red ginseng (peeled, steamed, and dried), extract (tincture or boiled extract), powder, tea, tablet, or capsule [1,2]. It has been reported that ginseng exhibits a wide range of beneficial pharmacological effects including immunomodulation, antitumor, antioxidation, antidepression, hypoglycemic, inhibition of gastric lesions, attenuation of leptin-induced cardiac hypertrophy, heart protection against ischemia and reperfusion injury, prevention of glucose-induced oxidative stress, prevention of diabetic nephropathy, retinopathy, and cardiomyopathy [6–10]. This broad spectrum of biological activity of ginseng has originated from its multiple bioactive components,

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namely ginsenosides, polysaccharides (PSs), peptides, poly-acetylenic alcohols, and gintonin [11−13].

1.1.2. The composition of ginseng polysaccharides

Ginsenosides were considered to be responsible for most of ginseng's pharmacological effects. However, recent studies indicate that ginseng polysaccharides (GPs), one of the active components of ginseng [14], also possess a wide range of biological and phar-maceutical activities, including immune-modulation, antitumor, antiadhesive, antioxidant and hypoglycemic activities [8,15]. Especially, GPs are known for their immunostimulatory effects [10,16,17] and a major contributor to the bioactivity of herbal medicines, providing great potential applications in food, phar-maceuticals, and other industries. Therefore, GPs were extensively studied for their constituents and chemical structures. GPs are biopolymers formed from a complex chain of monosaccharides rich in L-arabinose, D-galactose, L-rhamnose, D-galacturonic acid, D-glu-curonic acid, and D-galactosyl residue linked together through glycosidic bonds, resulting in complex macromolecular architec-tures [7,18,19]. Their molecular weights range from 3500 Da to 2,000,000 Da [19], which contributes to their diverse physico-chemical properties and biological activities [8,15,19,20].

GPs include acidic and neutral PSs. The pharmacological effects of GPs, including immunomodulation, can be attributed to these acidic and neutral PS components [15]. While the acidic GPs contain different amounts of uronic acids and neutral sugars [15,21], the neutral PSs mainly contain different ratios of neutral sugar residues [3]. So far, the studies about American GPs have mainly been centered on acidic PSs, resulting in relatively limited research that explores neutral PSs. However, researchers also have interest in neutral PSs of American GPs, because neutral PSs are also one of the important active components in the American ginseng roots. The PSs from ginseng roots have many bioactivities, such as immuno-modulation, antitumor, and hypoglycemic activities [11,22], and contain 60% neutral starch-like PSs, 15% arabinogalactans, and 25% pectins [20]. Similarly, the PSs from ginseng leaves are also bioac-tive, and contain about 70% arabinogalactans and 20% pectins.

1.1.3. The immune functions of GPs

GPs enable enhancement of the production of cytokines and reactive oxygen species by stimulating macrophages [23,24]. In a recent study, GP was shown to stimulate dendritic cells (DCs) resulting in enhanced production of interferon-γ (IFN-γ) [25]. It was reported that acidic GPs promoted the production of cytotoxic cells against tumors and stimulated macrophages to produce helper types 1 and 2 (Th1 and Th2) cytokines [26,27]. An acidic GP from *P. ginseng* has been shown to display immunomodulatory effects either in an immunostimulatory or in an immunosuppres-sive manner, depending on timing of treatments and disease en-vironments [28]. This acidic GP was also shown to modulate the antioxidant defense systems such as superoxide dismutase and glutathione peroxidase enzymes, probably via inducing regulatory cytokines [15,29]. Therefore, acidic GPs have been considered as the major bioactive species for immune modulations. Tomoda et al [30] reported that two acidic PSs of *P. ginseng* enhance the phagocytic activity of macrophages, and Sonoda et al [31] found that an acidic GP of *P. ginseng* was a potent inducer of interleukin-8 (IL-8) pro-duction by human monocytes and THP-1 cells. Shin et al [32] re-ported that an acidic PS of *P. ginseng* shows immune modulatory activities via macrophage NO production. Recently, Lemmon et al [29] reported that the immunostimulatory effects of acidic GPs of *P. quinquefolius* are mediated by PS with a molecular weight higher than 100 kDa. It was reported that acidic GPs promoted the pro-duction of cytotoxic cells against tumors and stimulated macro-phages to produce helper types 1 and 2 (Th1 and Th2) cytokines

[26,27]. Intravenous pretreatment of GP attenuated the produc-tion of serum proinflammatory and antiinflammatory cytokines after septic bacterial infection [33].

In addition, Ginsan, an acidic GP from of *P. ginseng*, is a well-known medicinal herb and has been shown to have critical ef-fects on immune cells, which shows an immunomodulatory acidic GP from *P. ginseng* [27]. Kim et al [26] showed that Ginsan induces Th1 cell and macrophage cytokines. Ginsan enhances the produc-tion of cytokines and reactive oxygen species by macrophages [24] and stimulates the phagocytic activity of macrophages [23]. Also, Ginsan induces the maturation of DCs [25], profoundly enhancing the production of IL-12, IL-10, and tumor necrosis factor alpha (TNF-α) by DCs and showed that Ginsan may modulate DC function by altering cytokine levels [25]. For neutral GPs, it was reported that neutral GPs of *P. ginseng* stimulate the proliferation of lymphocytes, increase the cytotoxicity of natural killer cell, enhance the phago-cytosis and NO production by macrophages, and increase the level of TNF-α in serum [21,34]. Due to these results, many scientists have considered both acidic and neutral GPs as stimulators in the im-mune system. X. Zhang et al and Kim et al reported that both acidic and neutral GPs of *P. ginseng* (Asian ginseng) may stimulate B cells, T cells and macrophages [20,35]. In addition, they considered the relation of acidic and neutral GPs as the supporter, in which neutral GPs help the enhancement of immunostimulatory effects of acidic GPs. In fact, W. Ni et al reported that neutral GPs of *P. ginseng* enhance macrophage production of NO [21].

On the contrary to immunostimulatory effects of GPs, recent studies showed that GPs also suppress the proinflammatory re-sponses. Recently, it was reported that a novel neutral PS (PPQN, 3.1 kDa) was isolated from American ginseng roots and could suppress inflammation by inhibiting the secretion of inflammatory-related mediator nitric oxide (NO) and cytokines (TNF-α, IL-6, and IL-1β) compared to Lipopolysaccharide (LPS) treatment, impli-cating the therapeutic implications of PPQN in inflammatory-related diseases like tumors, atherosclerosis, and so on [3]. As an example, one study reported that GPs inhibit immunological re-sponses associated with collagen-induced arthritis [36]. Other studies also suggest that CVT-E002, a poly-furanosyl-pyranosyl polysaccharide-rich herbal and unique extract product of the root of American ginseng (*P. quinquefolium*), suppresses the inflamma-tory immune responses, reducing the activation of neutrophils [37], inducing the production of IL-2, IFN-γ, TNF-α, and IL-6 in spleen [7,19,38], and increasing the proliferation of splenic B lymphocytes, bone marrow, and natural killer cells.

1.1.4. The working mechanisms of GPs in pathogen protection

Intravenous pretreatment of GP attenuated the production of serum proinflammatory and antiinflammatory cytokines after septic bacterial infection [33]. Also, this intravenous pretreatment of GPs in mice enhances macrophage-mediated bactericidal activity by reducing the number of *Staphylococcus aureus* which is present in the spleen, kidney, and blood and exerts a protective effect against infected septic mice by suppressing early acute inflamma-tion [33,39]. In addition, recent studies reported that pretreatment with GP suppressed acute inflammatory responses at an early phase resulting in the enhancement of antimicrobial activities and protection of mice from *Staphylococcus aureus*-induced sepsis as an antiinflammatory function [33,39]. As an example, CVT-E002 has been shown to be effective for preventing acute respiratory illness caused by influenza and respiratory syncytial virus [7,40]. Another study revealed that intranasal administration of GPs showed a protective effect on influenza viral infection by lowering the levels of inflammatory cytokines (IL-6) and lung viral titers [28]. Because GPs were reported to significantly increase the viability of perito-neal macrophage cells [8] and ginseng was shown to inhibit
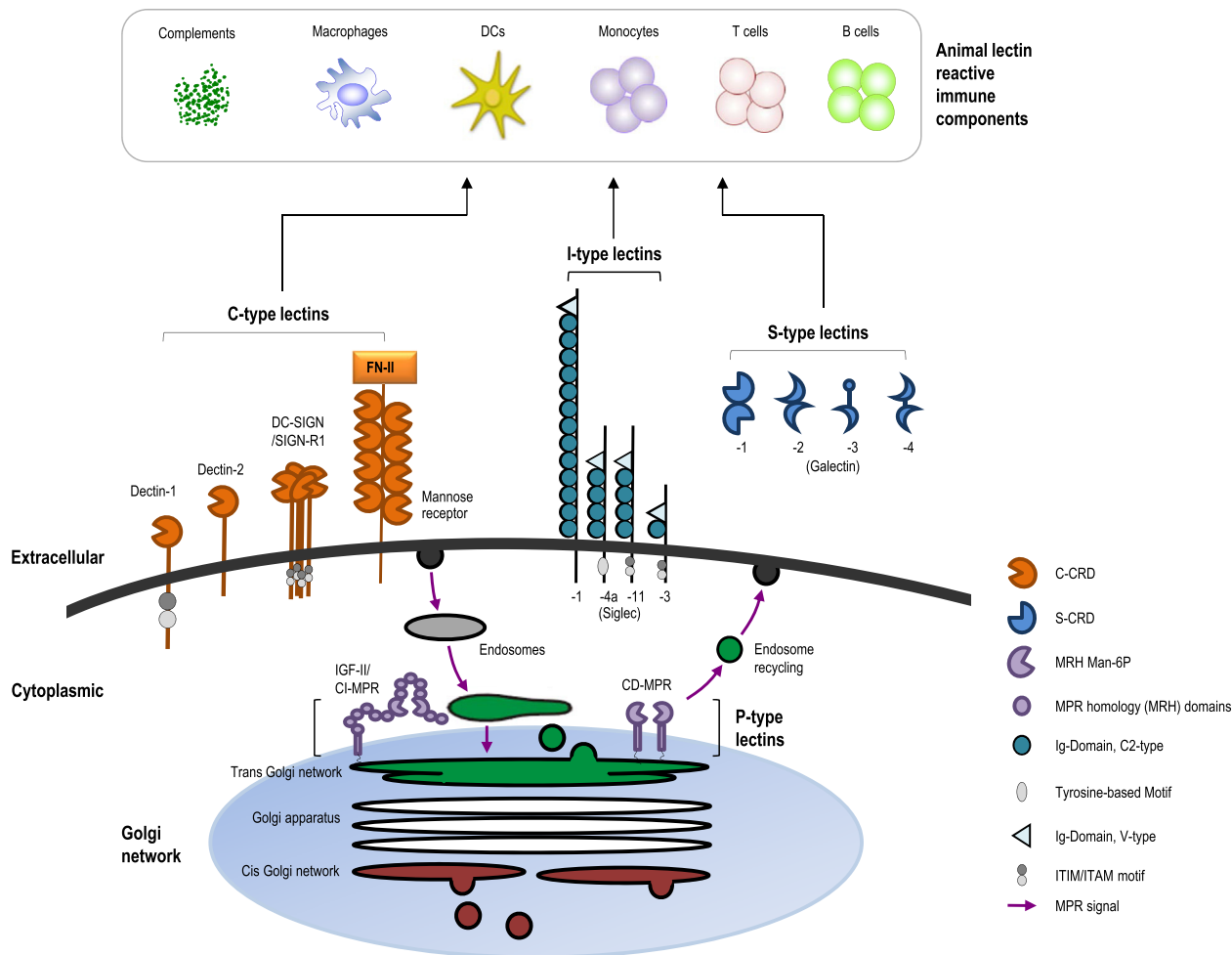
Fig. 1. The structure, cellular distribution, and reactive immune components of animal lectins. Domain structure models, the location of several representative animal lectins, and the immune cells reacting with animal lectins. Carbohydrate-recognition domains (CRDs) of each lectin are depicted in the respective whole structures. S-type lectins are secreted into the extracellular matrix of body fluids. C-type and I-type lectins are localized to the plasma membrane, and P-type lectins are located in luminal compartments of the secretory pathway. CD-MPR, cation-dependent mannose-6-phosphate receptor; CI-MPR, cation-independent mannose-6-phosphate receptor; CRD, carbohydrate-recognition domain; DC, dendritic cell; DC-SIGN, DC-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin; IGF, insulin-like growth factor; MRH Man-6P, mannose 6-phosphate receptor homology; ITIM/ITAM motif, immunoreceptor tyrosine-based inhibition/immunoreceptor tyrosine-based activation motif.

degradation of long-lived proteins and to stimulate protein synthesis similar to polypeptide growth factors [41], it was suggested that maintaining the cell viability under the condition of viral infection-induced stress might be an another alternative mechanism for the protective effects of GP.

It was reported that the recognition and binding of plant PSs by Toll-like receptor 4 (TLR4) leads to the recruitment of various cytoplasmic Toll/IL-1 receptor (TIR) domain-containing adaptors such as myeloid differentiation factor 88 (MyD88), TIR domain-containing adaptor protein (TIRAP), and TIR (Toll/interleukin-1 receptor)-domain-containing adapter-inducing interferon-β (TRIF)-related adaptor molecule (TRAM) [42]. It was also shown that the expression of TLRs including TLR2, TLR4, and the adaptor molecule MyD88 is significantly reduced in murine macrophages by GP pretreatment *in vitro*, which were increased in murine macrophages with the stimulation of *S. aureus* [33,39]. On the contrary, Friedl et al [16] and Lemmon et al [29] showed that American GP extracts may mediate the immunostimulatory effect by the inducible nitric oxide synthase (iNOS), mitogen-activated protein kinase (MAPK) kinases such as p38, extracellular signal-regulated kinases 1/2 (ERK1/2), phosphoinositide 3-kinase (PI3K), and nuclear factor kappa B (NF-kB) signaling pathways [16,29]. Therefore, these results suggest that GPs might be associated with the ability

of the extract's PS fractions to bind to TLR4 receptor and upregulate or downregulate TLR4 receptor expression, which triggers or inhibits the intracellular signaling cascades and the production of proinflammatory mediators under basal or LPS endotoxic conditions, respectively.

1.2. Animal lectins

1.2.1. Introduction to animal lectins

Animal lectins are carbohydrate-binding proteins which are highly variable in their amino acid sequences, widely distributed in microorganisms, viruses, animals and higher plants with different functions, structures, tissue localizations, and carbohydrate-binding specificities [43]. Animal lectins were discovered before plant lectins, although many were not recognized as carbohydrate binding proteins for many years after first being reported [44]. Although plant and animal lectins do not have homologous primary structures, they have similar preferential binding to carbohydrates [45]. Animal lectins are neither immune origin nor catalyst, in contrast to antibodies or enzymes, and are able to detect or bind complex carbohydrate structures specifically through the carbohydrate-recognition domain (CRD) [46,47]. Each animal lectin possess its own CRD which has an identical sequence motif of 115 to

130 amino acid residues and four cysteines that is thoroughly conserved and form two disulfide bonds [47,48].

Animal lectin activity is found in association with an astonishing diversity of primary structures [44]. At least 12 structural families are known to exist and bind structures other than carbohydrates via protein-protein, protein-lipid or protein-nucleic acid interactions [44]. Their roles in glycol-recognition systems include complement activation, cell recognition, cell adhesion, cell migration, cell signaling, and morphogenesis. Moreover, animal lectins are able to take part in defense mechanisms, importantly by recognizing a carbohydrate of pathogens [47,48]. Animal lectins are means of attachment to various cells or viruses via the surface carbohydrate types of the cells to be attached [49]. The function in recognition or cell surface interaction of animal lectins has been implicated in direct first-line defense against pathogens [44]. For example, the mannose specific receptor, presented on the surface of macrophages, can bind to the infectious organisms which expose mannose-containing glycans on their surface, enabling them to ingest and kill the foreign organisms [49]. In addition, animal lectins are involved in cell trafficking, immune regulation, and prevention of autoimmunity [44]. Animal lectins are classified into four families based on structure or function. These are the C-type (calcium-requiring) lectins, P-type (mannose-6-phosphate binding) lectins, S-type (galectins) lectins, and I-type (immunoglobulin-like) lectins (Fig. 1) [47]. Within each family, they have similar sequences and structural properties [46]. Recently, other lectin types have been found, including M-type, L-type, chitinase-like, and F-type lectins. In this review, four traditional families of animal lectins are introduced (Table 1).

1.2.2. C-type lectins

C-type lectins are endocytic receptors which are mostly expressed by macrophages, DCs, and some endothelial cells. C-type lectins require Ca^{2+} for activity and have common sequence motif of 14 invariable and 18 highly conserved amino acid residues [50,51]. As they have multi CRDs, C-type lectins are able to recognize a wide range of carbohydrate-based ligands from endogenous molecules to conserved structures found in bacteria, fungi, virus-infected cells, and parasites called pathogen-associated molecular patterns [52]. After recognition, C-type lectins subsequently participate in the uptake for degradation in order to facilitate direct elimination by macrophages or antigen presentation by DCs and macrophages in Major histocompatibility complex (MHC) molecules at the cell surface, resulting in stimulating the adaptive immune system [53,54]. For example, C-type lectins can recognize diverse bacterial pathogens and induce cytokine production and Th17 responses in antibacterial immunity [55], and are critical in systemic infections with pathogens like Cryptococcus neoformans in antifungal immunity of Th1 effector cells [55]. In addition, they are involved in clearance, homeostasis, and immunomodulation [56]. Many C-type lectins play primary roles in immunity. C-type lectins include Dectins, DC-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN), SIGN-R1, mannose receptor (MR), Collectin (MBL, SP-A, SP-D) and selectins (L-, P-, E-) (Table 2).

1.3. Dectin-1

Dectin-1 specifically binds to β-1,3 and β-1,6 linked glucans of fungi, plant cell walls, and bacteria, including Candida albicans, Saccharomyces cerevisiae, Coccidioides posadasii, and Pneumocystis carinii, but cannot recognize monosaccharides or glucans with other linkages. However, C. neoformans, Histoplasma capsulatum, and Aspergillus fumigatus are not targeted by Dectin-1, in spite of the presence of β-glucans in their cell wall [57,58]. Dectin-1 plays a primary role in inducing proinflammatory mediators like TNF-α in

response to fungal pathogens. Also, Dectin-1 contains an immunotyrosine activation motif within its cytoplasmic tail, helping TLR2 signaling pathway by interaction with the immunotyrosine activation motif of Dectin-1 [57]. Signaling by Dectin-1 regulates various cellular responses including phagocytosis and the production of inflammatory cytokines such as IFNs, IL-23, IL-6, and IL-1 [58]. Dectin-1 expressed on DCs and macrophages can recognize N-glycans of the surface of tumor cells, following nuclear translocation, and the induction of several genes such as Inam, which is known to induce tumor killing by NK cells by hemophilic interactions.

1.4. DC-SIGN

DC-SIGN was originally identified as a receptor for intercellular adhesion molecule-3 (ICAM-3) that induces DC-mediated T-cell proliferation [58]. It was subsequently unveiled to bind ICAM-2 on vascular endothelial cells, regulating DCs migration through interaction of N-linked high mannose structures consisting of from five to nine terminal mannose units [57]. DC-SIGN, which is expressed by DCs, decidual and alveolar macrophages facilitates high-affinity binding to high mannose oligosaccharides through tetramerization [57]. Mannose-dependent interactions demonstrate the ability of DC-SIGN to bind human immunodeficiency virus (HIV) and various pathogens, including Mycobacterium tuberculosis, C. albicans, Leishmania mexicana, A. fumigatus, Helicobacter pylori, and Schistosoma mansoni [58]. For instance, DC-SIGN recognizes mannosylated lipoarabinomannan, which is a mannose-capped glycolipid found in the cell wall of M. tuberculosis. This interaction can induce the secretion of the immunosuppressive cytokine, IL-10, from DCs which expresses DC-SIGN [57]. DC-SIGN expression is mostly induced by IL-4, and is downregulated by IFN-γ, TGFβ, and dexamethasone [58,59].

1.5. Eight mouse genes homologous to DC-SIGN (SIGN-Related gene)

The murine DC-SIGN homologues were reported to help to identify the roles of DC-SIGN in infection and inflammation and to play important roles in bacterial, fungal, and parasitic infections. There are seven mouse genes in the mouse DC-SIGN locus, containing SIGN-R1-5 and SIGN-R7, 8, and a pseudogene, SIGN-R6 [60,61]. The mRNA of three SIGN-R genes encode type II transmembrane proteins (SIGN-R1, 325 amino acids; SIGN-R3, 237 amino acids; SIGN-R4, 208 amino acids), but SIGN-R2 gene only encodes a CRD without a cytosolic domain and a transmembrane domain (SIGN-R2, 178 amino acids) [62]. Amino acid sequence similarities between the CRD of human DC-SIGN and the murine homologues are 69% for SIGN-R1, 65% for SIGN-R2, 68% for SIGN-R3, and 70% for SIGN-R4 [62].

SIGN-R1, a murine homologous transmembrane of the DC-SIGN, is expressed by splenic marginal zone macrophages and peritoneal macrophages [53,57]. Similar to DC-SIGN, SIGN-R1 is essential for the recognition and clearance of Streptococcus pneumoniae-derived capsular PSs. Moreover, it can also recognize C. albicans, M. tuberculosis, S. pneumoniae CPS, HIV, and yeast derived zymosan particles in a mannose inhibitable manner [57]. SIGN-R1 directly binds to C1q and dominantly regulates the immunoglobulin-independent classical complement pathway for C3 deposition of blood borne S. pneumoniae [63]. In SIGN-R1 deficient mice, C3 deposition is abolished and innate resistance against pneumococci is reduced [63,64]. Also, SIGN-R1 interacts specifically with 2,6 sialylated Fc fragments of immunoglobulins, resulting in the anti-inflammatory activity of intravenous immunoglobulin, which has been widely used to treat autoimmune diseases including immune

Table 1
The classification of lectins based on structure of carbohydrate-recognition domain (CRD)

Lectin	Expressed cell types	Ligands	Location	Role	Example	Species		
						Human	Mouse	Plant
C-type lectin	DC[a], Mø[b], LC[c], Mo[d], T[e]	Various (mannose, fucose, β-glucan, glucosamine)	Extracellular, transmembrane	Recognition of pathogens, clearance, endocytosis, adhesion, immune-modulation	MR, DC-SIGN, SIGN-Rs, Dectin, Selectin	O	O	O
P-type lectin	Eukaryotic cells	Man-6-phosphate	Secretory pathway, endosome	Endocytosis, intracellular targeting of lysosomal enzymes (lysosome biogenesis)	CD-MPR, IGF-II/CI-MPR	O	O	X
S-type lectin		β-galactoside	Secrete (cytoplasm), extracellular	Cell adhesion, growth regulation, cell migration, immune responses	Galectin (1-14)	O	O	X
I-type lectin	Mast, Bf, Mø, Mo	Sialic acid	Membrane	Regulation of myeloid cell inter-action, differentiation of myeloid cells, adhesion, signaling	Siglecs (CD33-related subgroup, sialoadhesin, CD22 and MAG)	O	O	X
M-type lectin		Mannose glycan	Endoplasmic reticulum	α-Mannosidase, handling of N-linked glycoproteins	EDEM1, EDEM2 and EDEM3	O	O	O
L-type lectin		High-mannose Glycan	Intracellular, Golgi, endoplasmic reticulum, ERGIC[g]	Protein sorting, assisting secretion of specific glycoproteins	ERGIC-53, ERGL, VIP36, and VIPL	O	O	O
Chitinase-like lectin	Neutrophil, Mø, epithelial cell	Chito-oligosaccharide	Extracellular	Collagen metabolism	YKL-40, Ym1, Oviduction	O	O	O
F-type lectin		Fucose-terminating oligosaccharide	Extracellular	Innate immunity	Fucolectins	X	X	X

B, B cell; DCs, dendritic cells; dMø, decidual macrophage; ERGIC, ER-Golgi intermediate compartment; LC, Langerhans cell; Mø, macrophage; Mo, monocyte; T, T cell

Table 2
A summary of the C-type lectin receptors dealt with in this review

Lectin	Expressed cell types	Ligands	Pathogens	Species Human	Mouse	Plant
MR	Mø[a], DC[b] subset, Lymphatic and hepatic endothelium	Mannose, Fucose, N-acetyl glucosamine, Sulphated sugar	Yeast, bacteria, HIV[n], C. albicans, L. donovani, P. carinii, Klebsiella pneumonia, Trypanosoma cruzi, M. tuberculosis, capsular polysaccharides of S. pneumoniae	O	O	O
DC-SIGN	DC, dMø[c], aMø[d]	Mannose type CRD, Mannan, ManLam, ICAM-2, ICAM-3	HIV, Mycobacterium tuberculosis, C. albicans, Leishmania mexicana, A. fumigatus, Helicobacter pylori, Schistosoma mansoni	O	X	X
SIGN-R1	MZ Mø[e], pMø[f]	Mannose type CRD, Dextran, ICAM-3	C. albicans, M. tuberculosis, S. pneumoniae, CPS, HIV, yeast-derived zymosan particles	X	O	X
Dectin-1	DC, LC[g], Mø, PMN[h]	β-glucan, T-cell ligand	C. albicans, Saccharomyces cerevisiae, Coccidioides posadasii, Pneumocystis carinii	O	O	X
Dectin-2	H: Mo[i], B[j], Activated CD4+ T[k] M: Mø, PMN, LC	Mannose type ligands, CD4/CD25+ T-cell ligand	C. Albicans	O	O	X
L-selectin	Leukocyte	s6SLex [l]	Arenavirus, Hantavirus, Coronavirus, Filovirus, Orthomyxovirus	O	O	X
P-selectin	Platelets, Endothelium	sLe[x m], s6SLex	HSV[o], VZV[p]	O	O	X
E-selectin	Activated endothelium	sLe[x], s6SLe[x]	Porphyromonas gingivalis	O	O	X

aMø, alveolar macrophage; B, B cell; DCs, dendritic cells; dMø, decidual macrophage; HIV, Human immunodeficiency virus; HSV, Herpes simplex virus; LC, Langerhans cell; Mø, macrophage; Mo, monocyte; MZ Mø, marginal zone macrophage; pMø, peritoneal macrophage; PMN, polymorphonuclear cell; s6SLe[x], sialyl 6-sulpho Lewis[x]; sLe[x], sLe[x], sialyl Lewis[x]; T, T cell; VZV, Varicella zoster virus

thrombocytopenia, rheumatoid arthritis, and systemic lupus erythematosus [65]. SIGN-R3 makes a unique contribution to the protection of the host against bacterial infection such as *M. tuberculosis*, but SIGN-R1 and SIGN-R5 do not share this function. Although both SIGN-R1 and SIGN-R3 recognize *M. tuberculosis* and mycobacterial surface glycoconjugates, only SIGN-R3 which is expressed in lung phagocytes can interact with *M. tuberculosis* via an intracellular tyrosine-based motif that may induce inflammatory cytokine production in collaboration with TLR2 [60].

1.6. MR and selectins

MR (CD206) is described in myeloid cells and functions as a viral recognition receptor on the cell membrane for yeast, bacteria, HIV, and a wide variety of pathogens, such as *C. albicans*, *Leishmania donovani*, *P. carinii*, *Klebsiella pneumonia*, *Trypanosoma cruzi*, *M. tuberculosis* [66−68] and capsular PSs of *S. pneumoniae* through a mannose-type CRD and pathogen-associated high mannose structures [69]. MR which is mainly expressed in immune cells induces uptake and presents mannosylated antigens such as lipoarabinomannan on MHC class II of metallophilic macrophages, resulting in influencing immune responses [70]. For instance, the interaction between MR and hepatitis B virus (HBV) surface antigen (HBsAg) enhances viral uptake by DCs, resulting in the impairment in the function of DCs and the ineffective antiviral response of chronic HBV [71]. The recognition of viral surface glycoproteins by MR is also beneficial to influenza virus [72] and HIV [73] invasion into host cells. In addition, MR is able to mediate the clearance of endogenous inflammatory glycoproteins bearing ligands of the mannose-type CRD [57]. The expression of MR is upregulated by cytokines like IL-4, IL-13, and IL-10, but IFN induces a downregulatory effect to MR [58].

Selectins are cell adhesion molecules and have three groups, including E-selectin (endothelial) and P-selectin (platelet) on endothelium, and L-selectin (leukocyte) on leukocytes [74]. Selectins play roles in leukocyte recruitment from the bloodstream into sites of inflammation [55,74]. The recruitment of leukocytes proceeds initially by attachment leading to the rolling of leukocytes along endothelial vasculature via selectin-carbohydrate interaction. E-selectin (M.W. 115 kDa) is expressed by endothelial cells after stimulation with activators like TNF-α, IL-1, or bacterial lipopolysaccharide [55]. These cytokines also upregulate the expression of P-selectin (M.W. 140 kDa), which is expressed by endothelial cells and platelets [55]. Also, P-selectin in released to the cell surface from storage vesicles in endothelial cells and platelets minutes after stimulation by a number of activators, such as thrombin or histamine [75]. L-selectin (M.W. 90−110 kDa) is expressed by leukocytes and aids in the homing of leukocytes. L-selectin has high expression on naïve T lymphocytes but, once T lymphocytes are activated, the expression of L-selectin is low or lacking [45]. E-, P-, and L-selectin are composed of an N-terminal C-type lectin CRD, an epidermal growth factor-like subunit, a number of short consensus repeat units, a membrane spanning region, and a C-terminal cytoplasmic tail [76]. There is approximately 72% homology for analogous selectin CRDs across species, and ~52% homology between different selectins within a species [76].

1.6.1. P-type lectins

P-type lectins are intracellular transmembrane glycoproteins with specificity for mannose-6-phosphate (M6P) to identify and route lysosomal enzymes to the lysosomal compartment (MPR signal) and they have two groups. One is the 43−46 kDa cation-dependent M6P receptor (CD-MPR) which requires Ca^{2+} for activity and contains single extracellular domain, followed by a single transmembrane domain [47]. The other is the 275−300 kDa

insulin-like growth factor II/cation-independent M6P receptor (IGF-II/CI-MPR) which does not require cation for activity and has a large extracellular domain containing two high-affinity binding sites [46]. The CRDs of P-lectins for M6P are located in the extracellular domain of CD-MPR and in extracellular repeats 3 and 9 with high affinity for IGFII/CI-MPR [46]. They are similar both in size and in sequence to the repeating units that consisted of short *N*-terminal extracellular domain and *C*-terminal cytoplasmic tail [77]. Their function is the intracellular targeting of lysosomal enzymes (lysosomal hydrolases) in the trans-Golgi network vertebrate animals and delivering them to prelysosomal compartments [78]. Also, the *C*-terminal cytoplasmic tail of the receptor which targets amino acid sequence plays a role in recognizing signal for transport to the endosomal compartment [47]. IGF-II/CI-MPR has the capacity for endocytosis of ligands from the cell surface and serves to turn over IGF by endocytosis, but not CD-MPR [47,78].

1.6.2. S-lectins

S-lectins, galectins (from 1 to 14), consist of globular galectin-type CRDs which are specific for β-galactoside ligands and have conserved cysteine residues [51]. They are found predominantly in mammals, but not in plants [46]. S-lectins have a relatively simple structure and share a highly homologous domain named the S-carbohydrate recognition domain (S-CRD) [46]. S-lectins mostly contain multiple sugar-binding sites, as the presence of two type of S-CRD in a single polypeptide or its dimer [51]. The function of S-lectins may be to crosslink *N*-acetyllactosamine-containing structures found at cell surfaces or in the extracellular matrix [79]. S-Lectins are conserved in unrelated organisms including frogs, birds, and mammals, meaning that β-galactoside binding to lectin may be important biologically [47]. Mammalian S-lectins are conserved in eight residues of the S-CRDs and involved in growth regulation, cell adhesion, cell migration, and immune responses [47]. For example, galectin-1 mediates cell adhesion and apoptosis, and regulates cellular proliferation. Galectin-3 mediates cell adhesion, regulates inflammation, pre-mRNA splicing, and protects against induced apoptosis. Galectin-4 and galectin-6 have a function in cell−cell and cell−extracellular matrix crosslinking and galectin-5 is involved in maturation and erythrocyte adhesion [46,47].

1.6.3. I-type lectins

I-type lectins are members of the immunoglobulin (Ig) superfamily [46]. They share the structural motif, the Ig fold, with Ig-like domains consisted of similar two planes of β-pleated sheets [80]. The β-sheets are established about 70−110 amino acids, crosslinked by a disulfide bond and contain several hydrogen-bonded antiparallel chains [51]. I-type lectins are classified into two domains according to the number and arrangement of β-strands present in the domains [81]. One is the amino terminal, extracellular domain, which is similar to the variable region (V-type domain) of IgG and is necessary for sialic acid-dependent binding [81]. The other is the constant region (C-type domain) of IgG that has various forms from 1 to 16 [46]. I-type lectins function as not only cell adhesion molecules but also growth factor receptors and extracellular matrix molecules [47]. The major subclasses of I-type lectins are the sialic acid-binding immunoglobulin superfamily lectins (Siglecs) which contain an homologous *N*-terminal V-type domain with the sialic acid binding site and variable numbers of C-type domains [46]. V-type domain and adjacent C-type domains of Siglecs have conserved cysteine residues, resulting in formation of conventional intrasheet and interdomain disulfide bonds [81]. The *C*-terminal cytoplasmic tail of most Siglecs has immunoreceptor tyrosine-based motifs in the intracellular domain for signaling events [81]. Sialoadhesin found on the surface of macrophages is a member of the Siglecs family [46]. It contains a V-type domain and 16 C-type domains [51]. The *N*-terminal V-type domain of sialoadhesin enables binding of sialic acid in the ligands of neutrophils, monocytes, NK cells, B cells, and cytotoxic T cells with sialoadhesin [47].

2. Animal lectins: potential receptors for GPs

The diverse roles of botanical PSs have been reported. The antitumor effect of botanical PSs was first known more than 100 years ago when it was found that PSs could alleviate cancer in cancer patients [82]. For example, lentinan from *Lentinus edodes* and schizophyllan from *Schizophyllum commune* have antitumor activities and have been used clinically for cancer therapy [35]. Through several experiments, it was suggested that the antitumor effects of botanical PSs might be due to potentiation of the response of precursor T cells and macrophages to cytokines produced by lymphocytes after specific recognition of tumor cells [83]. Also, botanical PSs of mushroom are known to stimulate natural killer cells, T cells, B cells, and macrophage-dependent immune system responses [84]. In addition, arabinogalactans of botanical PSs possess complement fixation activity and induce chemotaxis of human macrophages, T cells, and NK cells [85].

Although the roles of botanical PSs have been continuously identified, the mechanism of action is not clear yet, because the receptors of botanical PSs remain unknown. However, many scientists have proposed that various pattern recognition receptors (PRRs) might be receptors for botanical PSs. For example, Shao et al [86] suggested that the receptor of PS from the roots of *Astragalus membranaceus*, a medicinal herb, might be MR, TLR4, β-glucan receptor, etc. Schepetkin and Quinn [87] also introduced PRRs including TLR4, MR, and dectin-1 as potential receptors of PS polymers. Especially, it was reported that specific glycans of botanical PSs act as immune stimulating agents and effective T cell immune adjuvants [88,89]. Therefore, it was suggested that animal lectins are strong candidates for receptors of botanical PSs among various PRRs, because animal lectins are specialized in recognizing various PSs [90].

With extensive research for GPs, the roles and chemical composition of GPs have gradually been discovered. For instance, the GPs of *P. ginseng*, the most common ginseng, are composed of sugars including mannose of 1.2∼2.8% by weight, glucose of 64.1∼82.8% by weight, galactose of 10.0∼26.6% by weight, and arabinose of 0.6∼5.4% by weight [91]. In addition, CVT-E002, an aqueous extract of the roots of North American ginseng, is composed of 80% poly-furanosyl-pyranosyl-saccharides including rhamnose, glucose, galacturonic acid, galactose, and arabinose [7]. Therefore, some of the animal lectins might recognize these glycan structures of GPs, because there are many animal lectins to recognize glycan structures of galactose, glucose, rhamnose, and mannose [47−49,51,57,58,69,92]. This could be speculated from the extensive research of specific receptors for botanical PSs in the above section. In particular, clustering of animal lectins might enhance the recognition of GPs, since clustering of simple binding sites in oligomers of the animal lectin polypeptides dramatically increases the affinity for diverse PS structures [93]. For example, Byeon et al [95] expected dectin-1 as a receptor of Red ginseng acidic PS, which are known to interact with PS fractions such as β-glucan and zymosan [94,95].

3. Concluding remarks

GPs which are isolated from a variety of traditional medicinal ginsengs involved in various innate immune responses, such as the production of cytokines and maturation of DCs *in vivo* and *in vitro*, show potential to be immunomodulators with wide applications

[23—25]. In addition, most of them are relatively nontoxic and do not cause significant side effects, which are major problems of immunomodulatory bacterial PSs and synthetic compounds. Thus, GPs are becoming ideal candidates for therapeutics for collagen-induced arthritis, inflammation, and inflammatory-related diseases like tumors, atherosclerosis, and so on [3,27,28,32,36]. Although the roles of GPs are being continuously identified, the detailed mechanisms of actions are not clear yet, because the receptors of GPs remain largely unknown. Therefore, it is tempting to speculate that animal lectins could be strong candidates of receptors for GPs. To prove this possibility, extensive researches for the specific structures of GPs and the interaction between GPs and animal lectins is required in the near future. By unraveling receptors of GPs *in vivo*, it is possible to specifically understand the detailed mechanism for the immunological activities of GPs in the immune system, giving insights into the development of GPs as therapeutic biomaterials for many immunological diseases.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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