Chapter 14
Glycans in Infection and Immunity

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14.1 Influenza Virus

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Keywords Influenza virus, Hemagglutin, Neuraminidase, Sialidase, Sulfatide

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1. Significance in the field of glycoscience and its current situation
   Influenza viruses are contagious respiratory pathogens and the viral infection is initiated by attachment of the viruses to sialic acid-containing sugar chains. The most severe influenza pandemic of 1918–19 caused over 50 million deaths worldwide. The influenza A and B viruses have two spike glycoproteins, hemagglutinin (HA) and neuraminidase (NA). A difference in the recognition of HA for molecular species of terminal sialic acids and sialic acid-galactose linkages, which are expressed on cells of the viral host, is a critical factor in the viral host range restriction. NA, which has sialidase enzymatic activity, plays an important role in the initiation of influenza virus infection and the budding of progeny virions from the host cell surface [1, 2]. Sialidase inhibitors based on the crystal structure of NA have been developed as anti-influenza drugs [3].
2. Impact on the other fields of research
   Anti-influenza drugs (sialidase inhibitors) have been developed using computer simulation based on the crystal structure of influenza virus NA. The interaction of HA with sialo-sugar chains would be interesting for the protein-glycan interaction.
3. Significance as the fundamental research
   Elucidation of the mechanisms of influenza virus replication, pathogenicity and transmission will be useful.
4. Possible application for industry and medicine, if any
   Sialic acid analogs (sialidase inhibitors) are widely used as anti-influenza drugs [3, 4].

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5. Future perspectives
   Other virus pathogens with sialidase activity including the human parainfluenza virus and mumps virus will also be useful. Compounds that inhibit binding of HA to sulfatide [5] would be likely candidates for anti-influenza drugs.
6. Problems to be solved
   Since there are no data regarding influenza virus receptors in host target cells, identification for the receptor(s) would be essential. This will take 10 years (Fig. 14.1).

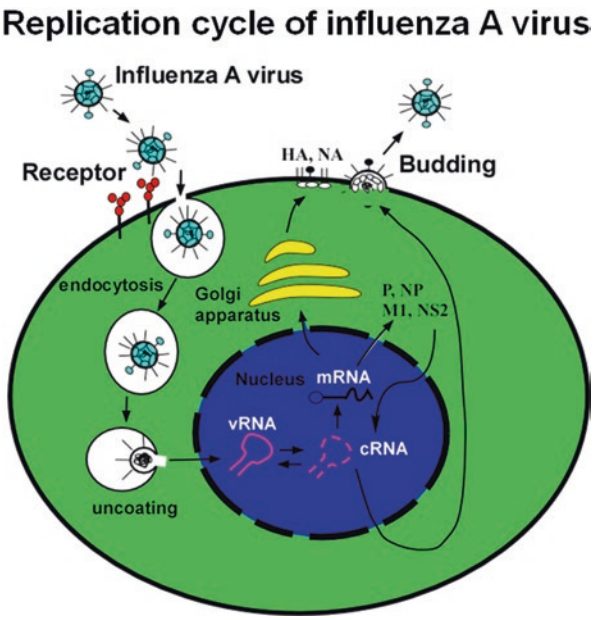

Fig. 14.1 Replication cycle of the influenza virus

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14.2 Recent Research Topics of Influenza

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Keywords Influenza virus, Hemagglutinin, Sialogycans, Interspecies transmission, Antiviral drug

1. Significance in the field of glycoscience and its current situation
   One of the viruses that have been known to use glycans as receptors is the influenza virus [6]. Human infections of animal influenza viruses has been reported, such as H5Nx highly pathogenic avian influenza viruses since 1997, H1N1 pandemic influenza in 2009, and recent H7N9 influenza virus infections since 2013 [7]. These cases cannot be explained only by relationship between the receptor specificity of viruses and sialoglycans in the host. Since it is becoming clear that there is a more complicated relationship between them, it is desirable to identify the true receptor of the virus and to predict virus transmission among hosts to control human and animal influenza.
2. Impact on the other fields of research
   By analyzing the expression profile of glycans in the host and sialoglycans recognized or used by the viruses, it is possible to predict virus transmission among hosts, especially the emergence of pandemic influenza viruses. These results can be applied to other virus infections in which the causative viruses use glycans as receptors.
3. Significance as the fundamental research
   Clarification of the diversity of sialoglycans expressed in humans and animals, and the expression kinetics before and after the infections will lead understanding of other infectious diseases. It is important to determine how virus binding is affected by sialic acids [8], and sulphated [9] and fucosylated [10] sialoglycans.
4. Possible application for industry and medicine, if any
   Neuraminidase inhibitors have been widely used as anti-influenza drugs, but ones that inhibit virus binding or internalization have not been successfully developed for clinical use. The search for sialic acid sugar chain derivatives strongly binding to hemagglutinin has the potential to reveal a new antiviral drugs.
5. Future perspectives
   Hemagglutinin is a lectin. It provides important knowledge for determining the specificity of other lectins, and hemagglutinin recognizes different glycans with several mutations in virus replication and contributes to host specificity.
6. Problems to be solved
   It is necessary to clarify the expression and dynamics of glycans of an influenza virus-infected host. In addition, it is necessary to clearly identify the glycans expressed in the host and the sugar chains really involved in the infection. This will be performed within 5 years (Fig. 14.2).

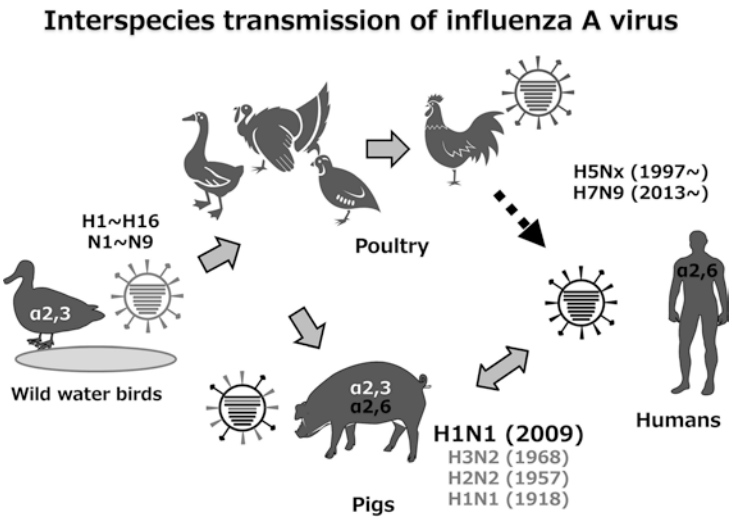

Fig. 14.2 Interspecies transmission of influenza A viruses. Human infections with animal influenza viruses have been reported in recent years, but it is not possible to explain this interspecies transmission by the receptor specificity of viruses and glycans expressed in host tissues. So the true receptors should be determined

Box 14.1: Influenza Drug Formulation

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Influenza viruses are classified as RNA viruses possessing negative-sense viral RNAs. They have hemagglutinin (HA) and neuraminidase (NA) on the surface of the viral particles. Influenza viruses bind through HA to sialic acid on the surfaces of target epithelial cells and then enter the cells. After replication, a large amount of influenza viruses is released from infected cells. NA is involved in the release of progeny virus from infected cells, by cleaving sialic acid on the cells binding to HA on the mature progeny viral particles. Therefore, NA is one of the targets for antiviral drugs. Typical NA inhibitors used against influenza are as follows; Oseltamivir (Tamiflu), Zanamivir (Relenza) and Laninamivir octanoate hydrate (Inavir). These drugs are used to treat flu symptoms caused by influenza virus in patients who have had symptoms for less than 2 days.

Box 14.2: Dengue Virus

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Dengue virus (DENV) is a single-stranded, positive-sense RNA flavivirus, which has three structural envelope (E), matrix (M) and capsid (C), and seven nonstructural (NS) proteins. Based on antigenic differences in the E protein, there are four serotypes of DENV. Dengue is a major arbovirus-borne infectious disease in tropical and subtropical regions of the world. About 390 million cases of dengue fever are estimated to occur each year globally. DENV cause a variable spectrum of disease that ranges from an undifferentiated fever to the potentially fatal dengue shock syndrome (DSS). Dengue hemorrhagic fever (DHF)/DSS is characterized by capillary permeability and a bleeding diathesis. DHF/DSS is an important cause of morbidity in Southeast Asia and occur almost exclusively in young children. Unlike the neighboring areas, most of the Taiwanese dengue patients are adults. The adult dengue has high morbidity and mortality. In 2015, Taiwan experienced its largest dengue outbreak since 1981. A cumulative total of 43,784 dengue cases, including 212 deaths have been confirmed. More effective and efficient integrated dengue control programs that include various surveillance systems, a network of rapid diagnostic laboratories, and rapid responses would be needed for better control of dengue. Especially early diagnosis of dengue is crucial to provide timely evidence-based case management because initial symptoms are often nonspecific.

14.3 Pathogens and GPI Anchors

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Keywords African trypanosome, Malaria parasites, Candida, Variant surface glycoproteins

1. Significance in the field of glycoscience and its current situation
   Trypanosomes, malaria parasites and other protozoan pathogens are unicellular organisms whose cell surfaces are covered by GPI-anchored proteins and/or protein-free GPI, which act to protect the organisms from the host immune system [11]. GPI-anchored proteins are also major components of the cell walls of pathogenic fungi such as Candida. In prokaryotic cells, there are no known GPI-anchored proteins, however, Mycobacteria, such as Tuberculosis bacilli, have abundant GPI-like glycolipids on their cell walls [12]. Because GPI-anchors and GPI-like glycolipids are essential for the growth of these pathogens or cell wall integrity, their biosynthetic pathways are promising targets for anti-pathogen drug development [13]. Therefore, studies on GPI-anchors in pathogens are important for infectious disease control. Because a host has similar GPI-anchors, it is critical to target pathogen-specific enzymes for selective toxicity. Drugs inhibitory for such targets are under screening [14].
2. Impact on other fields of research
   Protozoan parasites cause many diseases not only in humans but also in domestic animals. Knowledge obtained through research on human pathogens and GPI should have a big impact on veterinary medicine.
3. Significance as fundamental research
   GPI is a membrane-anchor of proteins ubiquitously used by eukaryotes. In particular, GPI is the major type of protein membrane anchor in single cell organisms. Research on GPI is therefore important for fundamental scientific research [11].
4. Possible application for industry and medicine, if any
   Protozoan diseases are prevalent mainly in developing countries and are often called neglected diseases [13]. They are not very attractive targets of pharmaceutical companies in developed countries, however, they may provide business opportunities for companies in developing countries.
5. Future perspectives
   Once a drug that effectively inhibits GPI biosynthesis in one particular pathogen is developed, similar drugs may be developed for inhibition of GPI biosynthesis in other pathogens.

6. Problems to be solved
   GPI biosynthesis is critical for the human body. To use inhibitors of GPI biosynthesis as anti-infection drugs, drugs that specifically inhibit GPI biosynthesis in pathogens but not in the host need to be developed [14]. This will occur within 10 years (Fig. 14.3).

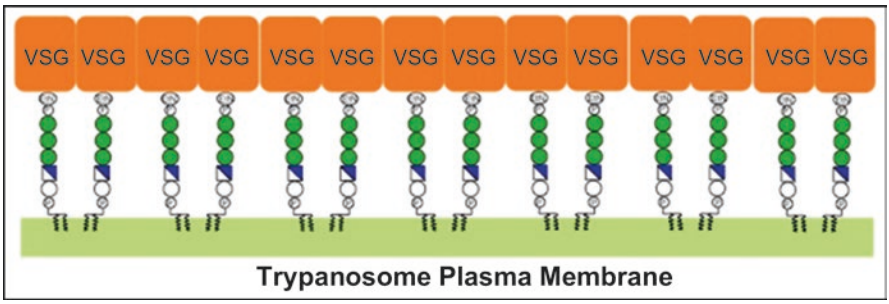

Fig. 14.3 The surface of African trypanosome, a unicellular parasite that causes sleeping sickness, is protected from the host immune system by a coat of GPI-anchored proteins, termed Variant Surface Glycoproteins (VSG)

14.4 Sugar Chain-Mediated Interaction Between Microbes and Higher Animals

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Keywords Symbiosis, Milk oligosaccharides, Mucin-type *O*-glycans

1. Significance in the field of glycoscience and its current situation
   Previous studies on sugar chain-mediated interactions between microbes and animals mainly focused on elucidation of how bacterial adhesions (sugar-binding proteins) recognize host sugar chain receptors and thereby trigger invasion into host cells. On the other hand, many researchers have recently been focusing on how host-derived sugar chains are involved in establishment of symbiosis between gut microbes and a host. Mucin glycoproteins and milk oligosaccharides, both of which are secreted into intestinal lumen of hosts, play important roles in shaping the gut microbiota [15, 19], which significantly influences host health and disease. Elucidation of sugar chain-driven symbiosis and dysbiosis will lead to a better understanding of the physiology as well as pathology of higher animals including humans.
2. Impact on the other fields of research
   Immunologists have significantly contributed to elucidation of the molecular basis of symbiosis between gut microbes and hosts. They approached this topic from the host (animal) side [16, 18]; however, undoubtedly, approaches from the microbe side are equally required. Fortunately, current studies on sugar chain (mucin glycoprotein and milk oligosaccharid)-mediated symbiosis and dysbiosis are being mainly conducted by microbiologists. Thus, researchers in both fields can effectively complement each other to obtain a comprehensive understanding of interactions between gut microbes and hosts.
3. Significance as the fundamental research
   Comprehensive understanding of how host-derived glycans affect the gut microbiota composition is anticipated. In addition, because gut microbial enzymes acting on host-derived glycans show very high substrate specificity, they can be utilized for precise determination of sugar chain structures.
4. Possible application for industry and medicine, if any
   Mucin sugar chains and milk oligosaccharides are promising targets for the development of functional foods and pharmaceuticals. Quite recently, Western countries put milk oligosaccharide 2′-fucosyllactose to practical use, i.e., they started to add the compound to formula milk for fortification.

5. Future perspectives
   Recent regeneration medical techniques have made it possible to differentiate iPSC from gut organoids [17]. Construction of a symbiosis model using individual intestinal cells and gut microbes may allow precise understanding of the sugar chain-mediated interactions between gut microbes and hosts.
6. Problems to be solved
   The number of genetically amenable gut microbes is very limited, despite that more than hundred bacterial species inhabit the intestines. The lack of available genetic tools for gut microbes has significantly hampered a detailed experimental approach from the microbe side in animal models. This will be resolved within 5 years (Fig. 14.4).

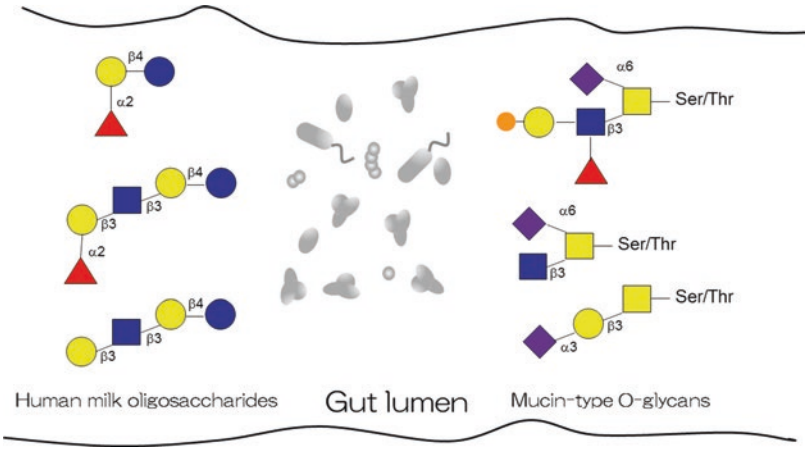

Fig. 14.4 Host-derived glycans significantly contribute to shaping of the gut microbiota

14.5 Current Status and Future Directions of Study on Glycosylation for Gut Microbiota and the Mucosal Immune Network

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Keywords Fut2, α1,2-fucose, Commensal bacteria, Autoimmune diseases, Mucosal immunity

1. Significance in the field of glycoscience and its current situation
   The study of the gut microbiota is now one of the hottest research fields in life science, in particular, the sugar chains expressed on host intestinal epithelial cells interact with microorganisms including commensal bacteria. The sugar chains on epithelial cells not only construct a symbiotic environment in the intestinal tract but also provide an opportunity for infection by pathogenic microorganisms, such as *Helicobacter pylori* and norovirus [20]. It has been reported that an inactive type gene polymorphism in Fut2, which is one of the glycosyltransferases, causes disturbance of the gut microbiota, and development of various infections and autoimmune diseases, such as Crohn's disease and type I diabetes [21]. Therefore, it is extremely important for glycoscience to understand the roles of glycochains and their regulation in the gut microbiota and mucosal immune network in the fields of biology and medicine.
2. Impact on the other fields of research
   The sugar chains, α1,2-fucose, expressed on host intestinal epithelial cells are closely related to regulation of the gut microflora. The host-bacterial interaction mediated by α1,2-fucose has a great impact on many research fields, such as microbiology, immunology, and cell biology. In the context of medical application, α1,2-fucose has been reported to be associated with various diseases, such as autoimmune diseases, cancer, and metabolic diseases as well as infectious diseases.
3. Significance as the fundamental research
   Numerous bacteria constantly colonize the intestinal tract and establish a peaceful symbiotic relationship with the host. Most of the mechanism of this symbiotic relationship between the host and gut microbiota remains unknown. It is biologically important to clarify the biological role of glycosylation in the symbiotic mechanism in the intestines.

4. Possible application for industry and medicine, if any
   As represented by viable bacterial drugs, research on the roles of glycosylation in the gut microflora and mucosal immunity will lead to novel industrial and medical applications. In addition, the sugar chains expressed on intestinal epithelial cells are closely related to infectious diseases involving pathogenic microorganisms and autoimmune diseases such as inflammatory bowel disease. Understanding of gut glycosylation will lead to the development of new preventive and therapeutic approaches for these diseases.
5. Future perspectives
   Sugar chains that interact with commensal bacteria are limited to specific molecules such as α1,2–fucose. The roles of other sugar chains in the regulation of the gut microbiota are expected to be clarified in future studies. Although it has been reported that immune cells are involved in the induction and regulation of α1,2-fucose [22, 23], more detailed elucidation of the role of glycosylation in the gut microbiota-immune network should be performed.
6. Problems to be solved
   Molecules derived from gut microflora for the induction of sugar chains such as α1,2-fucose expressed on intestinal epithelial cells remain unknown. In addition, the mechanism by which Fut2 and α1,2-fucose-deficient humans are susceptible to autoimmune diseases such as inflammatory bowel diseases should be clarified. This will take 10 years (Fig. 14.5).

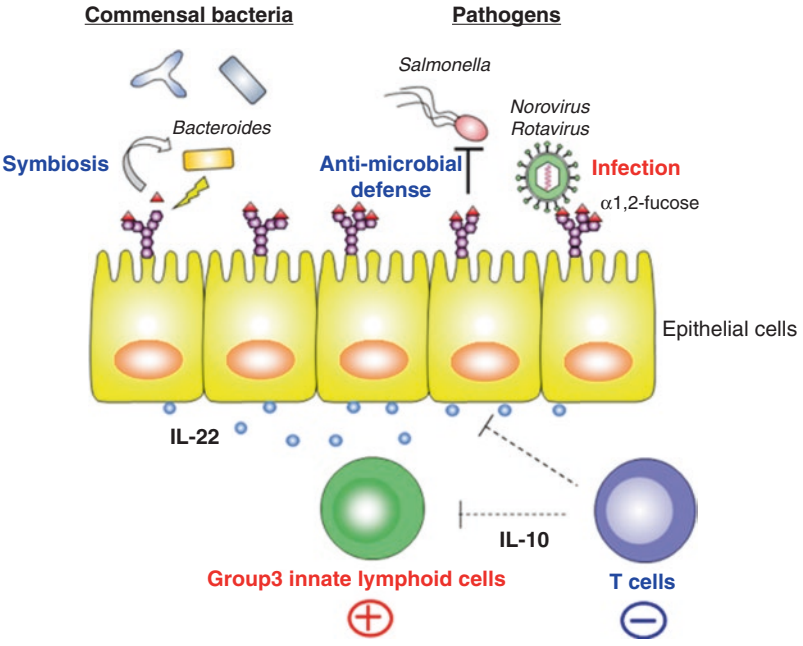

Fig. 14.5 α1,2-fucose is added to the end of a sugar chain expressed on the intestinal epithelial cells. α1,2-fucose creates a symbiotic environment for intestinal bacteria and eliminate pathogenic bacteria, but provides an opportunity for virus infection. α1,2-fucose is induced and regulated by immune cells such as group 3 innate lymphoid cells and T cells

14.6 Carbohydrate-Mediated Interactions Between Microbial and Higher Animal Cells (Fungi)

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Keywords Opportunistic infection, Fungi, Yeast, Glucan, Innate immune system

1. Significance in the field of glycoscience and its current situation
   Invasive aspergillosis and invasive candidiasis are major life-threatening nosocomial invasive fungal infections. Difficulty in the biological detection of invasive fungal infections is related to the low yields of culture-based methods. There is extensive literature on the diagnostic value of fungal polysaccharide detection, including that of β-(1,3)-glucan, and mannan or galactomannan, found in Aspergillus and Candida, respectively. In contrast, the innate immune system of mammals constituents the first line of defense against invading microbes. Fungal cell wall components (β-glucans, *N*- and *O*-linked mannans) are recognized by host receptors like C-type lectins (dectins, mannose receptor, etc.) and Toll-like receptors [24–28]. Such recognition leads to activation of a variety of host signaling cascades and production of anti-microbial compounds. Early diagnosis of a fungal infection has been shown to significantly increase the survival rate of the patient. Optimal exploitation of glucans and mannans in anti-cancer treatments, vaccines, and in priming host defenses will require a mechanistic understanding of how each receptor works.
2. Impact on the other fields of research
   A better understanding of the recognition mechanism by fungal cell wall components will allow not only improvement of the host defense against fungal pathogens but also analysis of the protein (enzyme or lectin)-carbohydrate interactions.
3. Significance as the fundamental research
   It is very important to examine the oligosaccharide structures and the existence of key enzymes (genes) of pathogenic fungi in the phylogenetic tree.
4. Possible application for industry and medicine, if any
   The development of new drugs and therapies to control fungal diseases, and immune strength-ameliorating food.
5. Future perspectives
   Understanding the recognition mechanisms for fungal cell wall components in mammals may facilitate the development of new drugs and therapies to control fungal diseases.
6. Problems to be solved
   Since there are no data regarding possible receptors for galactofuranose-containing oligosaccharides from Aspergillus sp., identification of the receptor(s) in vivo such as C-type and X-type lectins is essential. This will be performed within 5 years (Fig. 14.6).

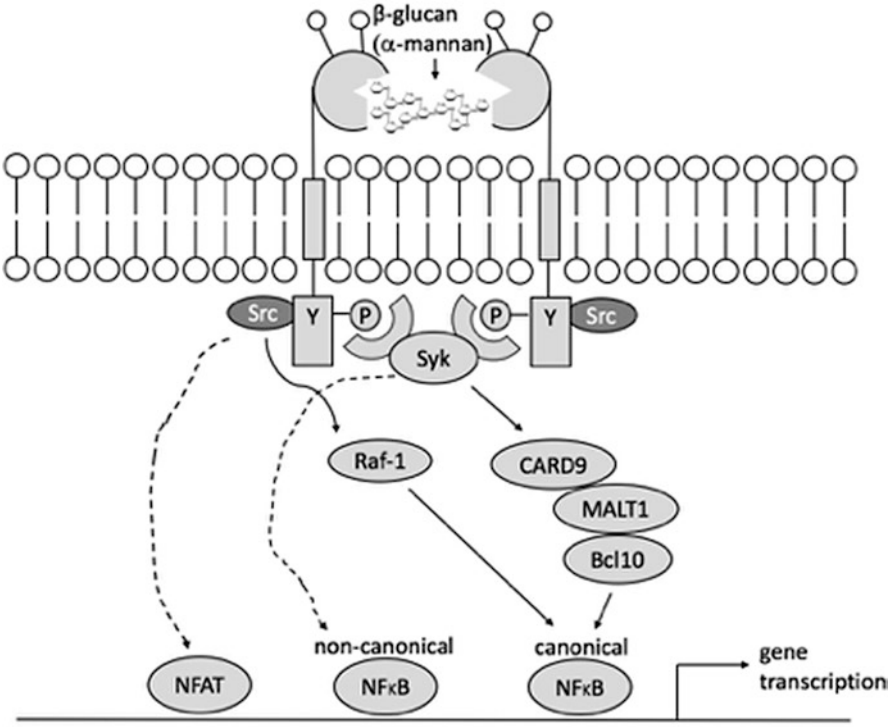

Fig. 14.6 Dectin-mediated signal transduction. On ligand binding, dectins become tyrosine phosphorylated, and induce an intracellular signaling cascade that results in various cell-specific responses. (Modified from Marakalala et al. [29])

14.7 *Plasmodium* and Protozoa in General

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Keywords *Plasmodium*, *Toxoplasma*, *Babesia*, Sialic acid, Heparan sulfate

1. Significance in the field of glycoscience and its current situation
   Protozoa are eukaryotic unicellular organisms with functions and structures similar to mammalian cells. Some protozoan species infect humans and animals, and induce clinical diseases with various degrees of pathogenicity. Therefore, protozoan parasites are often considered to be pathogens of veterinary and medical importance. At present, effective and safe therapeutic drugs and vaccines are not available for most protozoan diseases. Many pathogenic protozoan species invade the host cells, where they can survive and proliferate. Invasion of protozoa into the host cells is mediated by surface or secretory molecules of the parasites and receptors on the host cell membrane (sialic acids, heparan sulfate, etc.) [30–32]. Compounds similar to these carbohydrate receptors were found to block the cellular invasion by several protozoan parasites, including *Plasmodium*, *Toxoplasma*, *Babesia*, and *Cryptosporidium* [33, 34]. Thus, elucidation of the mechanisms associated with the receptor-ligand interaction will facilitate the development of novel therapeutic agents and vaccines.
2. Impact on the other fields of research
   Several pathogens, such as protozoa, viruses, bacteria, and Rickettsia, share conserved mechanisms for the recognition of carbohydrate receptors. Therefore, the findings of investigations on carbohydrate recognition by protozoa will be useful for elucidating the mechanisms adopted by other pathogens as well.
3. Significance as the fundamental research
   The mechanisms of parasitism and pathogenesis of protozoa will be revealed through elucidation of the molecular mechanisms associated with host cell recognition, invasion, internalization, replication, and egress.
4. Possible application for industry and medicine, if any
   Sugar chain derivatives with structures similar to the sugar moieties on the surface of host cells are potential inhibitors of protozoa growth. Thus, therapeutic agents can be developed based on sugar chain derivatives. Additionally, the protozoan molecules that are involved in host cell recognition could be potential candidates for subunit vaccines.

5. Future perspectives
   Babesia parasites do not infect erythrocytes with reduced sialic acid levels on their membranes. Similarly, a low heparan sulfate content in host cells results in a decreased infection rate of *Toxoplasma* parasites. Therefore, genetically engineered livestock animals resistant to *Babesia* and *Toxoplasma* infections could be created.
6. Problems to be solved
   Identification of sugar chain receptors on the host cell membrane and analyses of their structures are essential. After such structural analyses, the synthesis of sugar chain derivatives and their analogues, safety and toxicity testing, and evaluation as therapeutic agents are important before the novel compounds can be considered effective and safe. This will be accomplished within 5 years (Fig. 14.7).

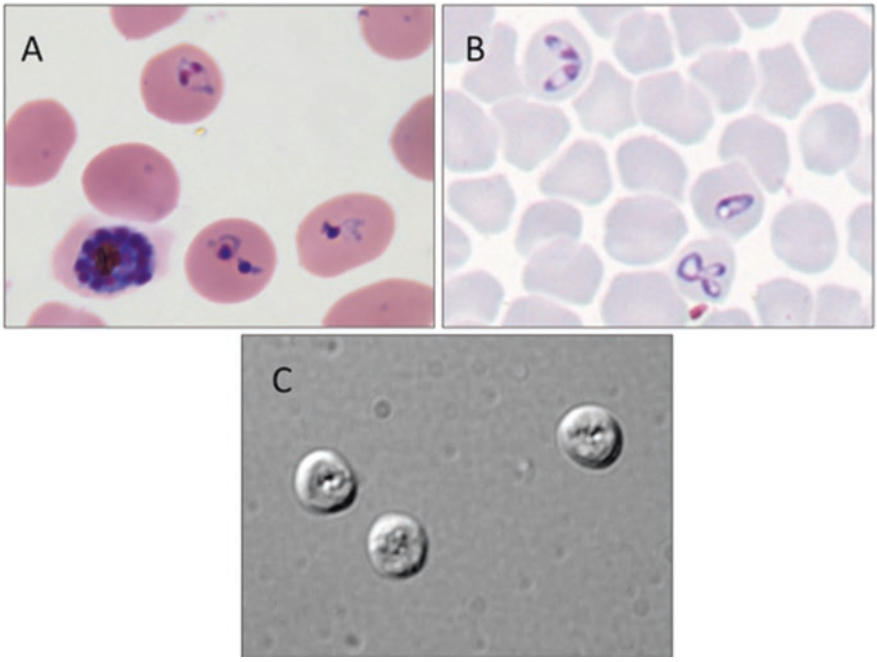

Fig. 14.7 Microscopic images of *Plasmodium* (**a**), *Babesia* (**b**), and *Cryptosporidium* (**c**)

14.8 GPI Anchor Deficiencies

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Keywords Paroxysmal nocturnal hemoglobinuria, Inherited glycosylphosphatidylinositol deficiency, Rare diseases, Intractable diseases, Anti-complement drugs

1. Significance in the field of glycoscience and its current situation
   There are two forms of GPI anchor deficiencies: paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disease whereas inherited glycosylphosphatidylinositol deficiency (IGD) is inherited [35–38]. Both are rare and designated intractable diseases by the Ministry of Health, Labour and Welfare of Japan. PNH is known for over 100 years and the estimated number of patients in Japan is approximately 1000 or bigger, whereas IGD was discovered in 2006 and the current numbers of patients in Japan and worldwide are approximately 30 and 200, respectively [39]. The number of reported IGD patients is quickly increasing with application of whole exome analysis for diagnosis of rare genetic diseases. Significance of studies on GPI deficiencies is that they help understanding physiological roles of GPI-anchored proteins in vivo.
2. Impact on other fields of research
   PNH is characterized by hemolysis and thrombosis caused by dysregulation of complement activation. Eculizumab, anti-C5 monoclonal antibody, is effective in preventing hemolysis and thrombosis in patients with PNH [37]. The successful use of eculizumab in PNH triggered trials on other diseases involving complement activation, which proved effectiveness of complement inhibition in atypical hemolytic uremic syndrome and other diseases, leading to active development of various anti-complement drugs.
3. Significance as fundamental research
   Research on PNH and IGD will demonstrate clinical symptoms that occur when levels of 150 or more GPI-anchored proteins are reduced to various extents. These findings will lead to understanding of physiological roles of various GPI-anchored proteins.
4. Possible application for industry and medicine, if any
   Eculizumab, an anti-C5 monoclonal antibody, has been used effectively and safely for many patients with PNH [37]. This stimulated development of various anti-complement drugs for a number of diseases, in which complement-activation is suspected to play roles in clinical symptoms.
5. Future perspectives
   Clinical symptoms of IGD vary in the severity and the affected organs/tissues, dependent upon what gene is affected and how deeply the mutations affect functions of the gene. IGD therefore is a typical disease that requires development of patient-specific therapeutic measures [38, 39]. Progress in development of therapies of IGD will contribute to advance precision medicine.

6. Problems to be solved
   Development of therapeutic measures for IGD is a current problem. In particular, drugs that restore reduced biosynthesis of GPI in patients' cells need to be developed (Fig. 14.8).

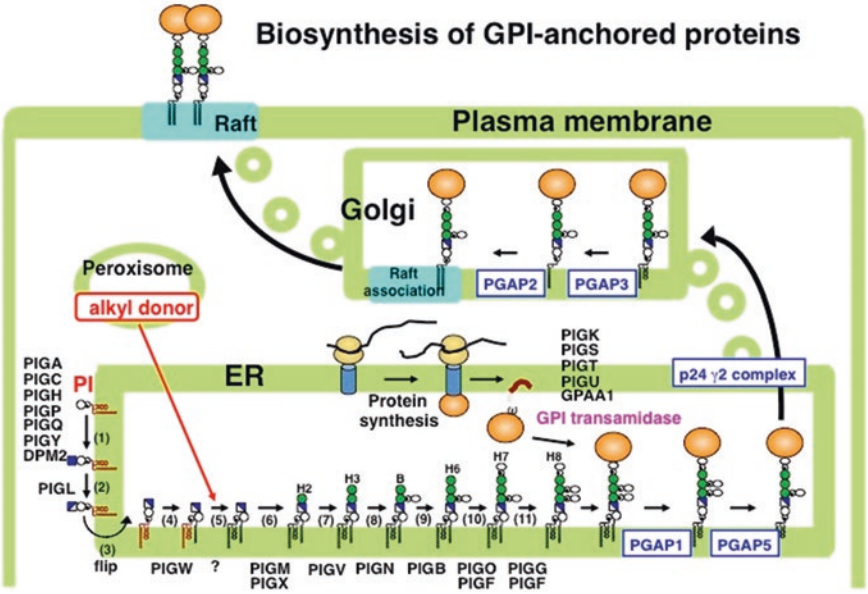

Fig. 14.8 More than 25 proteins working in the endoplasmic reticulum and the Golgi apparatus are involved in biosynthesis of GPI-anchored proteins. Mutations in genes for those proteins cause PNH and IGD. Genes for biosynthesis and protein attachment of GPI are termed PIG genes whereas those involved in maturation of GPI after protein attachment are termed PGAP genes

14.9 Defense Mechanism

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Keywords Defense mechanism, Innate immunity, Microorganism, Pattern recognition receptors (PRRs)

1. Significance in the field of glycoscience and its current situation
   In the biological defense mechanism against infectious diseases, microbial cell-surface molecules, especially glycans and glycoconjugates, play an important role in activating the immune system [40–44]. Namely, these sugar chains and glycoconjugates from various microorganisms are recognized by innate immunity receptors such as TLR, CLR, NLR, etc., which leads to activation of the immune system against infection, and to modulation of the balance of cellular and humoral immunity. It also leads to activation of the acquired immune system, in which the antibody production is enhanced. These research fields in Japan are one of the front lines in the world, especially regarding the discovery of innate immune receptors and their ligands, and also their important functions.
2. Impact on the other fields of research
   The defense mechanism against infectious diseases, especially activation of the immune system and modulation of the immune balance, is closely related to the immunity in the anti-cancer mecahnism, transplant tolerance and rejection, and also allergies, etc. Therefore, the findings in this research field have great impacts on the development in these other related fields.
3. Significance as the fundamental research
   Understanding the molecular basis of the defense mechanism, which includes the structures and functions of cell-surface sugar chains and glycoconjugates, is fundamental for the comprehension of and development of therapies for various diseases including infectious ones.
4. Possible application for industry and medicine, if any
   Immunomodulatory carbohydrate compounds derived from microorganisms have been the key compounds as to understanding the defense system and also for developing medicines (including immune adjuvants) for infections, cancer, transplant rejection and allergies.
5. Future perspectives
   Understanding of microbial glycans/glycoconjugates will lead to comprehensive understanding of our own endogenous glycans/glycoconjugates, based on the molecular structural similarities and differences, which would lead to comprehension of the defense system for various diseases.
6. Problems to be solved
   Because of the difficulty in obtaining or synthesizing microbial glycans and glycoconjugates comprehensively, many structure-activity relationships have not been revealed yet. This will take 10 years (Fig. 14.9).

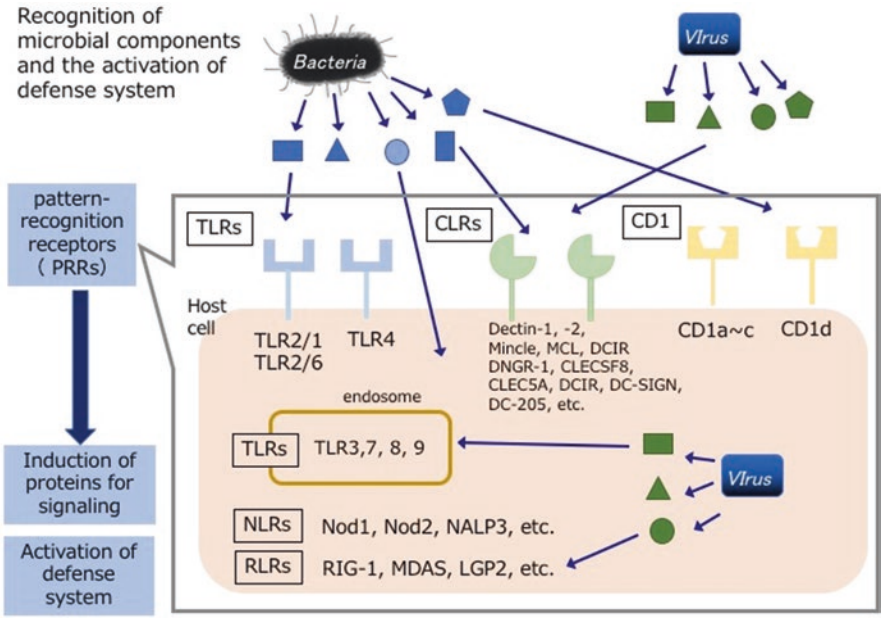

Fig. 14.9 Microbial molecules are recognized by pattern recognition receptors (PPRs) of the host cells, and activate the defense mechanism via the induction of proteins for the signaling

14.10 Siglecs

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Keywords Sialic acids, Self-nonself discrimination, Immune checkpoint molecule

1. Significance in the field of glycoscience and its current situation
   Siglecs comprise a family of receptor-type lectins that recognize glycans containing sialic acids [45–47]. The distribution of sialic acids in nature is limited to deuterostomes (including vertebrates and echinoderms), microbes that express sialic acids being rare. Therefore, sialic acids can be a molecular marker of "self" for the immune system of vertebrates. Siglecs are a part of the immune recognition machinery that recognizes sialic acids as a marker of self, and contribute to the self-nonself discrimination by the immune system. Siglecs are as important glycan-related molecules as C-type lectins and galectins. The basic functions of Siglecs have been elucidated through studies on the knockout mice that lack a Siglec gene. Although there are notable differences between human and mouse Siglecs, knowledge on the functions of human Siglecs is also accumulating though studies of genetic polymorphisms in human Siglec genes and human phenotypes, such as disease susceptibility.
2. Impact on the other fields of research
   As a group of molecules that recognize glycans and participate in self-nonself discrimination, studies of the Siglec family may make as essential contributions as those on C-type lectin-like receptors to the understanding of the immune system.
3. Significance as the fundamental research
   Discovery of the Siglec family has provided an answer to a long-standing question, i.e., "why do sialic acids exist?"
4. Possible application for industry and medicine, if any
   Antibody therapies targeting some Siglecs to treat leukemia/lymphoma are already in the advanced stages of clinical development. Recent studies have revealed that some Siglecs may play similar roles as immune checkpoint molecules, and thus it is implied that blockade of these Siglecs may be beneficial for the treatment of some types of cancer.
5. Future perspectives
   It is suggested that Siglecs may be useful as targets of drug and/or antigen delivery.

6. Problems to be solved, and the years that will take to solve the problems
   It is already possible to target Siglecs with antibodies, whereas the targeting of Siglecs using glycans still requires further study [48]. Development of glycan-based ligands with high affinity and selectivity is awaited. This will take 10 years (Fig. 14.10).

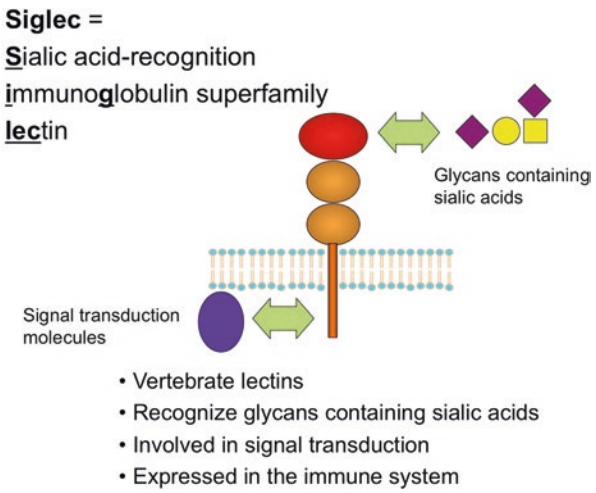

Fig. 14.10 The extracellular domain of Siglecs consists of multiple immunoglobulin-like folds, and the amino-terminal domain is primarily responsible for their interaction with glycans. Most Siglecs also associate with signal transduction molecules at the intracellular or transmembrane domain, and participate in signal transduction

14.11 Collectins

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Keywords Lectin, Collagen, Complement, Host defense, Neuronal maturation

1. Significance in the field of glycoscience and its current situation
   Collectins comprise a family of C-type lectins possessing a collagen like-region in their structure. Six types of collectins are found in humans [49]. Pulmonary collectins (SP-A and SP-D) have emerged in terrestrial animals with opsonizing activation as their main function with no complement system activation activity. The other four types of collectins (MBL (MBP), CL-K1, CL-L1 and CL-P1) all activate the complement system through the recognition of bacterial surface carbohydrates. Once bacteria or any other microorganisms are recognized, they are either phagocytized via opsonization or led to cell lysis through disruption of the cell wall via the complement cascade as a part of the biological defense system [49]. Therefore, the bacterial surface carbohydrate pattern recognition function of collectins is suggested to play an important role in the innate immune system [50].
2. Impact on the other fields of research
   Mutation in the *CL-K1/L1* or *MASP3* gene has been determined to cause 3MC syndrome, and CL-K1/L1 induced complement activation has been found to play a role in an organism's development [51]. This complement activation is reported to be involved in neuronal maturation in neonatal animal models [52].
3. Significance as the fundamental research
   The lancelets, the oldest vertebrates have more than 60 collectin genes. Six of these genes are conserved in humans [53]. Collectins in humans are assumed to have become indispensable for survival by linking the carbohydrate recognition function to many biological functions.
4. Possible application for industry and medicine, if any
   MBL and SP-D are possible drug candidates for direct virus inhibitors or antibiotics. CL-K1, CL-L1 and CL-P1 are possible drug candidates for neuronal maturation factors.
5. Future perspectives
   There have been many reports about the role of collectins in neuronal maturation or migration in animal models, and they may allow a better understanding of the pathologies of neurological disorders. This may lead to the early diagnosis of the disorders or the development of new drugs.
6. Problems to be solved
   The current understanding is based on the studies on model organisms. The functions of collectins in humans need to be analyzed. This will be performed within 5 years (Fig. 14.11).

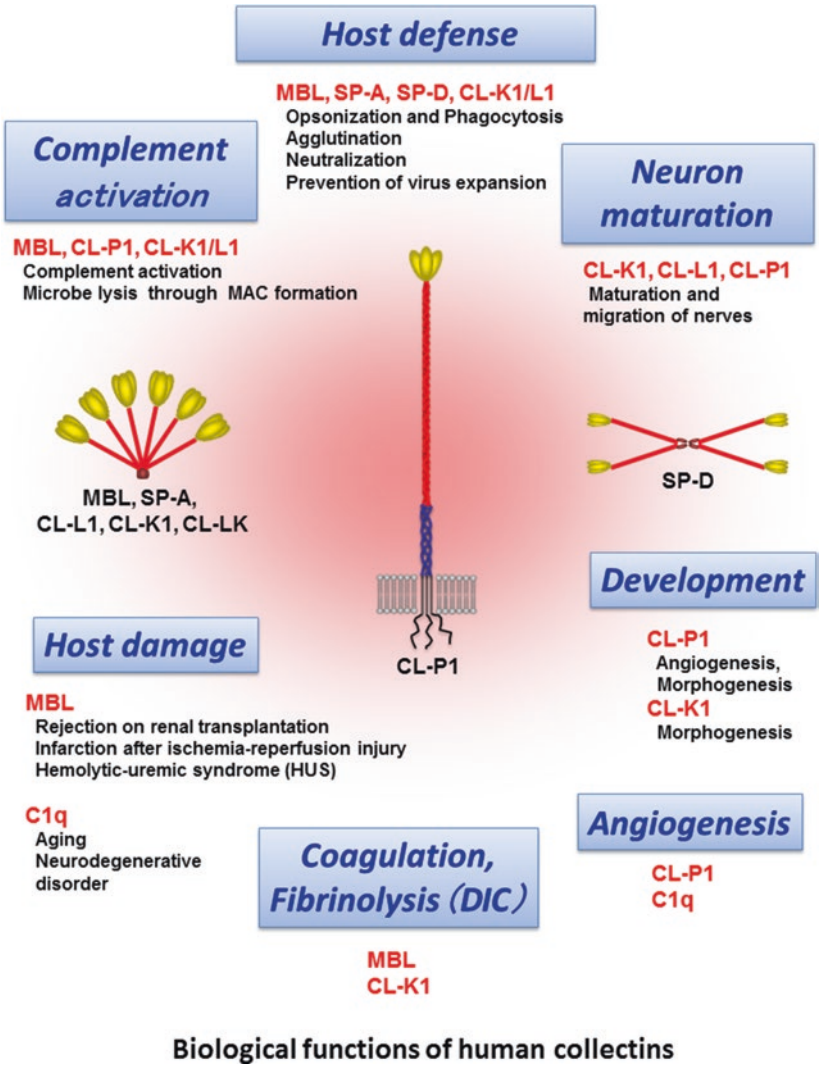

Fig. 14.11 Biological functions of human collectins

14.12 Autoimmune Disease, Immunosuppressive Drugs

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Keywords Inhibitory receptor, Inflammation, Autoimmunity, Immune suppression

1. Significance in the field of glycoscience and its current situation
   Rheumatoid arthritis, systemic lupus erythematosus and type I diabetes are representative autoimmune diseases. Although they are thought to be caused by an immune response against self-antigens, the mechanisms of autoimmune diseases have remained unclear [54]. On the other hand, immune cells express a variety of inhibitory receptors such as PILR and Siglec that recognize sugar chain structures, and these receptors play an important role in regulation of immune responses [55–57]. Therefore, it is important to develop certain molecules that are specifically directed forward sugar chain-recognizing inhibitory receptors. However, such a molecule has not been identified yet. Therefore, development of regulatory molecule targeting sugar chain-recognizing receptors would be important for immune regulation.
2. Impact on other fields of research
   Sugar chain-recognizing receptors are involved in herpes simplex virus infection and varicella zoster virus infection [58]. In addition, some cancers show immune evasion via sugar chain-recognizing inhibitory receptors. Therefore, development of a method to regulate sugar chain-recognizing inhibitory receptors is important not only for autoimmune diseases but also for viral infections and cancers.
3. Significance as fundamental research
   Sugar chains are present on all cells in the body. Therefore, elucidation of how these sugar chains are involved in immune responses is important to understand the immune regulatory mechanism and immune cell development.
4. Possible application for industry and medicine, if any
   Because sugar chain-recognizing inhibitory receptors are involved in immune regulation as well as viral infection, certain molecules that regulate sugar chain-recognizing inhibitory receptors could be candidates for immune regulatory drugs, anti-virus drugs and anti-tumor drugs.

5. Future perspectives
   Studies on sugar chain recognition by immune cells have not focused on immunology so much. However, considering that there are a lot of sugar chain-recognizing inhibitory receptors, further analyses of these sugar chain-recognizing inhibitory receptors would be important.
6. Problems to be solved
   The exact binding specificity of many sugar chain-recognizing inhibitory receptors has remained unclear. Sugar chain-recognizing inhibitory receptors have been thought to recognize only the sugar chain structure. However, some receptors such as PILRα recognize both sugar chain structure and the protein structure. Further analyses of recognition by these receptors would be important (Fig. 14.12).

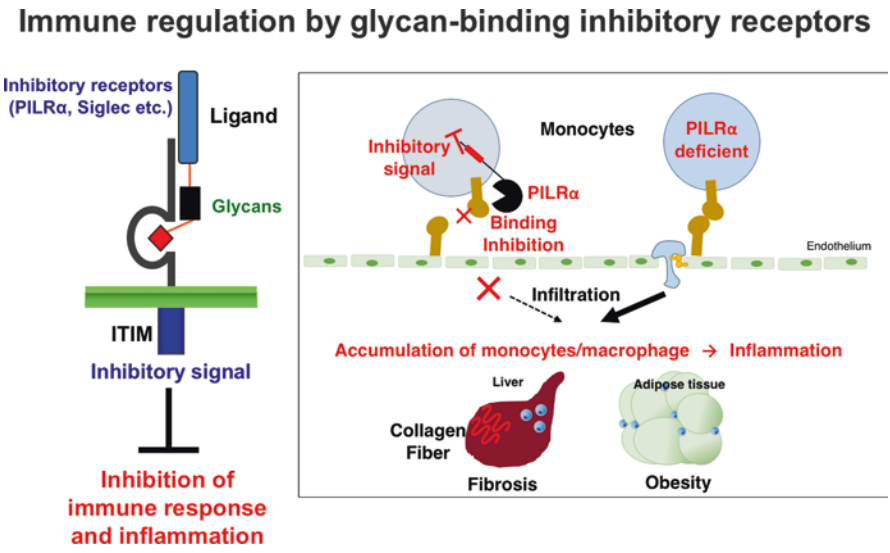

Fig. 14.12 Immune receptors express a variety of inhibitory receptors that recognize the sugar chain structure. In particular, PILRα, which is mainly expressed on monocytes and macrophages, plays an important role in the regulation of inflammation [55–57]

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