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Involvement of β-glucan receptors on the antitumor activity of β-glucans

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ABSTRACT

β-glucans consisting of β-(1,3)-linked glucose as the main chain (hereafter simply called "β-glucan") are suggested to have the potential for many beneficial effects on health. Among known beneficial effects, the most notable effect of β-glucan would be the antitumor effect. The antitumor effect of β-glucan has been known since the mid-twentieth century. In current cancer treatments where immune checkpoint inhibitors are attracting attention, it is expected that the combined administration of β-glucan will exhibit a greater therapeutic effect. The antitumor effect of β-glucan is believed to be closely linked to the receptors that recognize β-glucan. On the other hand, it has been clarified that there are many receptors for the recognition of β-glucan, in addition to CR3 (complement receptor 3) and dectin-1 (dendritic cell-associated C-type lectin-1), the well-known β-glucan receptors. This review focused on various β-glucan receptors reported previously and discusses the molecular mechanisms through which β-glucans exhibit antitumor effects.

1. Introduction

β-glucans consisting of β-(1,3)-linked glucose (hereafter simply called "β-glucan") function as dietary fibers and immune modifiers. The health-promoting effects of β-glucans delivered from various organisms, including cereals (barley [*Hordeum vulgare* L.] and oat [*Avena sativa* L.]), yeast (e.g. *Saccharomyces cerevisiae* and *Aureobasidium pullulans*), mushroom (e.g. *Lentinula edodes, Schizophyllum commune, Trametes versicolor*, and *Ganoderma lucidum*), seaweed (e.g. *Laminaria Digitata* and other *Laminaria*), algae (e.g. *Euglena gracilis*) and bacteria (e.g. *Alcaligenes faecalis* and other *Agrobacterium* species and *Alcaligenes*) have been reported, and these β-glucans are consumed as health-promoting foods or supplements.

β-glucan is a major compound in the cell wall of fungi causing opportunistic infection [1], such as *Candida albicans, Cryptococcus neoformans*, and *Aspergillus fumigatus*. Thus, the administration of β-glucan mimics fungal infection, resulting in the activation of immunity. The research using experimental animals showed that oral administration of β-glucan is not only effective for the resistance of fungal infections [2] but also effective in protecting from bacterial and protozoal infections [3] as well as virus infections [4–6]. Oral administration of β-glucan has been reported to activate adaptive immunity in aged mice, suggesting that β-glucan is effective in stimulating immunity without affecting homeostasis by oral administration [7]. It has also been suggested in humans that oral administration of β-glucan is effective for the activation of immunity and the prevention of infectious diseases [8,9]. β-glucan also can suppress excess inflammations. It has been reported that β-glucan exhibits anti-inflammatory effects against experimentally induced colitis [10], hepatitis [11], and burn sepsis [12] in mice. Also in humans, the administration of β-glucan has been shown to suppress the serum level of cytokines in patients with ulcerative colitis and Crohn's disease [13], and to improve allergy symptoms [14].

Beneficial effects of β-glucan on metabolic syndrome and its related diseases such as fatty liver disease, atherosclerosis, and type 2 diabetes have been reported. The results of animal experiments showed that oral administration of β-glucan ameliorates high-fat diet-induced NAFLD (nonalcoholic fatty liver disease) [15,16] and high-fat diet-induced atherosclerosis [17]. In addition, the studies using the mouse and the rat models for type 2 diabetes showed that oral administration of β-glucan improves metabolic profile including blood glucose level [18,19]. It is suggested in humans that the oral administration of β-glucan decreases blood cholesterol levels, and the consumption of β-glucan is thought to be effective for the risk reduction of metabolic syndrome [20,21].

Since the next-generation sequencer has become commonly used,

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and the analysis of gut microbiota has become easier, it is clarified that the microbiota is involved in various diseases [22]. The findings that oral administration of β-glucan can modulate gut microbiota suggest that β-glucan has the potential to act as a prebiotic. The potential for the beneficial effects of the oral administration of β-glucan through modulating the microbiota of livestock and poultry has been reported [23–25]. Related to the beneficial effects of β-glucan on metabolic syndrome described above, the studies using experimental animals showed the significance of modulating microbiota after oral administration of β-glucan on improving metabolic disorders caused by high-fat diet [26]. Interestingly, it has also been suggested the possibility that the administration of β-glucan is effective for the improvement of dementia through modulation of the microbiota [27,28]. It has also been reported in humans that consumption of β-glucan may lead to favorable changes in the microbiota, resulting in the reduction of the risk factor for cardiovascular diseases related to metabolic syndrome [29]. Further, the results of a human intervention study on children with autism spectrum disorder demonstrated that the bacteria involved in the production of amyloid curli, which is linked to the onset of Alzheimer's disease, were decreased in the microbiota after oral administration of β-glucan, suggesting that consumption of β-glucan may be effective to prevent Alzheimer's disease [30].

As described, it has been suggested that β-glucan exhibits various health benefits. Nevertheless, the most notable effects of β-glucan would be antitumor effects. The studies on the antitumor effects of β-glucan date back a long time, and started with the discovery that microbial components inhibited the growth of tumor cells experimentally transplanted into mice [31]. In the 1950s, zymosan, a polysaccharide derived from *S. cerevisiae* containing β-glucan as a main compound was found to exhibit antitumor activity [32,33]. Depending on these backgrounds, the studies on the antitumor effects of β-glucan progressed. In Japan, Lentinan [34,35] derived from the fruiting body of the shiitake mushroom (L. *edodes*) has been approved as an anticancer drug for the application of intravenous injection. In addition, schizophyllan (or sizofiran) [36] derived from the suehirotake mushroom (*S. commune*) and Krestin [37,38] derived from the mycelium of the CM-101 strain of the kawaratake mushroom (*T. versicolor*) have also been approved in Japan for the application of intramuscular injection and oral administration respectively. Since these antitumor drugs containing β-glucan did not always exhibit outstanding effects under clinical conditions, in principle, these β-glucan drugs were not used for monotherapy, but for combination with chemotherapy or radiotherapy to alleviate side effects and to support immunity. Later, these β-glucan drugs were discontinued, and molecular-targeted drugs are now at the center of attention for cancer therapy. Nevertheless, research on the antitumor effects of β-glucan is still being conducted, and the effectiveness of combination therapy of β-glucan with antibodies targeting tumor cells or immune checkpoint inhibitors has been demonstrated [39–41].

As mentioned, β-glucan is known to be a major component of the cell walls of fungi that cause opportunistic infections. Consequently, the anticancer effect of β-glucan is often understood to be exerted through activating the immune system by mimicking fungal infections. Although this is true in a broad sense, closely considering the physiological functions of β-glucan receptors and the effects of β-glucan on β-glucan receptors suggest that the antitumor effects of β-glucan are not restricted to exhibit through simple activation of the immune system. The mechanism to exhibit antitumor effects of β-glucan is thought to include the acquisition of the ability of immune cells to attack tumor cells escaped from antitumor immunity, the similarity of β-glucan with tumor-specific sugar chains, and the induction of direct cell death against tumor cells. This review focuses on various receptors involved in recognizing β-glucan and discusses the molecular mechanisms that exhibit antitumor effects of β-glucan based on physiological functions.

2. CR3 (complement receptor 3)

CR3 (complement receptor 3) also known as Mac-1 (macrophage-1 antigen), integrin αM/β2, and CD (cluster of differentiation) 11b/CD18 is the first discovered receptor for the recognition of β-glucan [42]. CR3 consists of a heterodimer of CD11b (integrin αM) and CD18 (integrin β2). An endogenous ligand of CR3 is the complement component iC3b (inactivated complement component 3b), and the iC3b recognition site of CR3 has been identified to be the I domain consisting of approximately 200 amino acids located near the N-terminus of CD11b subunit [43]. On the other hand, the β-glucan recognition site of CR3 is distinct from the I domain, and the lectin-like domain placed near the transmembrane domain on the C-terminus of CD11b is responsible for the recognition [44,45].

The complement system was originally discovered as an immune system that "complements" the function of antibodies, which recognize specific antigens for the inactivation and the elimination of pathogens, hence the name complement system. However, while antibodies are an immune mechanism that is evolutionarily acquired in vertebrates after cartilaginous fish, the complement system is also found in invertebrates that do not have antibodies. Therefore, it is considered that the complement system has been established before antibodies in the course of evolution [46,47]. Although the name complement system is widely used, to understand the complement system, it should be noted that the complement system is not an immune mechanism that was originally acquired to complement the function of antibodies.

Three activation pathways for the complement system are classified [48–50]. The first one is the classical pathway which is the initially identified pathway in activating the complement system and initiated by an antibody binding to an antigen. The second is the lectin pathway initiated by binding lectin, such as MBL (mannose-binding lectin) and ficolin, to a target molecule. The last one is the alternative pathway which supports the classical pathway and the lectin pathway and activates complement components in a self-activation and self-replicating manner. When the complement system is activated through these pathways, a complement component C3 present in bodily fluids is cleaved into C3a and C3b, and C3b covalently binds to the target molecule (opsonization). The opsonization of C3b activates the phagocytosis of phagocytes. The opsonization of C3b also activates the downstream complement cascade to form MAC (membrane attack complex), which makes a pore on the surface of the target (e.g. fungi, bacteria, virus, and tumor cell) and kills them.

The complement component iC3b recognized by CR3 is the inactivated form of C3b as suggested by the name. Unlike C3b, iC3b cannot activate the downstream complement cascade, iC3b is hence not able to induce cell death by forming MAC. The conversion of C3b to iC3b is processed by proteolytic cleavage that is catalyzed with a serine protease, complement factor I, and its co-factor MCP (membrane cofactor protein, also known as CD46) [51,52]. In addition, CR1 (complement receptor 1, also known as CD35) which is known to be a receptor for the recognition of C3b is also involved in the proteolytic cleavage mediated by the complement factor I [52]. This pathway for the inactivation of C3b is not only thought to exist to control the activation of the complement system but also to protect autologous cells from the attack of the complement system. MCP is known to be ubiquitously expressed in almost all cells. It is thought that when autologous cells are opsonized with C3b, the opsonized C3b is immediately converted into inactive iC3b through the inactivation pathway-mediated proteolytic reaction, thereby preventing cell death caused by the formation of MAC [53].

Overexpression of MCP is found in many tumor cells [53,54], suggesting that the conversion pathway of C3b to iC3b is important for the immune escaping strategy of tumor cells. The tumor cells opsonized with iC3b can escape from phagocytosis and oxidative burst by neutrophils or cell killing by natural killer cells, but when the presence of β-glucan makes tumor cells susceptible to these antitumor responses [55–58]. This effect of β-glucan is CR3-dependent and requires that iC3b and

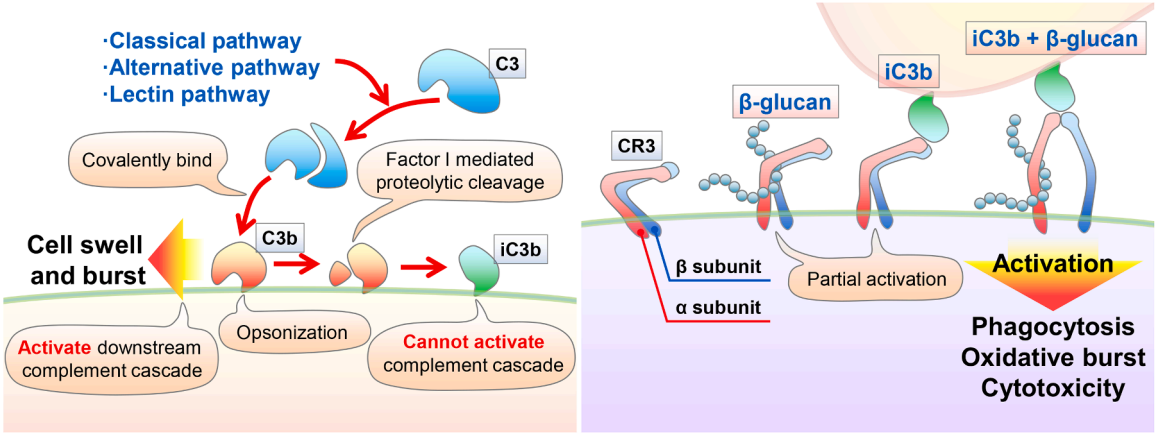

Fig. 1. The function of iC3b on the complement system and the effect of β-glucan on CR3 activation.

β-glucan bind to CR3 simultaneously. In other words, CR3 does not transduce the activation signal which induces phagocytosis and oxidative burst to neutrophils or natural killer cells when CR3 recognizes iC3b (or β-glucan) alone, but CR3 transduces the activation signals to these immune cells when CR3 simultaneously recognizes iC3b and β-glucan.

The effect of β-glucan co-stimulation with iC3b for the activation of CR3 is thought to be developed as a host-defense mechanism against the infection of fungi carrying β-glucan as a major compound of the cell wall. Some pathogenic fungi causing opportunistic infections can convert C3b to iC3b [59,60]. Even if these pathogenic fungi convert C3b to iC3b to escape from the cell death induced by the activation of the complement system, neutrophils, and natural killer cells expressing CR3 on the cell surface can recognize these fungi as extracellular pathogens and eliminate these through the activation of CR3 mediated signaling pathway by the simultaneous recognition of iC3b and β-glucan present in the fungal cell wall. As commented above, many tumor cells overexpressed MCP can rapidly convert C3b to iC3b, resulting that the tumor cells can escape from the cell death induced by the formation of MAC after the activation of the complement system. At the same time, the tumor cells lack the glycans recognized by CR3. Thus the iC3b opsonized tumor cells do not activate the CR3-mediated signaling and can escape from the attack of immune cells including neutrophils and natural killer cells. On the other hand, in the presence of β-glucan, CR3 expressed on the surface of neutrophils and natural killer cells recognized the iC3b opsonized tumor cells as pathogen-like matters in a similar way to the iC3b opsonized fungal cells, and then the iC3b opsonized tumor cells become susceptible to the attack from these immune cells. This phenomenon is thought to play an important role in the antitumor effects of β-glucan. Further, this phenomenon also suggests that the therapeutic effect of tumor-specific monoclonal antibodies that induce opsonization of tumor cells with iC3b through the classical pathway-mediated activation of the complement system may be enhanced by the simultaneous treatment with β-glucan. Indeed, it has been shown using mouse tumor models that the therapeutic effect of tumor-specific monoclonal antibodies is enhanced by the combination treatment with β-glucan [61,62].

Leukadherin-1 (also known as ADH-503) is a small molecule that targets CR3 [63]. The binding site of leukadherin-1 in CR3 is the I domain of CD11b, which is responsible for binding to iC3b, ICAM (intercellular adhesion molecule) -1, ICAM-2, and fibrinogen. This differs from the β-glucan binding site, the lectin-like domain located near the transmembrane domain of CD11b. Leukadherin-1 strengthens the binding of CR3 to ICAM-1 and ICAM-2 in the extracellular matrix, whereas β-glucan inhibits the binding of CR3 to these molecules [64]. Although, there are some functional differences between leukadherin-1 and β-glucan, the function thought to be involved in the antitumor effects is resembled. Leukadherin-1 enhances the binding of CR3 to iC3b as similar to β-glucan [63], and the stimulation with β-glucan alone partially activates CR3 as similar to leukadherin-1 [65]. It has been reported that the combination treatment with leukadherin-1 and anti-PD-1 (programmed death-1, also known as CD279) antibody, which is an inhibitor of the PD-1/PD-L1 (programmed death ligand 1, also known as CD274) checkpoints, can enhance the therapy sensitivity of the tumor cells that are resistant to anti-PD-1 antibody monotherapy [66]. A similar effect has also been shown with β-glucan [67], suggesting the significance of CR3 in tumor immunity, and the importance of modulating CR3 function in tumor therapy.

3. Dectin-1 (dendritic cell-associated C-type lectin-1)

C-type lectins are calcium-dependent glycan-recognition molecules. C-type lectins expressed in macrophages and dendritic cells play an important role in recognizing extracellular pathogens and activating the immune system. Dectin-1 (dendritic cell-associated C-type lectin-1, also known as CLEC7A [C-type lectin domain containing 7A] and SCARE2 [scavenger receptor class F member 1]) is a member of the C-type lectin family and was found as a receptor for β-glucan expressed in macrophages [68]. Dectin-1 was initially identified by subtractive cDNA cloning as a gene abundantly expressed in a dendritic cell-like cell line, XS52 cells, but with low expression in non-dendritic cells including a macrophage-like cell line, J774 [69]. Although dectin-1 was discovered in this way, it is now commonly understood that dectin-1 is a major receptor for recognizing β-glucan expressed on the surface of macrophages [70]. Eight alternatively spliced isoforms of dectin-1 were identified in humans, but only two major isoforms of these, decin-1A and dectin-1B are responsible for recognizing β-glucan [71].

Considering the role of dectin-1 in the antitumor effects of β-glucan, it is notable that dectin-1 not only acts as a receptor for the recognition of β-glucan but also acts as a receptor for the recognition of the N-glycan structure specifically expressed on the surface of tumor cells [72]. When dectin-1 is expressed on dendritic cells and macrophages recognize the N-glycan structure expressed on tumor cells, dectin-1 activates the transcription factor IRF5 (Interferon regulatory factor-5) through the activation of the downstream signaling pathway, and enhances tumor cell killing by natural killer cells through the cell-to-cell contact. This IRF5 activation is also induced by curdlan, β-glucan produced by *Alcaligenes faecalis* var. myxogenes [72]. Therefore, β-glucan is thought to be effective in enhancing antitumor immunity via dectin-1 by mimicking the glycans expressed on the surface of tumor cells.

Experiments using mice showed that although dectin-1 can bind with high affinity to both soluble and insoluble particulate β-glucans, only insoluble particulate β-glucans such as zymosan and curdlan can activate the dectin-1-mediated signaling pathway [73,74]. In addition, these studies also showed that a soluble β-glucan, laminarin acts as an antagonist which inhibits the dectin-1-mediated signaling pathway

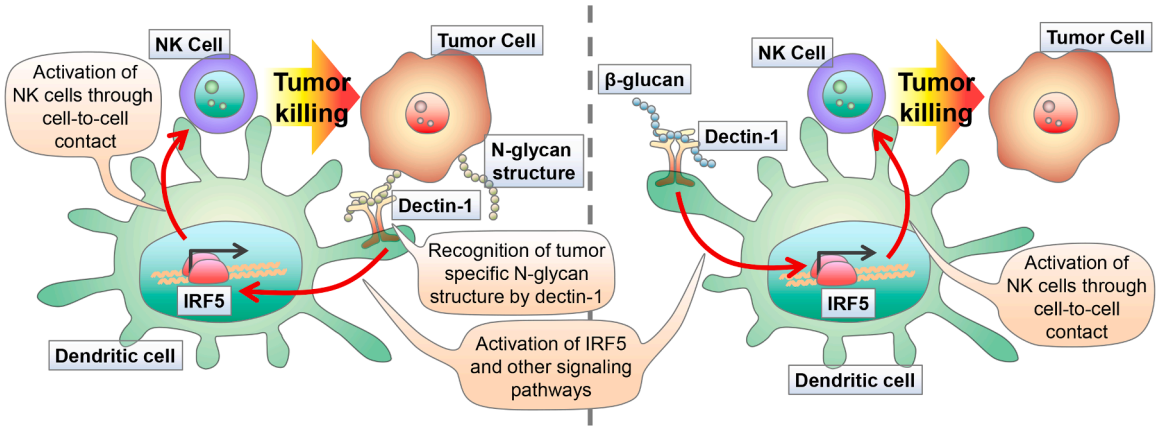

Fig. 2. Dectin-1 cross-reacts with β-glucan and tumor-specific N-glycan.
NK cell: natural killer cell

activated by these insoluble particulate β-glucans. Human and mouse dectin-1 share 60% amino acid sequence identity and are structurally similar, but differ in the N-linked glycosylation sites [75]. Two dectin-1 isoforms responsible for recognizing β-glucan, dectin-1A, and dectin-1B are distinct in the length of the stalk region outside the cell membrane. Mouse dectin-1A and dectin-1B isoforms have two N-linked glycosylation sites in CRD (carbohydrate recognition domain) responsible for recognizing β-glucan. Human dectin-1A has an N-linked glycosylation site in the stalk region connecting to the CRD, and human dectin-1B, which has a shorter stalk region, has no N-linked glycosylation sites. This difference in N-linked glycosylation sites is thought to influence the responsiveness of human dectin-1 and mouse dectin-1 to β-glucan. According to experimental data using the cells ectopically expressed two isoforms of human and mouse dectin-1 reported by InvivoGen, human dectin-1B does not respond to laminarin, but dectin-1A responds to laminarin and activates downstream signaling [76]. In this report, mouse dectin-1A and dectin-1B isoforms do not react to laminarin as previously reported [73,74]. Therefore, it should be noted that the dectin-1 response to soluble β-glucan may differ between humans and mice.

A study using monoclonal antibodies to analyze the expression of the dectin-1 isoforms, dectin-1A and dectin-1B in humans demonstrated that both dectin-1A and dectin-1B are expressed in peripheral blood monocytes, macrophages, dendritic cells, neutrophils, and eosinophils. On the other hand, mature monocyte-derived macrophages and dendritic cells express almost exclusively dectin-1B [77]. Therefore, it is likely that also in humans, soluble β-glucans act as a dectin-1 antagonist of on these cells expressed dectin-1B only.

Dectin-1 deficient mice injected intravenously with B16F1 melanoma cells have been shown to exhibit enhanced lung metastasis of B16F10 melanoma cells compared to normal mice, suggesting the significance of dectin-1 in eliminating tumor cells [72]. However, analysis of other tumors using dectin-1 deficient mice has shown that expression of dectin-1 in tumor-associated macrophages contributes to tumor progression [78,79]. It has been reported that in lung adenocarcinoma, tumor-resident Aspergillus sydowii is enriched, and this β-glucan expressed fungi is involved in tumor initiation and progression through the activation of the signaling pathway mediated by dectin-1 in myeloid-derived suppressor cells [80]. Further, a chemically induced colorectal tumor model using carcinogenic hypersensitive mice showed that dectin-1 deficiency suppresses intestinal tumorigenesis, and oral administration of laminarin also suppresses the development of mouse colorectal tumors [81]. On the other hand, there is also a report that oral administration of particulate insoluble β-glucan reduces the incidence of chemically induced colitis and associated colorectal cancer [82]. In addition, particulate insoluble β-glucan derived from the cell wall of S. cerevisiae has been consumed by many people for so long as a supplement. Therefore, particulate insoluble β-glucan does not probably promote tumor initiation and progression under conventional conditions. However, these phenomena suggest that activation of the dectin-1 signaling pathway does not necessarily have an antitumor effect. Especially, it should be noted that in immune cells infiltrated in tumor tissue, activation of the dectin-1-mediated signaling pathway may promote tumor progression.

Antitumor drugs administered by injection containing β-glucan as an active compound, such as Lentinan and schizophyllan, are soluble β-glucan because there is a side effect that injection of particulate insoluble β-glucan causes granuloma formation [83]. On the other hand, granuloma formation by administration of soluble β-glucan is barely observed, and a few are observed only when soluble β-glucan was administered at quite high concentrations. It has been reported that schizophyllan, a soluble β-glucan, has an antitumor effect on an experimental tumor in mice and that this antitumor effect is inhibited by anti-dectin-1 antibodies which inhibit the binding of schizophyllan to dectin-1 [84]. Interestingly, these observations indicate that the dectin-1 binding of soluble β-glucan, which is thought to act as a dectin-1 antagonist in mice, is involved in its antitumor effect. About these observations, it would be necessary to consider the possibility that not all soluble β-glucans act as dectin-1 antagonists in mice. However, it would also be indispensable to consider the possibility that the function of soluble β-glucan as a dectin-1 antagonist is involved in the antitumor effect of β-glucans by inhibiting the dectin-1-mediated signaling pathways.

As mentioned above, since dectin-1 is a receptor that recognizes N-glycan structures specifically expressed in tumor cells, there is no doubt that dectin-1 plays an important role in tumor immunity. On the other hand, it is notable that the dectin-1-mediated signaling pathway can work positively and negatively on tumor immunity. This may prove important to understand the molecular mechanism to exert antitumor effects of β-glucan.

4. Langerin

Langerin (also known as CD207) was discovered as a C-type lectin receptor specifically expressed on Langerhans cells, a subset of dendritic cells [85]. Langerhans cells are antigen-presenting dendritic cells that reside in epithelia and possess Birbeck granules which are characteristic rod- or tennis racket-shaped cytoplasmic organelles. Langerin is crucial for Birbeck granules formation in Langerhans cells [85–87]. Subsequent studies have revealed that Langerin-positive subsets of dendritic cells other than Langerhans cells exist in various tissues [88,89]. Langerin expressed in these dendritic cells, including Langerhans cells, is thought

to play an important role in host defense against fungal infections in the epithelium and the epidermis of mucosal tissues as a receptor for β-glucan [90].

It has been reported the possibility that a decrease in Langerin-positive dendritic cells in oral epithelium is related to the onset and progression of oral squamous cell carcinoma [91]. In addition, it has been reported that when apoptotic/necrotic cells of a mouse melanoma cell line, B16-F1 cells are administered as a vaccine, resistance to the tumor cells is acquired, and Langerin-positive cells are recruited to the vaccination site [92]. These findings suggest the possibility that Langerin is involved in the recognition of tumor cells and the activation of tumor immunity. Studies on the glycan binding specificity of Langerin suggested that Langerin is involved in recognizing glycans expressed on the surface of tumor cells [93,94]. This function of Langerin is similar in recognizing the N-glycan structure of glycans expressed on tumor cells by dectin-1, a β-glucan receptor belonging to C-type lectin in the same family as Langerin. Therefore, like dectin-1, Langerin expressed on dendritic cells may activate antitumor immunity after the stimulation with β-glucan.

A notable function of Langerin is that a subpopulation of Langerin-positive dendritic cells in the intestinal Peyer's patches is involved in β-glucan sampling [95,96]. It has been reported that Langerin expressed in dendritic cells mediates efficient antigen presentation through MHC (major histocompatibility complex) class I and class II molecules [97]. Therefore, Langerin may be involved in producing antibodies against orally administered β-glucan. Interestingly, it has been reported that human anti-β-(1,6)-glucan antibodies affinity-purified from human serum using pustulan (linear and unbranched β-(1,6)-glucan derived from *Lasallia pustulata*) column are cross-reacted with tumor-associated carbohydrate antigens and able to bind to certain tumor-derived cell lines [98]. This may suggest that oral administration of β-glucan with β-(1,6)-linked branches exhibits antitumor activity by producing anti--β-glucan antibodies via Langerin.

5. NKp30 (activating natural killer receptor p30)

NKp30 (activating natural killer receptor p30, also known as NCR3 [natural cytotoxicity triggering receptor 3] or CD337) is a β-glucan receptor and was reported to be an important molecule in natural killer cells for the activation of cell killing against opportunistic fungi, such as *C. neoformans* and *C. albicans*, through the recognition of β-glucan present on the cell surface of these fungi [99]. NKp30 was identified as a member of NCR (natural cytotoxicity receptor) family constitutively expressed in natural killer cells and discovered following NKp46 (activating natural killer receptor p46, also known as NCR1 or CD335) and NKp44 (activating natural killer receptor p44, also known as NCR2 or CD336) [100]. NCRs are important activating receptors on natural killer cells for recognizing tumor cells [101–103]. Natural killer cells recognize the cells expressing ligands binding to these receptors, and losing or reducing expression of MHC class I on the cell surface as tumor cells, and exhibit the cell killing activity to these cells. In almost all mouse strains including C57BL/6 and BALB/c widely used for research, NKp30 exists as a pseudogene and is not expressed as a functional protein [104].

So far, B7-H6 (B7 homolog 6) [105], BAT3 (HLA-B-associated transcript 3, BAG6 [Bcl2-associated anthogene 6], also known as Scythe) [106], and galectin-3 [107] have been identified as endogenous ligands for Nkp30. B7-H6 is a B7 family molecules known to act as co-stimulatory and co-inhibitory molecules for immune cells. B7 family molecules are thought to be crucial for the control of immune response. On a side note, PD-L1, widely known as a target molecule for immune checkpoint inhibitors for tumor treatment, is also a B7 family molecule known as B7-H1 (B7 homolog 1) [108,109]. B7-H6 is expressed in tumor cells and is barely expressed in normal cells. It is thought that natural killer cells exert cell-killing activity against tumor cells by recognizing B7-H6 via NKp30. B7-H6 expressed on the surface of tumor cells can be released as a soluble molecule by metalloproteases. Unlike membrane-bound B7-H6, soluble B7-H6 is known to inhibit the activation of natural killer cells via NKp30 [110].

Another endogenous ligand for NKp30, BAT3 is a nuclear factor that has been reported to interact with CBP (CREB-binding protein)/p300 (E1A binding protein p300) and be involved in the acetylation of the p53 tumor suppressor protein [111]. Therefore, BAT3 is not expressed on the cell surface but is recognized by NKp30 after being released from the cells. Interestingly, it has been reported that free soluble BAT3 suppresses NKp30-mediated activation of natural killer cells, while BAT3 exposed on the surface of exosome enhances the cell-killing activity of natural killer cells via NKp30 [106,112]. This observation is thought to suggest that crosslinking (aggregation) of NKp30 molecules is necessary for the activation of NKp30, and at the same time that the presence of a ligand on the target cell is not required for the activation of the cell-killing activity of natural killer cells via NKp30. Exosomes are very small, a type of extracellular vesicle secreted from cells with a diameter of 50–150 nm. Exosomes contain cell-derived components such as nucleic acids, proteins, lipids, amino acids, and metabolic products on

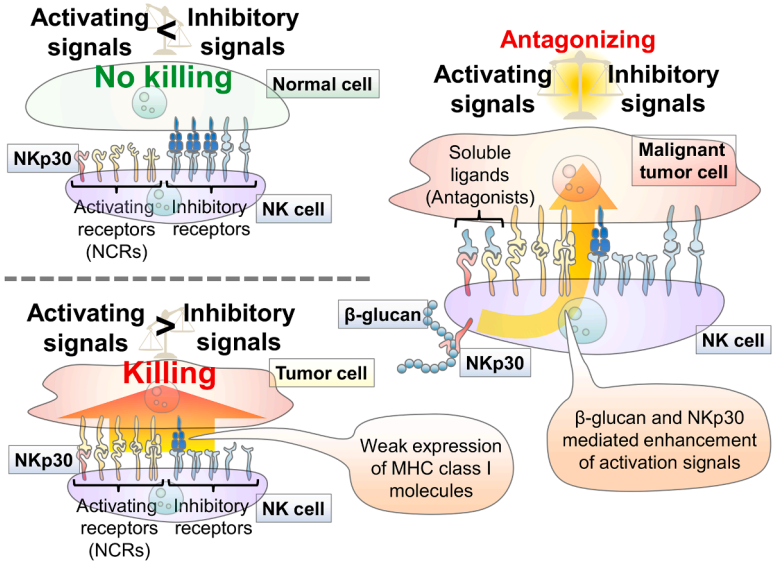

Fig. 3. β-glucan modulates activating /inhibitory signals of natural killer cells.
NK cell: natural killer cell

their surface and inside. Exosomes play an important role in cell-to-cell communication [113,114]. The activation of p53 through the acetylation via BAT3 and CBP/p300 has been reported to be involved in exosome secretion by stress response [115]. Therefore, BAT3 is thought to be involved in suppressing tumor development through both the stress-induced secretion of exosome exposing BAT3 and the activation of tumor-killing activity of natural killer cells via BAT3/NKp30 mediated signaling.

Galectin-3 is a member of the galectin family responsible for recognizing β-galactoside containing glycans and is known to be overexpressed in a variety of tumor cells [116,117]. Galectin-3 is mainly present in the cytoplasm, but it also translocates into the nucleus, localizes on the cell surface, and is released into the serum after secretion into the extracellular matrix. It has been reported that Galectin-3 released from cells works as a ligand for NKp30 and suppresses the NKp30-mediated activation of the cell-killing activity of natural killer cells [107]. These NKp30 activating/inhibitory ligands, B7-H6, BAT3, and galectin-3 are thought to control the activation of natural killer cells via NKp30 and play an important role in maintaining homeostasis in the body. Hence, the disruption of this NKp30 activation/inhibition balance may be involved in tumor development.

It has been reported that soluble β-glucan does not inhibit natural killer cell-mediated cytotoxicity against *C. neoformans* and *C. albicans* through the recognition of β-glucan present on these fungal cell surface via NKp30, but rather enhances the cell-killing activity against these fungi [99]. This suggests that β-glucan can activate the cell-killing activity of natural killer cells through cross-linking (aggregation) of NKp30, similar to BAT3 exposed on the surface of exosomes. It is considered that whether natural killer cells exert the cell-killing ability against target cells is determined by the balance between inhibitory signals such as MHC class I and activating signals from NCRs including NKp30 [118–120]. β-glucan is thought to be able to modulate the activating/inhibitory signal balance to the activating through the activation of the NKp30-mediated signaling pathway, and this effect may be involved in the part of the molecular mechanism to exhibit the antitumor activity of β-glucan.

NKp30 has been reported to be expressed not only in natural killer cells but also in some subpopulations of T cells. It has been reported that NKp30 can induce in human peripheral blood $V\delta1^+$ T cells after stimulation with γc cytokines such as IL-15 in combination with TCR (T-cell receptor) agonists [121]. In addition, there has been reported to be a subpopulation of $CD8^+$ T cells in human peripheral blood which expresses NKp30 distinct from $V\delta1^+$ T cells and is induced by IL-15 stimulation [122]. Notably, these T cell subpopulations can exert strong antitumor activity in an NKp30-dependent manner. Further studies to investigate the effect of β-glucan on these T cell subpopulations via NKp30 are awaited.

6. Scavenger receptors

Scavenger receptors were originally proposed based on the discovery of molecules expressed on the cell surface of macrophages that do not bind to native low-density lipoprotein (LDL), but recognize modified LDL such as oxidized LDL, and remove modified LDL by phagocytosis and subsequent degradation acting like a "scavenger" (means a street cleaner) [123]. It has now been revealed that scavenger receptors function as pattern recognition receptors that recognize a wide range of ligands, including not only modified LDL but also apoptotic cells, aging products such as AGEs (advanced glycation endproducts), and pathogens. Thus, scavenger receptors are assumed to play an important role in maintaining homeostasis in the body [124,125]. On a side note, dectin-1, a widely known receptor for β-glucan, is also classified as one of the scavenger receptors belonging to class E member 2 (termed SCARE2).

Among the molecules belonging to the scavenger receptor superfamily, SCARF1 (scavenger receptor class F member 1, also known as SREC-I [scavenger receptor expressed by endothelial cell-I]) and CD36 (cluster of differentiation 36, also known as SCARB3 [scavenger receptor class B member 3]) have been reported to recognize *C. neoformans* and *C. albicans* in a β-glucan-dependent manner, and play an important role in host defense against these opportunistic fungal infections [126]. Originally, SCARF1 has been identified as a molecule expressed in endothelial cells belonging to the scavenger receptor superfamily and was cloned from HUVEC (human umbilical vein endothelial cells) [127]. SCARF1 expression has been reported to be decreased in correlation with the progression and prognosis of hepatocellular carcinoma [128]. It has been suggested that SCARF1 expressed in endothelial cells of hepatocellular carcinoma is involved in the activation of antitumor immunity by promoting infiltration of effector T cells. SCARF1 is the human orthologue of CED-1 in *Caenorhabditis elegans*, with 24% homology [129]. CED-1 in *C. elegans* plays an important role in removing apoptotic cells. Similar to CED-1, its orthologue in humans, SCARF1 is also an important receptor for the phagocytosis of apoptotic cells, and it has been reported that SCARF1 recognizes apoptotic cells through binding to the complement component, C1q [130]. C1q is known to be involved in the complement cascade initiation via the classical pathway through the recognition of antibodies bound to antigens. In addition, it has been reported that C1q is also functional for recognizing apoptotic cells through the binding to nucleoli, and is important for the degradation of nucleolar antigens [131]. Nuclear antigens are one of the autoantigens found in the sera of patients with SLE (systemic lupus erythematosus), an autoimmune disease. The C1q deficiency is known to cause SLE in both humans and mice [132], and similar to this, mice lacking SCARF1 have been reported to spontaneously develop SLE-like autoimmune disease due to a failure to remove autoantigens derived from apoptotic cells [130].

Like SCARF1, CD36 has been reported to play an important role in removing apoptotic cells through the recognition of oxidized phosphatidylserine exposed on the cell membrane of apoptotic cells [133]. However, unlike SCARF1, little is known about the involvement of CD36 in the development of autoimmune diseases. The studies on the involvement of CD36 in diseases seem to be focused on the function of CD36 as a scavenger receptor in macrophages, that is, the recognition and the uptake of modified LDL [134,135]. ApoE (apolipoprotein E) deficient mice spontaneously develop atherosclerosis [136]. On the other hand, it was reported that ApoE and CD36 double knockout mice, which were established by cross ApoE deficient mice and CD36 deficient mice, showed suppression of atherosclerotic lesions compared to the parental ApoE deficient mice [137]. Macrophages isolated from ApoE and CD36 double knockout mice showed impaired uptake of modified LDL and suppression of foam cell transformation of macrophages which causes atherosclerotic lesions. Therefore, CD36 is recognized as an important factor involved in the development of atherosclerosis. This function of CD36 is also thought to play an important role in tumor immunity. It has been reported that CD36-mediated uptake of oxidized LDL leads to tumor progression by inducing ferroptosis (iron-dependent non-apoptotic cell death) or reducing cytokine production in tumor-infiltrating $CD8^+$ T cells [138,139].

CD36 is also known as FAT (fatty acid translocase) and is involved in recognizing long-chain fatty acids and subsequent uptake [140]. Hence, CD36 is thought to be important in regulating fatty acid metabolism [141]. Lipid metabolism is also involved in the function of CD36 in tumors, and it has been reported that CD36-mediated lipid uptake promotes M2 polarization of macrophages, resulting in suppression of antitumor immunity through promoting the production of anti-inflammatory factors and the infiltration of regulatory T cells [142,143]. In addition, CD36-mediated metabolic control is involved in the survival of regulatory T cells, which promote tumor progression through immunosuppression [144].

Furthermore, CD36 is also functional as a receptor for thrombospondin-1 and thrombospondin-2, known to be endogenous inhibitors of angiogenesis [145,146]. Although thrombospondin does

not necessarily act in a tumor-suppressing manner [147,148], angiogenesis is assumed to be essential for tumor growth and hypertrophy, and thrombospondin has been reported to exhibit antitumor effects in many tumors through the inhibition of angiogenesis [149,150]. Therefore, in that the transducing thrombospondin-mediated inhibitory signaling against angiogenesis, CD36 is considered to act in an antitumoral manner [151]. Thus, CD36 is a molecule that can act both progressively and suppressively in tumors. Nevertheless, although there are some exceptions [152], a correlation between CD36 expression and prognosis has been reported in many cancers [153–156], and in principle, CD36 can be assumed to be an important molecule promoting tumor progression.

CD5 is a scavenger receptor that has long been used as a pan T cell marker. It has been shown that the CD5 extracellular domain binds to zymosan, *C. neoformans*, and *C. albicans* in a β-glucan-dependent manner, suggesting that CD5 can act as a β-glucan receptor [157]. CD5 is expressed on T cells and B-1a cells, a subpopulation of B cells, and is highly expressed on regulatory T cells and regulatory B cells [158]. CD5 expression has also been observed in some DLBL (diffuse large B-cell lymphomas), and CD5 expression has been reported to be associated with a worse prognosis in DLBL patients [159].

Since the immune activation in response to antigens mediated by TCR and BCR (B-cell receptor) is enhanced in CD5 deficient mice, CD5 is thought to negatively regulate TCR and BCR-mediated signaling [160–162]. Therefore, CD5-mediated signaling is considered to act on antitumor immunity inhibitory. The analysis results of tumor-infiltrating T cells from lung cancer patients have shown that the expression level of CD5 is inversely proportional to the cytolytic effect of T cells against tumor cells [163]. Further, it has been shown that blocking the function of CD5 using a specific monoclonal antibody enhances antitumor immunity [164,165]. On the other hand, it has been reported that CD5 protects tumor-specific T cells from activation-induced cell death (AICD) [166,167], and CD5 expression on tumor cells has been shown to correlate with prognosis in DLBL [168, 169]. Thus, in addition to immune suppression, it is thought that CD5-mediated signals are involved in cell survival.

The expression of CD5 is not restricted in immune cells related to acquired immunity. Interestingly, the expression of CD5 has been found in a subtype of dendritic cells, a member of innate immune cells [170]. It has been demonstrated that the expression of CD5 on the surface of dendritic cells correlates with the activation of $CD4^+$ and $CD8^+$ T cells and that mice lacking CD5 are impaired the efficacy of an anti-PD-1 antibody, an immune checkpoint inhibitor [171]. On the other hand, the expression of CD5 on dendritic cells has also been reported to show a suppressive effect on tumor immunity [172]. The background why these controversial results were obtained may be related to the suppressive effect of CD5 on TCR- and BCR-mediated signaling is not always a ligand-dependent manner [173], and that CD5 can work as an endogenous ligand for CD5 [174]. Nevertheless, overall, appropriate CD5 signaling would appear to be important for maintaining homeostasis of the body and the immune system.

Although these scavenger receptors have been reported to work as pattern recognition receptors for the recognition of β-glucan present on the cell surface of fungi, little is known about the effect of β-glucan on tumor immunity via these receptors. The studies on the β-glucan effects on these scavenger receptors are awaited.

7. EphA2 (Ephrin type-A receptor 2)

The interaction between ephrins and ephrin receptors plays an important role in the development, regeneration, and maintenance of homeostasis of various organs [175]. EphA2 (ephrin type-A receptor 2), one of the nine molecules of ephrin type-A receptors (EphA1–8, EphA10) in humans, has been reported to act as a pattern recognition receptor that recognizes β-glucan expressed on the surface of fungal cells, in oral epithelial cells [176]. EphA2 can recognize β-glucan exposed on the cell surface of various fungi such as *C. albicans, S. cerevisiae, A. fumigatus*, and *Rhizopus delemar*. EphA2-deficient mice show more severe symptoms of oropharyngeal candidiasis caused by *C. albicans* infection, suggesting that EphA2 is crucial for oral immunity against fungal infections. EphA2 expression is also found in neutrophils in the oral mucosa, and EphA2 expressed on neutrophils has been subsequently shown to play an important role in the host defense against oropharyngeal candidiasis along with EphA2 expressed on oral epithelial cells [177]. Further, EphA2 expressed on lung epithelial cells has been suggested to be involved in the adhesion of the genus *Pneumocystis*, which causes Pneumocystis pneumonia, to alveolar epithelial cells and the induction of inflammation [178].

EphA2 is expressed in epithelial cells, especially in proliferating epithelial cells. EphA2 is a receptor tyrosine kinase which has a tyrosine kinase domain in the cytoplasm responsible for tyrosine kinase activity [179]. Elevated expression level of EphA2 is found in many solid tumors. Interestingly, the effect of EphA2 on tumor progression is exhibited in the absence of a ligand, while EphA2 suppresses tumor progression in the presence of its ligand ephrinA1 [179,180]. These bidirectional effects of EphA2 on tumor progression would be involved in that the tyrosine kinase activity of EphA2 is not affected in the presence or absence of ligands, resulting in EphA2 transducing different signals between the absence and presence of ligands. Decreased expression of ephrinA1 has been observed in many tumors. In addition, EphA2 is known to be degraded after internalization by endocytosis in the presence of ephrinA1, resulting in the decrease of EphA2 expression level and the suppression of tumor cell growth [179,180]. Therefore, EphA2 overexpressed on many solid tumor cells is thought to act for the tumor progression in the absence of ligands.

Several researches have shown that β-glucan can directly induce apoptosis in cultured cell lines derived from solid tumors without activating immune cells [181–183]. On the other hand, it has been reported that silencing of the EphA2 gene using siRNA (small interfering RNA) induces apoptosis in MSTO-211H cells derived from human biphasic mesothelioma [184] and MGC803 cells derived from human gastric cancer [185]. It has also been reported that stimulation with ephrinA1, an EphA2 ligand, induces EphA2-mediated apoptosis in MDA-MB-231 cells derived from human breast cancer [186]. These findings indicate that suppression of EphA2 expression and stimulation with an EphA2 ligand can induce apoptosis in tumor cells directly. Further, these findings suggest that the effect of β-glucan as an EphA2 ligand may be involved in the direct induction of apoptosis in cancer cells by β-glucan. The stimulation with β-glucan has been reported to enhance the sensitivity of A549 cells derived from human lung cancer cells to the antitumor drug etoposide through the EphA2-mediated signaling [187].

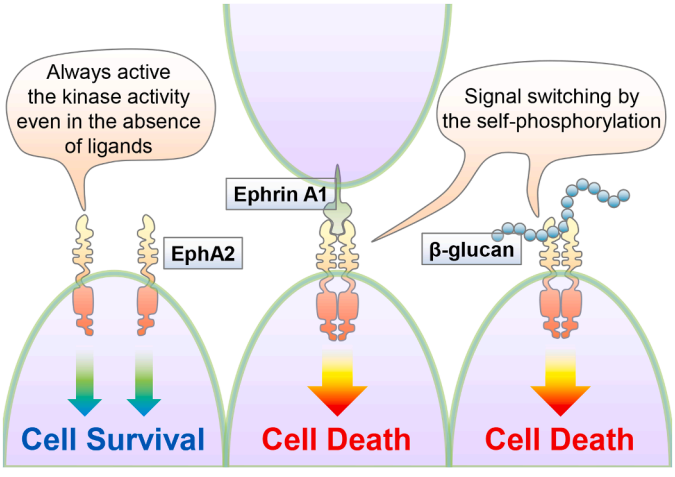

Fig. 4. EphA2 transmits different signals in the presence/absence of the ligands.

The extracellular ligand-binding domain of EphA2 is known to be proteolytically cleaved by MT1-MMP (membrane-anchored membrane type-1 matrix metalloproteinase), whose expression is upregulated in some cancers [188]. Therefore, it should be noted that the antitumor effect of β-glucan via EphA2 would be restricted to the tumor expressing intact EphA2. Nevertheless, to think about the molecular mechanism of the direct β-glucan effect on solid tumors, especially in epithelial cancer cells, to consider the involvement of EphA2 would be required.

8. CLEC2D (C-type lectin domain family 2 member D)

CLEC2D (C-type lectin domain family 2 member D, also known as LLT1 [lectin-like transcript 1]) has been cloned as a gene encoding a lectin-like molecule localized in the natural killer gene complex on human chromosome 12, where natural killer receptors belonging to the C-type lectin superfamily are concentrated [189]. It has been reported that CLEC2D forms homodimers and heterodimers with TLR2 and binds to *C. albicans* and a linear β-glucan, curdlan [190]. Therefore, CLEC2D is considered one of the C-type lectin receptors recognizing β-glucan. The expression of CLEC2D on the surface of immune cells is found in natural killer cells, T cells, B cells, macrophages, and dendritic cells, and induced on these immune cells by the activating stimulation [191–193]. It has been reported that the binding of β-glucan to the CLEC2D homodimer and heterodimer with TLR2 inhibits the activation of IRF5 through the ubiquitination of MyD88 and its degradation by the proteasome [190]. Dectin-1, a well-known pattern recognition receptor for β-glucan, has been reported to activate IRF5 in response to β-glucan [73]. Therefore, CLEC2D can be considered a receptor transducing a counter signal to the dectin-1-mediated signaling pathway.

Other than immune cells, CLEC2D is highly expressed in immune-privileged organs such as the brain, placenta, and testis [194]. It is known that CLEC2D also acts as a ligand for CD161 (also known as CLEC5B [C-type lectin domain family 5 member B], or NKR-P1A [NK cell receptor protein 1A]), which belongs to the same C-type lectin receptor as CLEC2D [193,195]. CD161 is expressed on the surface of a subset of human NK cells and T cells. CD161 is considered an inhibitory receptor that negatively regulates the cell-killing activity of these immune cells. The findings that CLEC2D is highly expressed in immune-privileged tissues may indicate the importance of CLEC2D in suppressing the activation of cytotoxic immune cells via CD161.

The CLEC2D-CD161 interaction-mediated signaling pathway is also thought to be utilized by tumor cells to escape attack from the immune system. Increased expression of CLEC2D has been observed in various tumors, including glioblastoma [196], germinal center-derived B-cell non-Hodgkin's lymphomas [197], prostate cancer [198], colorectal cancer [199], and triple-negative breast cancer [200]. It has been reported that inhibition of CLEC2D binding to CD161 using anti-CLEC2D antibodies or siRNA restores the killing ability of natural killer cells against these tumor cells [196–200], suggesting that blocking the CLEC2D binding to CD161 may be important in tumor therapy. The functional homolog of the CLEC2D in mice and rats has not been specified yet [193]. Therefore it is difficult to evaluate the influence of CLEC2D and CD161 interaction on tumor treatment with β-glucan in vivo. Nevertheless, disruption of CLEC2D and CD161 interaction may strengthen the antitumor effects of β-glucan.

9. Ficolin-2

Ficolin-2 (also known as L-ficolin), a molecule crucial for activating the complement system via the lectin pathway, has been reported to function as a pattern recognition receptor recognizing β-glucan [201]. Since a similar mechanism to the lectin pathway exists in the invertebrate sea squirt (*Ciona intestinalis*), the lectin pathway of the complement system is considered to be an important immune mechanism in innate immunity that has been conserved throughout evolution [202]. Therefore, it would be natural that a molecule for the recognition of β-glucan, a major component of the fungal cell wall, exists in the lectin pathway as a host defense mechanism against fungal infections.

Ficolin-2 is highly expressed in the liver [203], and ficolin-2 synthesized in the liver is assumed to be secreted as a soluble molecule and circulates throughout the body via the bloodstream. It has been reported that ficolin-2 and ficolin-3 (also known as H-ficolin) are involved in the recognition of apoptotic cells and the activation of the complement cascade, and are important for maintaining homeostasis of the body through the removal of apoptotic cells [204]. Ficolin-2 recognizes apoptotic cells by binding to DNA in a calcium-dependent manner. Thus ficolin-2 can recognize late apoptotic cells, apoptotic bodies, and necrotic cells, but not early apoptotic cells [205]. In addition, it has been reported that ficolin-2 binds to the envelope proteins E1 and E2 of the hepatitis C virus [206] and gp120 of the human immunodeficiency virus [207], and inhibits the entry of these viruses into cells.

It has been reported that the expression of the ficolin-2 gene is downregulated in liver cancer compared to normal tissues [208] and the level of ficolin-2 in liver tissue and serum is accordingly decreased [209]. In addition, it has been reported that the median level of ficolin-2 in the serum of multiple myeloma patients is reduced [210]. These findings suggest that ficolin-2 may have an antitumor effect. Although little is known about the function of ficolin-2 in antitumor immunity, it has been shown that forced expression of human ficolin-2 gene or mouse ficolin-A gene encoding human ficolin-2-like molecule in mice by intramuscular electroporation significantly inhibits the proliferation of transplanted CT26 cells, a colon tumor cell line [211]. It has been suggested that this antitumor effect may be involved in ficolin-2 recognizing and binding to N-acetylglucosamine expressed on the surface of tumor cells. Thus, it is not likely that β-glucan binding to ficolin-2 can contribute a positive effect on this antitumor effect of ficolin-2. Ficolin-2 binding to tumor cells through the recognition of N-acetylglucosamine increases the opsonization of tumor cells with complement component C3b through the activation of the lectin-pathway, and subsequently opsonized C3b degrades into iC3b. Therefore, β-glucan may indirectly support this antitumor effect of ficolin-2 via CR3 (see CR3 section of this review). In addition, the expression of ficolin-2 is increased by viral infections [207,209] and fungal infections [212]. Thus, it is possible that β-glucan can induce the expression of ficolin-2. It is expected that the effect of β-glucan on the function and the expression of ficolin-2 will be elucidated in the future.

10. TLRs (toll-like receptors)

TLR4 (toll-like receptor 4) is a receptor that recognizes LPS (lipopolysaccharide), a type of glycolipid present in the cell walls of gram-negative bacteria such as Escherichia coli [213–216]. LPS, also known as endotoxin, is a potent mediator of inflammation, and TLR4 is widely recognized as a receptor that plays a pivotal role in the inflammatory response induced by LPS. Interestingly, it has been suggested that TLR4 may act as a receptor recognizing β-glucan [217–219]. However, there is no evidence for the direct bind of β-glucan to TLR4. Thereby, TLR4 has not yet been broadly accepted as a pattern recognition receptor for the recognition of β-glucan.

On the other hand, there are β-glucan recognizing receptors that have been reported to interact with TLR4. For instance, it has been reported that SCARF1 (see scavenger receptors section in this review) is co-immunoprecipitated with TLR4 after stimulation with LPS. The SCARF1 binding to TLR4 enhances the signaling pathway mediated by TLR4 [220]. In addition, it has been shown that CD36 is co-immunoprecipitated with the heterodimer of TLR4 and TLR6 after stimulation with CD36 ligands, oxidized LDL, and β-amyloid. The CD36-TLR4-TLR6 complex formation is involved in activating inflammatory signaling [221]. Furthermore, it has been reported that ficolin-2 can be associated with TLR4 [211]. The ficolin-2 binding to TLR4 activates tumor immunity by activating macrophages and CD8+ T cells, although this function of ficolin-2 appears to be ligand-independent. It is

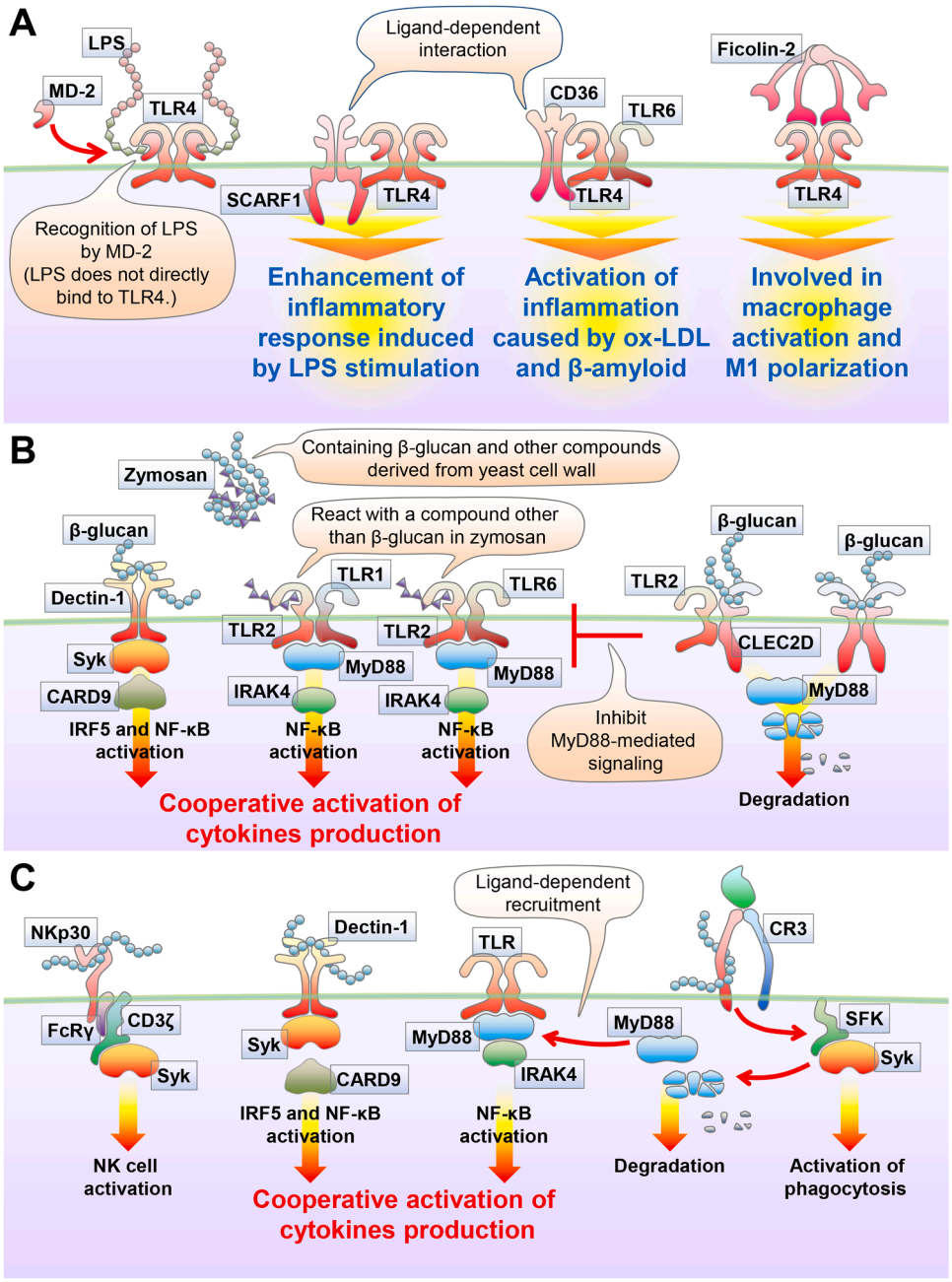

Fig. 5. β-glucan receptors modulate TLR-mediated signaling pathways.
(A) Interaction of β-glucan receptors and TLR4. (B) Role of β-glucan receptors- and TLR2-mediated signaling pathways on zymosan recognition. (C) Involvement of syk on the signaling pathways mediated by β-glucan receptors and TLRs. CARD9: caspase recruitment domain family member 9, IRAK4: interleukin 1 receptor-associated kinase-4, MD-2: myeloid differentiation factor 2, SFK: Src family kinase.

unclear how these β-glucan receptors affect TLR4 functions in the presence of β-glucan. Nevertheless, β-glucan may play a role in regulating the signaling pathway mediated by TLR4.

Including TLR4, 10 receptors in humans and 12 receptors in mice have been identified as members of the TLR family. These TLR family receptors recognize a specific pattern of molecules derived from viruses, bacteria, mycobacteria, fungi, and parasites, and play an important role in activating innate immunity and inducing adaptive immunity [222, 223]. Since many β-glucan receptors are involved in activating innate immunity similar to TLRs, it is thought to be natural that β-glucan receptors directly or indirectly affect the signaling pathway mediated by TLRs. Actually, in addition to the previously mentioned SCARF1, CD36, and ficolin-2, some β-glucan receptors have been suggested to be functional in regulating the TLR-mediated signaling pathway.

Zymosan, polysaccharides derived from S. cerevisiae containing β-glucan as a major compound, is not always known to activate a β-glucan receptor dectin-1 mediated signaling, but also the TLR2 mediated signaling pathway. It has been reported that the activation of the TLR2-mediated signaling pathway is required for inducing TNF-α production in macrophages after stimulation with zymosan [224–226]. Because highly purified β-glucan from zymosan is not able to activate TLR2 mediated signaling pathway, a component other than β-glucan contained in zymosan is believed to be involved in the activation of TLR2-mediated signaling after stimulation with zymosan [227]. This suggests that the dectin-1-mediated signaling pathway cooperates with the TLR2-mediated signaling pathway to produce cytokines such as

TNF-α and activate the immune system. Dimerization is required for the activation of the TLR2-mediated signal transduction pathway, and it has been reported that forming a homodimer of TLR2 is not sufficient to transduce the activation signal for the production of TNF-α in macrophages, and this activation is required to form a heterodimer with TLR1 or TLR6 [228]. Thus, in addition to TLR2, also TLR1 or TLR6 is thought to be indirectly involved in the induction of TNF-α after stimulation with zymosan. On the other hand, as mentioned in the CLEL2D section, it has been shown that a β-glucan receptor, CLEC2D can form a heterodimer with TLR2 and is involved in the degradation of MyD88, which is known to be an adaptor molecule downstream of TLR mediated signaling, via the ubiquitin-proteasome pathway [190]. Therefore, it should be noted that TLR2 is difficult to consider to be completely not involved in β-glucan stimulated signaling.

Syk (spleen tyrosine kinase) is involved in the cooperation between dectin-1 and TLR2 signaling pathways [227]. Dectin-1 contains an ITAM (immunoreceptor tyrosine-based activation motif)-like motif in its intracellular domain. Syk is recruited to the ITAM-like motif of dectin-1 after phosphorylation of the juxtamembrane tyrosine in the ITAM-like motif and acts to activate downstream signaling pathways mediated by dectin-1 [229]. In addition to the TLR2-mediated signaling pathway, dectin-1-induced activation of Syk also affects signaling pathways mediated by TLR4, TLR5, TLR7, and TLR9. The activation of Syk mediated by dectin-1 signaling induces cytokines such as TNF-α cooperatively with these TLRs [226,227].

Syk is also activated downstream of another major β-glucan receptor CR3, and is involved in enhancing phagocytosis of iC3b opsonized tumor cells by neutrophils via β-glucan [230]. In addition, although its response to β-glucan is unknown, NKp30 is also involved in the activation of Syk. NKp30 binds to CD3ζ homodimers or CD3ζ/FcRγ heterodimers that contain ITAM domains in a ligand-dependent manner, subsequently recruiting and activating Syk. This NKp30-mediated Syk activation in natural killer cells activates NF-κB and cell-killing activity [231,232]. Furthermore, Syk activation has been reported to be involved in the uptake of oxidized LDL and fatty acids via CD36 [233, 234], and CD5 has been shown to inhibit the activation of Syk after cross-linking of T cell receptors or B cell receptors [235].

It should be noted that Syk does not always act to transduce the signals for immune activation. CR3 is composed of a heterodimer of CD11b and CD18, and it has been reported that mice lacking CD11b, which contains the β-glucan binding domain, show increased susceptibility to LPS-induced sepsis due to enhanced TLR-mediated signaling [236]. This report also showed that activation of TLR4 causes CR3 activation, and the activation of Syk via CR3 negatively regulates TLR-mediated signaling pathways by inducing phosphorylation and proteasomal degradation of MyD88 and TRIF. A similar phenomenon has been observed with leukadherin-1 (see CR3 section in this review), a small molecule agonist that partially activates CR3 like β-glucan. It has been shown that stimulation with leukadherin-1 promotes the proteosome-mediated degradation of MyD88 and suppresses the signaling pathways mediated by TLR7 and TLR8 [237]. This suggests that the stimulation with β-glucan may also exhibit a similar effect through the partial activation of CR3 mediated signaling pathway.

These opposing effects of Syk on the TLR-mediated signaling pathway are thought to be due to differences in cells and activation forms. However, detailed molecular mechanism has not been clarified and further investigations are awaited.

11. Lactosylceramide

Lactosylceramide is known as a molecule recognizing β-glucan [238, 239]. Unlike other molecules reported as β-glucan receptors, lactosylceramide is not a gene-encoded protein, but a type of glycosphingolipid consisting of a sugar chain and ceramide. Glycosphingolipids are known to be a component of lipid rafts, and lactosylceramide is one of the many types of glycosphingolipids. Lipid rafts are thought to be structures like a "raft" that float on the cell membrane. Lipid rafts are defined as plasma membrane subdomains that are rich in glycosphingolipids and cholesterol, and containing intracellular signaling molecules anchored to the cell membrane via GPI (glycosylphosphatidylinositol)-anchored proteins and lipids [240–242]. The functional role of sphingoglycolipids in lipid rafts is to transduce the signals into cells via lipid raft domains by directly binding to ligands in trans, as well as to support the transduction of signals into cells when ligands bind to receptor proteins associated with lipid rafts.

It has been reported that lactosylceramide-rich lipid rafts on neutrophils are essential for phagocytosis of non-opsonized zymosan via CR3 [243]. In dendritic cells, dectin-1 binding to β-glucan is transported into lipid rafts [244], and the activation of dendritic cells after stimulation with β-glucan derived from the fungus Pneumocystis has been reported to require the accumulation of lactosylceramide in lipid rafts together with dectin-1 [245]. Further, lactosylceramide itself is involved in signal transduction, and the analyses using specific antibodies against lactosylceramide showed that lactosylceramide interacts with Lyn, a member of the Src family of kinases, in neutrophils and contributes to the production of superoxide [246]. It has been reported that stimulation with β-glucan can induce superoxide production in neutrophils in a lactosylceramide-dependent manner [247]. Based on these findings, lactosylceramide localized in lipid rafts is considered to play a role in supporting signal transduction via β-glucan and its receptors including CR3 and dectin-1. At the same time, lactosylceramide itself is thought to be also involved in the signal transduction to activate innate immunity through the binding to β-glucan.

Lactosylceramide is known to also act as a second messenger. It has been reported that lactosylceramide synthesis is induced after stimulation with TNF-α in HUVECs (human umbilical vein endothelial cells) and that the synthesized lactosylceramide acts to induce the expression of ICAM-1 (intercellular adhesion molecule-1) through the production of superoxide [248]. In addition, stimulation with VEGF (vascular endothelial growth factor) has been reported to induce lactosylceramide synthesis in HUVECs, and the synthesized lactosylceramide has been shown to promote angiogenesis through the induction of PECAM-1 (platelet endothelial cell adhesion molecule-1) [249]. Further, it has been revealed that lactosylceramide synthesis is also enhanced in astrocytes after stimulation with TNF-α and that the synthesized lactosylceramide promotes the proliferation of astrocytes through the induction of GFAP (glial fibrillary acidic protein) [250]. The important point here is that these phenomena are not only caused by intracellularly synthesized lactosylceramide but also by extracellular stimulation of lactosylceramide. Lactosylceramide is also present in serum, and serum lactosylceramide levels have been reported to increase in patients with pediatric inflammatory bowel disease [251], West Nile virus infection [252], and adenovirus infection [253]. In addition, it is interesting to note that a correlation has been found between serum lactosylceramide levels and baPWV (brachial-ankle pulse wave velocity) which is known to correlate with the progression of arteriosclerosis [254]. Considering these findings together with the effects of the stimulation with TNF-α for the induction of lactosylceramide synthesis in HUVECs and astrocytes as mentioned above [248,250], it is possible that under inflammatory conditions, lactosylceramide synthesis is promoted and consequently increases lactosylceramide levels in the serum. Further, the finding that lactosylceramide promotes angiogenesis [249] is noteworthy in light of the significance of angiogenesis in tumor tissues on tumor development. In the future, it is expected that studies will be conducted to assess the effect of β-glucan on circulated lactosylceramide in the serum.

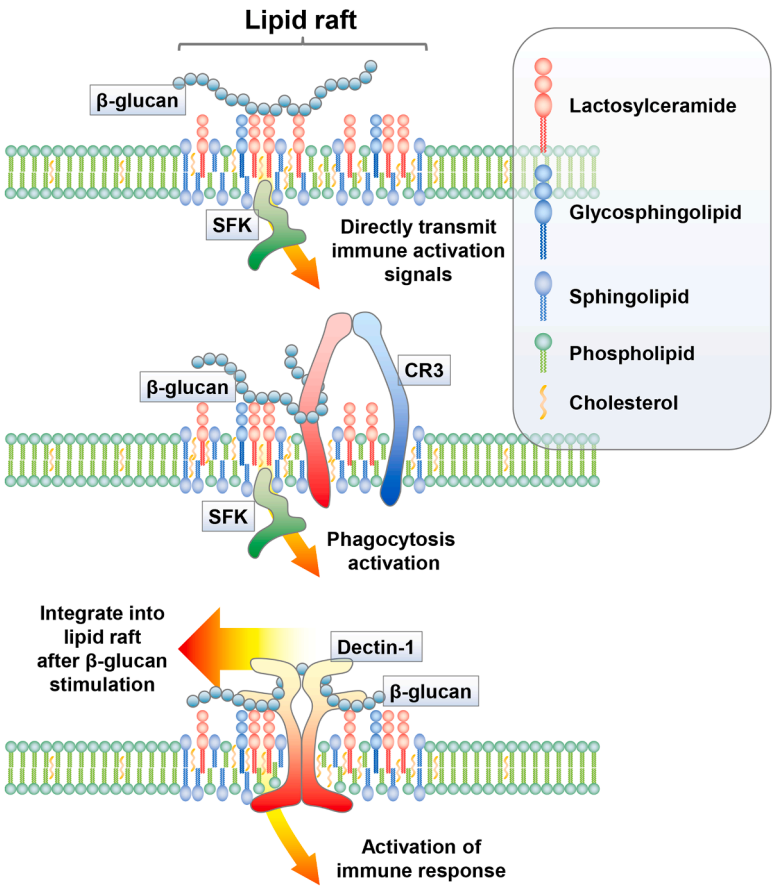

Fig. 6. Functions of lactosylceramide on immune response to β-glucan.
SFK: Src family kinase.

12. Future issues and conclusion

As described in previous sections, the progress of research on antifungal immunity has revealed that many molecules act as receptors for recognizing β-glucan. This may indicate the significance of host defense against fungal infections exposing β-glucan as a component of the cell walls and the requirement of multiple backup mechanisms to maintain antifungal immunity. On the other hand, in the pharmaceuticals and food science fields, few studies are focused on β-glucan receptors other than CR3 and dectin-1. In particular, regarding the anti-cancer effects of

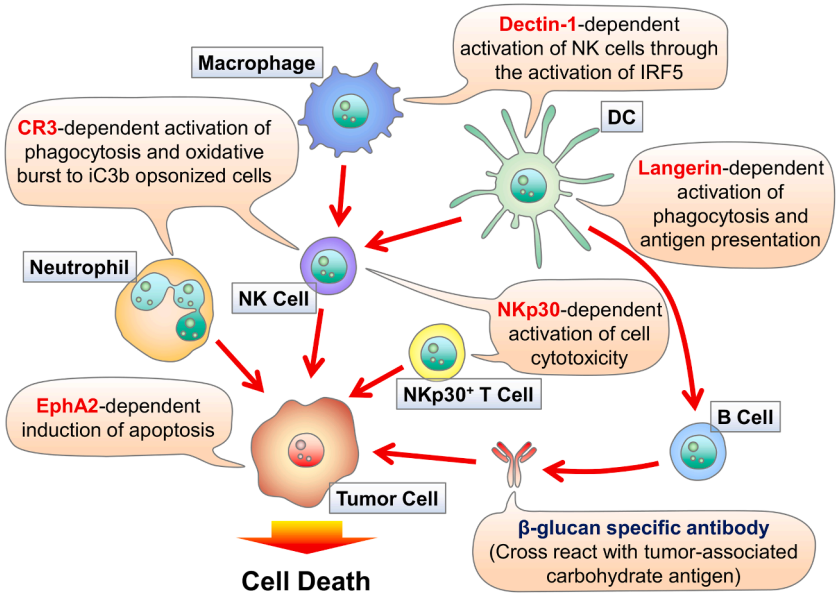

Fig. 7. The functions of β-glucan on tumor immunity through β-glucan receptors.
DC: dendritic cell; NK cell: natural killer cell

β-glucan, although many of the β-glucan receptors discussed in this review are involved in the development and progression of cancer, these receptors do not receive enough attention. This review focused on the receptors confirmed to recognize and bind to β-glucan. Although it is unclear whether they bind to β-glucan, other than the receptors mentioned in this review, there are receptors able to recognize fungi expressing β-glucan as a component of the cell wall. For example, SR-AI/AII (Scavenger Receptor A Type I/II, also known as MSR-A [type A macrophage scavenger receptor] or CD204) in macrophages is involved in the binding and phagocytosis of *S. cerevisiae* and *C. albicans* [255]; CL-11 (collectin-11, also known as CL-K1 [CDC Like Kinase 1]) has been reported to be able to bind to zymosan, *C. albicans*, and *Aspergillus humigatus* [256,257]; CL-P1 (collectin placenta 1, also known as SCARA4 [class A scavenger receptor 4], SRCL [scavenger receptor with C-type lectin] or COLEC12 [collectin subfamily member 12]) is involved in the phagocytosis of zymosan by vascular endothelial cells [258]. Further, it would also be noteworthy that the release of IL-1β after β-glucan stimulation in macrophages requires phagocytosis of β-glucan, i.e., recognition of β-glucan in the cytoplasm, and that the NLRP3 (NOD [nucleotide-binding oligomerization domain]-like receptor pyrin domain-containing protein 1]) inflammasome has been reported to be involved in this process [259]. Therefore, the number of β-glucan recognizing molecules may increase in the future.

When considering methods to enhance the antitumor effects of β-glucan, it would be significant to note that there are receptors among the β-glucan receptors, such as CD5 and CLEC2D (see CD5 and CLEC2D sections of this review), that can transmit immune suppressive signals. These receptors are thought to play an important role in suppressing excessive immune responses to maintain the body's homeostasis. However, at the same time, these receptors may weaken the anti-cancer effects of β-glucan. Particularly, on CLEC2D which negatively regulates the cytotoxic signals of natural killer cells and cytotoxic T cells via CD161, the antitumor effects of β-glucan may be able to enhance by blocking the interaction of CLEC2D to CD161 and β-glucan.

Among the molecules known as β-glucan receptors, there are receptors such as dectin-1 [260], SCARF-1 [261], and CD36 [262] that circulate in the body as soluble receptors. These soluble forms of β-glucan receptors are generally inactive and act to inhibit β-glucan binding to the receptors present on the cell surface. Lactosylceramide present in serum is the same. Attenuating the influences of these soluble β-glucan receptors would be an important factor in enhancing the effects of β-glucan, including the antitumor effects.

It is also interesting to note that some β-glucan receptors, such as dectin-1 [72], Langerin [94], and ficolin-2 [211], recognize tumor-associated glycans. It would be crucial for the molecular mechanism to exert the antitumor effect of β-glucan that β-glucan is recognized by receptors that recognize tumor-associated glycans, resulting in the activation of the antitumor immunity. On the other hand, in experiments using tumor-derived cell lines, it is necessary to be aware of the possibility that the function of these β-glucan receptors is masked depending on the glycan structure expressed on the cell surface.

The molecular mechanism in exerting the effects of β-glucan on the body is considered to be extremely complex, as the effects are the result of the combined molecular functions of various β-glucan receptors. Except for the molecules widely known as β-glucan receptors such as CR3 and dectin-1, most of the molecules reported as β-glucan receptors have not been analyzed enough in terms of the three-dimensional structure-based binding form with β-glucan or their binding specificity for structurally different β-glucans. The antitumor effects of β-glucan have been shown for a long time. Nevertheless, there are still many issues that are required for further investigations to clarify the molecular mechanism to exhibit the antitumor effects of β-glucan.

CRediT authorship contribution statement

Atsushi Iwai: Writing – review & editing, Writing – original draft, Conceptualization.

Table 1
β-glucan receptors discussed in this review.

	Expression	Major function	Confirmed binding β-glucans / fungal species
CR3	Phagocytic cells, natural killer cells, and specific subsets of B and T cells [263]	Recognition of iC3b opsonized molecules, and also functional as a cell adhesion molecule	Various β-glucans / fungal species
Dectin-1	Leucocytes, barely expressed in natural killer cells [264]	Major β-glucan receptor in activating the phagocytosis of unopsonized β-glucan particles in macrophages	Various β-glucans / fungal species Do not transduce activation signals by the stimulation with soluble β-glucan (human dectin-1B and mouse dectin-1A/B) [76]
Langerin	Langerhans cells and specific subsets of dendritic cells [88,89]	Birbeck granules formation in Langerhans cells	Curdlan, laminarin and zymosan / *Malassezia furfur, Saccharomyces* and *Candida* species but not with *Cryptococcus* species [90]
NKp30	Natural killer cells, and specific subsets of T cells [121,122] Do not express intact form in mice due to nonsense mutation [104]	Activation of cell-killing activity of cytotoxic lymphocytes	β-1,3-glucan but not bind to β-1,6-glucan (bind to curdlan and *Saccharomyces cerevisiae* derived β-glucan, weakly bind to laminarin, but not bind to pustulan) / *Cryptococcus neoformans, Candida albicans* [99]
SCARF1	Endothelial cells, dendritic cells, and macrophages [130]	Phagocytosis of apoptotic cells	Laminarin and zymosan / *Cryptococcus neoformans, Candida albicans* [126]
CD36	Phagocytes (macrophages, dendritic cells, microglia, and retinal pigment epithelium), microvascular endothelium, erythroid precursors, hepatocyes, adipocytes, myocytes, and specialized epithelia of the breast, kidney, and gut [265]	The uptake of modified low-density lipoprotein in macrophages Involved in the uptake of fatty acids	Laminarin / *Cryptococcus neoformans, Candida albicans* [126]
CD5	T cells, B-1a cells, regulatory lymphocytes, and a subset of dendritic cells [158]	Negative regulator for TCR- and BCR-mediated signalings	*Euglena gracilis, Saccharomyces cerevisiae, Hordeum vulgare* L. delived β-glucans / *Schizosaccharomyces pombe, Candida albicans*, and *Cryptococcus neoformans* [157]
EphA2	Epithelial cells [176,178] and neutrophils [177]	Involved in the development together with the ligand, ephrin A1	Laminarin and zymosan / *Candida albicans, Candida glabrata* and *Saccharomyces cerevisiae* [176]
CLEC2D	Lymphocytes, macrophages, and dendritic cells [191] Highly expressed in immune-privileged sites [194] The functional homolog is not specified in mice and rats [191].	Inhibition of cell-killing activity of cytotoxic lymphocytes as a ligand of CD161	Curdlan / *Candida albicans* [190]
Ficolin-2	Circulating in the blood Mainly synthesized in the liver [203]	Involved in the activation of the complement system through the lectin pathway	Curdlan [201]

Declaration of competing interest

The authors declare the following financial or non-financial interests which may be considered as potential conflicts of interest:

This study was funded by Aureo Co., Ltd., and Aureo-Science Co., Ltd. β-glucan-containing *Aureobasidium pullulans*-cultured fluid and its derivatives are marketed by Aureo Co., Ltd. Aureo Co., Ltd., and Aureo-Science Co., Ltd. hold patents for applications and process of β-glucan-containing *Aureobasidium pullulans*-cultured fluid. I am an employee of Aureo-Science Co., Ltd., and Aureo Co., Ltd. However, the funders did not have any role in the decision to publish or prepare the manuscript. There are no other patents, products in development, or marketed products to declare.

Data availability

No data was used for the research described in the article.

References

[1] R. Garcia-Rubio, H.C. de Oliveira, J. Rivera, N. Trevijano-Contador, Front. Microbiol 10 (2020) 1–13, https://doi.org/10.3389/fmicb.2019.02993.
[2] A.M.M. Basso, R.J.A. De Castro, T.B. De Castro, H.I. Guimarães, V.L.P. Polez, E. R. Carbonero, V.H. Pomin, C. Hoffmann, M.F. Grossi-De-Sa, A.H. Tavares, A. L. Bocca, Med. Mycol. 58 (2020) 227–239, https://doi.org/10.1093/mmy/myz042.
[3] C.H. Yun, A. Estrada, A. Van Kessel, B.C. Park, B. Laarveld, FEMS Immunol. Med. Microbiol. 35 (2003) 67–75, https://doi.org/10.1016/S0928-8244(02)00460-1.
[4] E.A. Murphy, J.M. Davis, A.S. Brown, M.D. Carmichael, J.A. Carson, N. Van Rooijen, A. Ghaffar, E.P. Mayer, Am. J. Physiol. - Regul. Integr. Comp. Physiol. 294 (2008) 1593–1599, https://doi.org/10.1152/ajpregu.00562.2007.
[5] D. Muramatsu, A. Iwai, S. Aoki, H. Uchiyama, K. Kawata, Y. Nakayama, Y. Nikawa, K. Kusano, M. Okabe, T. Miyazaki, PLoS One 7 (2012), https://doi.org/10.1371/journal.pone.0041399.
[6] X. Yu, D. Zhang, B. Shi, G. Ren, X. Peng, Z. Fang, M. Kozlowski, X. Zhou, X. Zhang, M. Wu, C. Wang, Z. Yuan, PLoS One 10 (2015) 1–12, https://doi.org/10.1371/journal.pone.0123559.
[7] L. Song, J. Yuan, S. Ni, Y. Zhou, X. Wang, Y. Chen, S. Zhang, Mol. Immunol. 117 (2020) 160–167, https://doi.org/10.1016/j.molimm.2019.10.019.
[8] K. Zhong, Z. Liu, Y. Lu, X. Xu, Eur. J. Nutr. 60 (2021) 4175–4187, https://doi.org/10.1007/s00394-021-02566-4.
[9] M. Jesenak, J. Majtan, Z. Rennerova, J. Kyselovic, P. Banovcin, M. Hrubisko, Int. Immunopharmacol. 15 (2013) 395–399, https://doi.org/10.1016/j.intimp.2012.11.020.
[10] Y. Nishitani, L. Zhang, M. Yoshida, T. Azuma, K. Kanazawa, T. Hashimoto, M. Mizuno, PLoS One 8 (2013), https://doi.org/10.1371/journal.pone.0062441.
[11] Z. Wang, K. Ma, M. Fujino, K. Kusano, S.Q. Yi, A. Iwai, X.K. Li, Heliyon 7 (2021) e07277, https://doi.org/10.1016/j.heliyon.2021.e07277.
[12] S.X. Wang, Q.Y. Liu, Y. Li, Burns 42 (2016) 1513–1521, https://doi.org/10.1016/j.burns.2016.04.003.
[13] D.T. Førland, E. Johnson, L. Sætre, T. Lyberg, I. Lygren, G. Hetland, Scand. J. Immunol. 73 (2011) 66–75, https://doi.org/10.1111/j.1365-3083.2010.02477.x.
[14] S.M. Talbott, J.A. Talbott, T.L. Talbott, E. Dingler, Food Sci. Nutr. 1 (2013) 90–101, https://doi.org/10.1002/fsn3.11.
[15] J.S. Choi, H. Kim, M.H. Jung, S. Hong, J. Song, Mol. Nutr. Food Res. 54 (2010) 1004–1013, https://doi.org/10.1002/mnfr.200900127.
[16] S. Aoki, A. Iwai, K. Kawata, D. Muramatsu, H. Uchiyama, M. Okabe, M. Ikesue, N. Maeda, T. Uede, Sci. Rep. 5 (2015), https://doi.org/10.1038/srep10457.
[17] S. Aoki, A. Iwai, K. Kawata, D. Muramatsu, H. Uchiyama, M. Okabe, M. Ikesue, N. Maeda, T. Uede, J. Funct. Foods. 18 (2015) 22–27, https://doi.org/10.1016/j.jff.2015.06.044.
[18] Y. Cao, S. Zou, H. Xu, M. Li, Z. Tong, M. Xu, X. Xu, Mol. Nutr. Food Res. 60 (2016) 2678–2690, https://doi.org/10.1002/mnfr.201600032.
[19] E.F. Andrade, A.R.V. Lima, I.E. Nunes, D.R. Orlando, P.N. Gondim, M. G. Zangeronimo, F.H.F. Alves, L.J. Pereira, Nutrients 8 (2016), https://doi.org/10.3390/nu8120792.
[20] S.S. Abumweis, S. Jew, N.P. Ames, Eur. J. Clin. Nutr. 64 (2010) 1472–1480, https://doi.org/10.1038/ejcn.2010.178.
[21] H.V.T. Ho, J.L. Sievenpiper, A. Zurbau, S. Blanco Mejia, E. Jovanovski, F. Au-Yeung, A.L. Jenkins, V. Vuksan, Br. J. Nutr. 116 (2016) 1369–1382, https://doi.org/10.1017/S000711451600341X.
[22] K. Hou, Z.X. Wu, X.Y. Chen, J.Q. Wang, D. Zhang, C. Xiao, D. Zhu, J.B. Koya, L. Wei, J. Li, Z.S. Chen, Target. Ther 7 (2022), https://doi.org/10.1038/s41392-022-00974-4.
[23] H. Uchiyama, A. Iwai, Y. Asada, D. Muramatsu, S. Aoki, K. Kawata, K. Kusano, K. Nagashima, D. Yasokawa, M. Okabe, T. Miyazaki, BMC Res. Notes. 5 (2012), https://doi.org/10.1186/1756-0500-5-189.
[24] Y. Wu, X. Li, H. Liu, Y. Du, J. Zhou, L. Zou, X. Xiong, H. Huang, Z. Tan, Y. Yin, Anim. Nutr. 7 (2021) 1345–1351, https://doi.org/10.1016/j.aninu.2021.04.006.
[25] W. Zhen, Y. Liu, Y. Shao, Y. Ma, Y. Wu, F. Guo, W. Abbas, Y. Guo, Z. Wang, Front. Microbiol. 12 (2021), https://doi.org/10.3389/fmicb.2021.766878.
[26] X. Mo, Y. Sun, X. Liang, L. Li, S. Hu, Z. Xu, S. Liu, Y. Zhang, X. Li, L. Liu, Carbohydr. Polym. 281 (2022) 119046, https://doi.org/10.1016/j.carbpol.2021.119046.
[27] M. Xu, X. Mo, H. Huang, X. Chen, H. Liu, Z. Peng, L. Chen, S. Rong, W. Yang, S. Xu, L. Liu, Int. J. Biol. Macromol. 161 (2020) 258–270, https://doi.org/10.1016/j.ijbiomac.2020.05.180.
[28] Q. Zhang, W. Zhao, Y. Hou, X. Song, H. Yu, J. Tan, Y. Zhou, H.T. Zhang, CNS Neurosci. Ther. 29 (2023) 1690–1704, https://doi.org/10.1111/cns.14132.
[29] Y. Wang, N.P. Ames, H.M. Tun, S.M. Tosh, P.J. Jones, E. Khafipour, Front. Microbiol. 7 (2016) 1–15, https://doi.org/10.3389/fmicb.2016.00129.
[30] K. Raghavan, V.D. Dedeepiya, N. Yamamoto, N. Ikewaki, T. Sonoda, M. Iwasaki, R.S. Kandaswamy, R. Senthilkumar, S. Preethy, S.J.K. Abraham, J. Alzheimer's Dis. 94 (2023) S241–S252, https://doi.org/10.3233/JAD-220388.
[31] Z.T. Mankowski, I.C. Diller, M.E. Fisher, Cancer Res 17 (1957) 382–386.
[32] W.T. Bradner, D.A. Clarke, C.C. Stock, Cancer Res 18 (1958) 347–351.
[33] W.Z. Bradner, D.A. Clarke, Cancer Res 19 (1959) 673–678.
[34] K. Ina, T. Kataoka, T. Ando, Anticancer. Agents Med. Chem. 13 (2013) 681–688, https://doi.org/10.2174/18715206113130500002.
[35] Y. Zhang, M. Zhang, Y. Jiang, X. Li, Y. He, P. Zeng, Z. Guo, Y. Chang, H. Luo, Y. Liu, C. Hao, H. Wang, G. Zhang, L. Zhang, J. Cancer Res. Clin. Oncol. 144 (2018) 2177–2186, https://doi.org/10.1007/s00432-018-2718-1.
[36] S. Chaichian, B. Moazzami, F. Sadoughi, H.Haddad Kashani, M. Zaroudi, Z. Asemi, J. Ovarian Res. 13 (2020) 1–12, https://doi.org/10.1186/s13048-020-00626-7.
[37] Y. Maehara, S. Tsujitani, H. Saeki, E. Oki, K. Yoshinaga, Y. Emi, M. Morita, S. Kohnoe, Y. Kakeji, T. Yano, H. Baba, Surg. Today. 42 (2012) 8–28, https://doi.org/10.1007/s00595-011-0075-7.
[38] H. Fritz, D.A. Kennedy, M. Ishii, D. Fergusson, R. Fernandes, K. Cooley, D. Seely, Integr. Cancer Ther. 14 (2015) 201–211, https://doi.org/10.1177/1534735415572883.
[39] M. Wang, Y. Bai, J. Pei, D. Li, X. Pu, W. Zhu, L. Xia, C. Qi, H. Jiang, Y. Ning, Front. Pharmacol. 13 (2022) 1–10, https://doi.org/10.3389/fphar.2022.887457.
[40] A.S.H. Chan, T.O. Kangas, X. Qiu, M.T. Uhlik, R.B. Fulton, N.R. Ottoson, K. B. Gorden, Y. Yokoyama, M.E. Danielson, T.M. Jevne, K.S. Michel, J.R. Graff, N. Bose, Front. Oncol 12 (2022) 1–19, https://doi.org/10.3389/fonc.2022.869078.
[41] X. Hu, Y. Shui, H. Hirano, K. Kusano, W.Z. Guo, M. Fujino, X.K. Li, Cancer Immunol. Immunother. 72 (2023) 719–731, https://doi.org/10.1007/s00262-022-03276-4.
[42] J.K. Czop, K.F. Austen, J Immunol 134 (1985) 2588–2593.
[43] T. Ueda, P. Rieu, J. Brayer, M.A. Arnaout, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 10680–10684, https://doi.org/10.1073/pnas.91.22.10680.
[44] B.P. Thornton, V. Větvicka, M. Pitman, R.C. Goldman, G.D. Ross, J. Immunol. 156 (1996) 1235–1246, https://doi.org/10.4049/jimmunol.156.3.1235.
[45] Y. Xia, G.D. Ross, J. Immunol. 162 (2009) 7285–7293.
[46] L.C. Smith, K. Azumi, M. Nonaka, Immunopharmacology 42 (1999) 107–120, https://doi.org/10.1016/S0162-3109(99)00009-0.
[47] M. Nonaka, Curr. Opin. Immunol. 13 (2001) 69–73, https://doi.org/10.1016/S0952-7915(00)00184-9.
[48] N.S. Merle, S.E. Church, V. Fremeaux-Bacchi, L.T. Roumenina, Front. Immunol. 6 (2015) 1–30, https://doi.org/10.3389/fimmu.2015.00262.
[49] C.Q. Schmidt, J.D. Lambris, D. Ricklin, Immunol. Rev. 274 (2016) 152–171, https://doi.org/10.1111/imr.12475.
[50] V. Afshar-Kharghan, J. Clin. Invest. 127 (2017) 780–789, https://doi.org/10.1172/JCI90962.
[51] T. Masaki, M. Matsumoto, I. Nakanishi, R. Yasuda, T. Seya, J. Biochem. 111 (1992) 573–578, https://doi.org/10.1093/oxfordjournals.jbchem.a123799.
[52] M.K. Liszewski, T.W. Post, J.P. Atkinson, Annu. Rev. Immunol. 9 (1991) 431–455, https://doi.org/10.1146/annurev.iy.09.040191.002243.
[53] M. Elvington, M.K. Liszewski, J.P. Atkinson, Antibodies 9 (2020) 1–14, https://doi.org/10.3390/antib9040059.
[54] A. Geller, J. Yan, Front. Immunol. 10 (2019) 1–13, https://doi.org/10.3389/fimmu.2019.01074.
[55] J.A. Cain, S.L. Newman, G.D. Ross, Complement 4 (1987) 75–86, https://doi.org/10.1159/000463011.
[56] V. Větvička, B.P. Thornton, G.D. Ross, J. Clin. Invest. 98 (1996) 50–61, https://doi.org/10.1172/JCI118777.
[57] V. Vetvicka, B.P. Thornton, T.J. Wieman, G.D. Ross, J. Immunol. 159 (1997) 599–605, https://doi.org/10.4049/jimmunol.159.2.599.
[58] Y. Xia, V. Větvička, J. Yan, M. Hanikýřová, T. Mayadas, G.D. Ross, J. Immunol. 162 (1999) 2281–2290, https://doi.org/10.4049/jimmunol.162.4.2281.
[59] G.S.T. Pfrommer, S.M. Dickens, M.A. Wilson, B.J. Young, T.R. Kozel, Infect. Immun. 61 (1993) 4360–4366, https://doi.org/10.1128/iai.61.10.4360-4366.1993.
[60] T. Meri, A. Hartmann, D. Lenk, R. Eck, R. Würzner, J. Hellwage, S. Meri, P. F. Zipfell, Infect. Immun. 70 (2002) 5185–5192, https://doi.org/10.1128/IAI.70.9.5185-5192.2002.
[61] F. Hong, R.D. Hansen, J. Yan, D.J. Allendorf, J.T. Baran, G.R. Ostroff, G.D. Ross, Cancer Res 63 (2003) 9023–9031.
[62] Y. Liao, R. Wang, X. Qin, X. Ma, X. Liu, S. Jia, C. Zhong, Int. J. Biol. Macromol. 220 (2022) 1356–1367, https://doi.org/10.1016/j.ijbiomac.2022.09.106.
[63] D. Maiguel, M.H. Faridi, C. Wei, Y. Kuwano, K.M. Balla, D. Hernandez, C.J. Barth, G. Lugo, M. Donnelly, A. Nayer, L.F. Moita, S. Schürer, D. Traver, P. Ruiz, R.

I. Vazquez-Padron, K. Ley, J. Reiser, V. Gupta, Sci. Signal. 4 (2011) 1–14, https://doi.org/10.1126/scisignal.2001811.
[64] Y. Xia, G. Borland, J. Huang, I.F. Mizukami, H.R. Petty, R.F. Todd, G.D. Ross, J. Immunol. 169 (2002) 6417–6426, https://doi.org/10.4049/jimmunol.169.11.6417.
[65] X.M. O'Brien, K.E. Heflin, L.M. Lavigne, K. Yu, M. Kim, A.R. Salomon, J. S. Reichner, J. Biol. Chem. 287 (2012) 3337–3348, https://doi.org/10.1074/jbc.M111.298307.
[66] R.Z. Panni, J.M. Herndon, C. Zuo, S. Hegde, G.D. Hogg, B.L. Knolhoff, M. A. Breden, X. Li, V.E. Krisnawan, S.Q. Khan, J.K. Schwarz, B.E. Rogers, R. C. Fields, W.G. Hawkins, V. Gupta, D.G. DeNardo, Sci. Transl. Med. 11 (2019), https://doi.org/10.1126/scitranslmed.aau9240.
[67] M. Wang, Y. Bai, J. Pei, D. Li, X. Pu, W. Zhu, L. Xia, C. Qi, H. Jiang, Y. Ning, Front. Pharmacol. 13 (2022) 1–10, https://doi.org/10.3389/fphar.2022.887457.
[68] G.D. Brown, S. Gordon, Nature 413 (2001) 36–37, https://doi.org/10.1038/35092620.
[69] K. Ariizumi, G.L. Shen, S. Shikano, S. Xu, R. Ritter, T. Kumamoto, D. Edelbaum, A. Morita, P.R. Bergstresser, A. Takashima, J. Biol. Chem. 275 (2000) 20157–20167, https://doi.org/10.1074/jbc.M909512199.
[70] G.D. Brown, P.R. Taylor, D.M. Reid, J.A. Willment, D.L. Williams, L. Martinez-Pomares, S.Y.C. Wong, S. Gordon, J. Exp. Med. 196 (2002) 407–412, https://doi.org/10.1084/jem.20020470.
[71] J.A. Willment, S. Gordon, G.D. Brown, J. Biol. Chem. 276 (2001) 43818–43823, https://doi.org/10.1074/jbc.M107715200.
[72] S. Chiba, H. Ikushima, H. Ueki, H. Yanai, Y. Kimura, S. Hangai, J. Nishio, H. Negishi, T. Tamura, S. Saijo, Y. Iwakura, T. Taniguchi, Elife 3 (2014) 1–20, https://doi.org/10.7554/eLife.04177.
[73] B.N. Gantner, R.M. Simmons, S.J. Canavera, S. Akira, D.M. Underhill, J. Exp. Med. 197 (2003) 1107–1117, https://doi.org/10.1084/jem.20021787.
[74] H.S. Goodridge, C.N. Reyes, C.A. Becker, T.R. Katsumoto, J. Ma, A.J. Wolf, N. Bose, A.S.H. Chan, A.S. Magee, M.E. Danielson, A. Weiss, J.P. Vasilakos, D. M. Underhill, Nature 472 (2011) 471–475, https://doi.org/10.1038/nature10071.
[75] Y. Kato, Y. Adachi, N. Ohno, Biol. Pharm. Bull. 29 (2006) 1580–1586, https://doi.org/10.1248/bpb.29.1580.
[76] InvivoGen, https://www.invivogen.com/review-clr-ligands/, 2013 (accessed 1 Octorber 2023).
[77] J.A. Willment, A.S. Marshall, D.M. Reid, D.L. Williams, S.Y.C. Wong, S. Gordon, G.D. Brown, Eur. J. Immunol. 35 (2005) 1539–1547, https://doi.org/10.1002/eji.200425725.
[78] D. Daley, V.R. Mani, N. Mohan, N. Akkad, A. Ochi, D.W. Heindel, K.B. Lee, C. P. Zambirinis, G.S.D.B. Pandian, S. Savadkar, A. Torres-Hernandez, S. Nayak, D. Wang, M. Hundeyin, B. Diskin, B. Aykut, G. Werba, R.M. Barilla, R. Rodriguez, S. Chang, L. Gardner, L.K. Mahal, B. Ueberheide, G. Miller, Nat. Med. 23 (2017) 556–567, https://doi.org/10.1038/nm.4314.
[79] X. Liu, K. Lv, J. Wang, C. Lin, H. Liu, H. Zhang, H. Li, Y. Gu, R. Li, H. He, J. Xu, Br. J. Cancer. 129 (2023) 721–732, https://doi.org/10.1038/s41416-023-02336-5.
[80] N.N. Liu, C.X. Yi, L.Q. Wei, J.A. Zhou, T. Jiang, C.C. Hu, L. Wang, Y.Y. Wang, Y. Zou, Y.K. Zhao, L. Le Zhang, Y.T. Nie, Y.J. Zhu, X.Y. Yi, L.B. Zeng, J.Q. Li, X. T. Huang, H. Bin Ji, Z. Kozlakidis, L. Zhong, C. Heeschen, X.Q. Zheng, C. Chen, P. Zhang, H. Wang, Cancer Cell 41 (2023) 1927–1944, https://doi.org/10.1016/j.ccell.2023.08.012. .e9.
[81] C. Tang, H. Sun, M. Kadoki, W. Han, X. Ye, Y. Makusheva, J. Deng, B. Feng, D. Qiu, Y. Tan, X. Wang, Z. Guo, C. Huang, S. Peng, M. Chen, Y. Adachi, N. Ohno, S. Trombetta, Y. Iwakura, Nat. Commun. 14 (2023), https://doi.org/10.1038/s41467-023-37229-x.
[82] Y. Xie, F. Shao, X. Duan, J. Ding, Y. Ning, X. Sun, L. Xia, J. Pan, J. Chen, S. He, D. Shen, C. Qi, Front. Pharmacol. 14 (2023) 1–13, https://doi.org/10.3389/fphar.2023.1017475.
[83] M. Hofer, M. Pospíšil, Molecules 16 (2011) 7969–7979, https://doi.org/10.3390/molecules16097969.
[84] Y. Ikeda, Y. Adachi, T. Ishii, H. Tamura, J. Aketagawa, S. Tanaka, N. Ohno, Biol. Pharm. Bull. 30 (2007) 1384–1389, https://doi.org/10.1248/bpb.30.1384.
[85] J. Valladeau, O. Ravel, C. Dezutter-Dambuyant, K. Moore, M. Kleijmeer, Y. Liu, V. Rie Duvert-Frances, C. Vincent, D. Schmitt, J. Davoust, C. Caux, S. Lebecque, S. Saeland, Immunity 12 (2000) 71–81, https://doi.org/10.1016/s1074-7613(00)80160-0.
[86] R. Mc Dermott, U. Ziylan, D. Spehner, H. Bausinger, D. Lipsker, M. Mommaas, J. P. Cazenave, G. Raposo, B. Goud, H. De la Salle, J. Salamero, D. Hanau, Mol. Biol. Cell. 13 (2002) 317–335, https://doi.org/10.1091/mbc.01-06-0300.
[87] A. Kissenpfennig, S. Aït-Yahia, V. Clair-Moninot, H. Stössel, E. Badell, Y. Bordat, J.L. Pooley, T. Lang, E. Prina, I. Coste, O. Gresser, T. Renno, N. Winter, G. Milon, K. Shortman, N. Romani, S. Lebecque, B. Malissen, S. Saeland, P. Douillard, Mol. Cell. Biol. 25 (2005) 88–99, https://doi.org/10.1128/mcb.25.1.88-99.2005.
[88] M. Merad, F. Ginhoux, M. Collin, Nat. Rev. Immunol. 8 (2008) 935–947, https://doi.org/10.1038/nri2455.
[89] S.Y. Chang, M.N. Kweon, Immunol. Rev. 234 (2010) 233–246, https://doi.org/10.1111/j.0105-2896.2009.00878.x.
[90] M.A.W.P. de Jong, L.E.M. Vriend, B. Theelen, M.E. Taylor, D. Fluitsma, T. Boekhout, T.B.H. Geijtenbeek, Mol. Immunol. 47 (2010) 1216–1225, https://doi.org/10.1016/j.molimm.2009.12.016.
[91] L.C. da Silva, F.P. Fonseca, O.P. de Almeida, B.A.L. de Almeida Mariz, M.A. Lopes, R. Radhakrishnan, M. Sharma, L.P. Kowalski, P.A. Vargas, Med. Oral Patol. Oral y Cir. Bucal. 25 (2020) e49–e55, https://doi.org/10.4317/medoral.23177.
[92] M.S. Ruiz, S. Mac Keon, S. Campisano, A.I. Bravo, S. Gazzaniga, R. Wainstok, Vaccine 32 (2014) 1229–1232, https://doi.org/10.1016/j.vaccine.2014.01.025.
[93] J. Plzák, Z. Holíková, B. Dvořánková, K. Smetana, J. Betka, J. Hercogová, S. Saeland, N.V. Bovin, H.J. Gabius, Histochem. J. 34 (2002) 247–253, https://doi.org/10.1023/A:1021793530802.
[94] H. Tateno, K. Ohnishi, R. Yabe, N. Hayatsu, T. Sato, M. Takeya, H. Narimatsu, J. Hirabayashi, J. Biol. Chem. 285 (2010) 6390–6400, https://doi.org/10.1074/jbc.M109.041863.
[95] M. De Jesus, G.R. Ostroff, S.M. Levitz, T.R. Bartling, N.J. Mantis, PLoS One 9 (2014), https://doi.org/10.1371/journal.pone.0091002.
[96] M. De Jesus, A.E. Rodriguez, H. Yagita, G.R. Ostroff, N.J. Mantis, Immunol. Lett. 168 (2015) 64–72, https://doi.org/10.1016/j.imlet.2015.09.008.
[97] J. Idoyaga, C. Cheong, K. Suda, N. Suda, J.Y. Kim, H. Lee, C.G. Park, R. M. Steinman, J. Immunol. 180 (2008) 3647–3650, https://doi.org/10.4049/jimmunol.180.6.3647.
[98] H. Dong, H. Dai, X. Hu, S.D. Xiong, X.M. Gao, J. Immunol. 192 (2014) 1302–1312, https://doi.org/10.4049/jimmunol.1301495.
[99] S.S. Li, H. Ogbomo, M.K. Mansour, R.F. Xiang, L. Szabo, F. Munro, P. Mukherjee, R.A. Mariuzza, M. Amrein, J.M. Vyas, S.M. Robbins, C.H. Mody, Nat. Commun. 9 (2018), https://doi.org/10.1038/s41467-018-03014-4.
[100] D. Pende, S. Parolini, A. Pessino, S. Sivori, R. Augugliaro, L. Morelli, E. Marcenaro, L. Accame, A. Malaspina, R. Biassoni, C. Bottino, L. Moretta, A. Moretta, J. Exp. Med. 190 (1999) 1505–1516, https://doi.org/10.1084/jem.190.10.1505.
[101] J. Koch, A. Steinle, C. Watzl, O. Mandelboim, Trends Immunol 34 (2013) 182–191, https://doi.org/10.1016/j.it.2013.01.003.
[102] P.H. Kruse, J. Matta, S. Ugolini, E. Vivier, Immunol. Cell Biol. 92 (2014) 221–229, https://doi.org/10.1038/icb.2013.98.
[103] A.D. Barrow, C.J. Martin, M. Colonna, Front. Immunol. 10 (2019) 1–20, https://doi.org/10.3389/fimmu.2019.00909.
[104] M. Hollyoake, R.D. Campbell, B. Aguado, Mol. Biol. Evol. 22 (2005) 1661–1672, https://doi.org/10.1093/molbev/msi162.
[105] C.S. Brandt, M. Baratin, E.C. Yi, J. Kennedy, Z. Gao, B. Fox, B. Haldeman, C. D. Ostrander, T. Kaifu, C. Chabannon, A. Moretta, R. West, W.F. Xu, E. Vivier, S. D. Levin, J. Exp. Med. 206 (2009) 1495–1503, https://doi.org/10.1084/jem.20090681.
[106] E. Pogge von Strandmann, V.R. Simhadri, B. von Tresckow, S. Sasse, K.S. S. Reiners, H.P. Hansen, A. Rothe, B. Böll, V.L. Simhadri, P. Borchmann, P. J. McKinnon, M. Hallek, A. Engert, Immunity 27 (2007) 965–974, https://doi.org/10.1016/j.immuni.2007.10.010.
[107] W. Wang, H. Guo, J. Geng, X. Zheng, H. Wei, R. Sun, Z. Tian, J. Biol. Chem. 289 (2014) 33311–33319, https://doi.org/10.1074/jbc.M114.603464.
[108] L. Ni, C. Dong, Mol. Cancer Ther. 16 (2017) 1203–1211, https://doi.org/10.1158/1535-7163.MCT-16-0761.
[109] B. Amir Taghavi, N. Alizadeh, H. Saeedi, N. Karim Ahangar, A. Derakhshani, K. Hajiasgharzadeh, N. Silvestris, B. Baradaran, O. Brunetti, Molecules 27 (2022) 1–15, https://doi.org/10.3390/molecules27113545.
[110] E. Schlecker, N. Fiegler, A. Arnold, P. Altevogt, S. Rose-John, G. Moldenhauer, A. Sucker, A. Paschen, E.P. Von Strandmann, S. Textor, A. Cerwenka, Cancer Res 74 (2014) 3429–3440, https://doi.org/10.1158/0008-5472.CAN-13-3017.
[111] T. Sasaki, E.C. Gan, A. Wakeham, S. Kornbluth, T.W. Mak, H. Okada, Genes Dev 21 (2007) 848–861, https://doi.org/10.1101/gad.1534107.
[112] K.S. Reiners, D. Topolar, A. Henke, V.R. Simhadri, J. Kessler, M. Sauer, M. Bessler, H.P. Hansen, S. Tawadros, M. Herling, M. Krönke, M. Hallek, E.P. Von Strandmann, Blood 121 (2013) 3658–3665, https://doi.org/10.1182/blood-2013-01-476606.
[113] G. Van Niel, G. D'Angelo, G. Raposo, Nat. Rev. Mol. Cell Biol. 19 (2018) 213–228, https://doi.org/10.1038/nrm.2017.125.
[114] R. Kalluri, V.S. LeBleu, Science (2020) 367, https://doi.org/10.1126/science.aau6977.
[115] M. Schuldner, B. Dörsam, O. Shatnyeva, K.S. Reiners, A. Kubarenko, H.P. Hansen, F. Finkernagel, K. Roth, S. Theurich, A. Nist, T. Stiewe, A. Paschen, G. Knittel, H. C. Reinhardt, R. Müller, M. Hallek, E.P. von Strandmann, Theranostics 9 (2019) 6047–6062, https://doi.org/10.7150/thno.36378.
[116] L. Song, J. wu Tang, L. Owusu, M.Z. Sun, J. Wu, J. Zhang, Clin. Chim. Acta. 431 (2014) 185–191, https://doi.org/10.1016/j.cca.2014.01.019.
[117] R. Dong, M. Zhang, Q. Hu, S. Zheng, A. Soh, Y. Zheng, H. Yuan, Int. J. Mol. Med. 41 (2018) 599–614, https://doi.org/10.3892/ijmm.2017.3311.
[118] E. Vivier, S. Ugolini, D. Blaise, C. Chabannon, L. Brossay, Nat. Rev. Immunol. 12 (2012) 239–252, https://doi.org/10.1038/nri3174.
[119] S. Paul, G. Lal, Front. Immunol. 8 (2017), https://doi.org/10.3389/fimmu.2017.01124.
[120] P.F. Pinheiro, G.C. Justino, M.M. Marques, Br. J. Pharmacol. 177 (2020) 4563–4580, https://doi.org/10.1111/bph.15222.
[121] D.V. Correia, M. Fogli, K. Hudspeth, M.Gomes Da Silva, D. Mavilio, B. Silva-Santos, Blood 118 (2011) 992–1001, https://doi.org/10.1182/blood-2011-02-339135.
[122] M.P. Correia, A. Stojanovic, K. Bauer, D. Juraeva, L.O. Tykocinski, H.M. Lorenz, B. Brors, A. Cerwenka, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) E5980–E5989, https://doi.org/10.1073/pnas.1720564115.
[123] J.L. Goldstein, Y.K. Ho, S.K. Basu, M.S. Brown, Proc. Natl. Acad. Sci. U. S. A. 76 (1979) 333–337, https://doi.org/10.1073/pnas.76.1.333.
[124] J. Canton, D. Neculai, S. Grinstein, Nat. Rev. Immunol. 13 (2013) 621–634, https://doi.org/10.1038/nri3515.
[125] Q. Taban, P.T. Mumtaz, K.Z. Masoodi, E. Haq, S.M. Ahmad, Cell Commun. Signal. 20 (2022) 1–17, https://doi.org/10.1186/s12964-021-00812-0.
[126] T.K. Means, E. Mylonakis, E. Tampakakis, R.A. Colvin, E. Seung, L. Puckett, M. F. Tai, C.R. Stewart, R. Pukkila-Worley, S.E. Hickman, K.J. Moore, S.

B. Calderwood, N. Hacohen, A.D. Luster, J. El Khoury, J. Exp. Med. 206 (2009) 637–653, https://doi.org/10.1084/jem.20082109.
[127] H. Adachi, M. Tsujimoto, H. Arai, K. Inouel, J. Biol. Chem. 272 (1997) 31217–31220, https://doi.org/10.1074/jbc.272.50.31217.
[128] D.A. Patten, A.L. Wilkinson, J.M. O'Rourke, S. Shetty, Front. Oncol. 10 (2020) 1–13, https://doi.org/10.3389/fonc.2020.565950.
[129] Z. Zhou, E. Hartwieg, H.R. Horvitz, Cell 104 (2001) 43–56, https://doi.org/10.1016/S0092-8674(01)00190-8.
[130] Z.G. Ramirez-Ortiz, W.F. Pendergraft, A. Prasad, M.H. Byrne, T. Iram, C. J. Blanchette, A.D. Luster, N. Hacohen, J. El Khoury, T.K. Means, Nat. Immunol. 14 (2013) 917–926, https://doi.org/10.1038/ni.2670.
[131] Y. Cai, B.H.D. Teo, J.G. Yeo, J. Lu, J. Biol. Chem. 290 (2015) 22570–22580, https://doi.org/10.1074/jbc.M115.670661.
[132] M. Botto, M.J. Walport, Immunobiology 205 (2002) 395–406, https://doi.org/10.1078/0171-2985-00141.
[133] M.E. Greenberg, M. Sun, R. Zhang, M. Febbraio, R. Silverstein, S.L. Hazen, J. Exp. Med. 203 (2006) 2613–2625, https://doi.org/10.1084/jem.20060370.
[134] G. Endemann, L.W. Stanton, K.S. Madden, C.M. Bryant, R.T. White, A.A. Protter, J. Biol. Chem. 268 (1993) 11811–11816, https://doi.org/10.1016/s0021-9258(19)50272-1.
[135] E.A. Podrez, M. Febbraio, N. Sheibani, D. Schmitt, R.L. Silverstein, D.P. Hajjar, P. A. Cohen, W.A. Frazier, H.F. Hoff, S.L. Hazen, J. Clin. Invest. 105 (2000) 1095–1108, https://doi.org/10.1172/JCI8574.
[136] A.S. Plump, J.D. Smith, T. Hayek, K. Aalto-Setälä, A. Walsh, J.G. Verstuyft, E. M. Rubin, J.L. Breslow, Cell 71 (1992) 343–353, https://doi.org/10.1016/0092-8674(92)90362-G.
[137] M. Febbraio, E.A. Podrez, J.D. Smith, D.P. Hajjar, S.L. Hazen, H.F. Hoff, K. Sharma, R.L. Silverstein, J. Clin. Invest. 105 (2000) 1049–1056, https://doi.org/10.1172/JCI9259.
[138] X. Ma, L. Xiao, L. Liu, L. Ye, P. Su, E. Bi, Q. Wang, M. Yang, J. Qian, Q. Yi, Cell Metab 33 (2021) 1001–1012, https://doi.org/10.1016/j.cmet.2021.02.015. .e5.
[139] S. Xu, O. Chaudhary, P. Rodríguez-Morales, X. Sun, D. Chen, R. Zappasodi, Z. Xu, A.F.M. Pinto, A. Williams, I. Schulze, Y. Farsakoglu, S.K. Varanasi, J.S. Low, W. Tang, H. Wang, B. McDonald, V. Tripple, M. Downes, R.M. Evans, N. A. Abumrad, T. Merghoub, J.D. Wolchok, M.N. Shokhirev, P.C. Ho, J.L. Witztum, B. Emu, G. Cui, S.M. Kaech, Immunity 54 (2021) 1561–1577, https://doi.org/10.1016/j.immuni.2021.05.003. .e7.
[140] N.A. Abumrad, M.R. El-Maghrabi, E.Z. Amri, E. Lopez, P.A. Grimaldi, J. Biol. Chem. 268 (1993) 17665–17668, https://doi.org/10.1016/s0021-9258(17)46753-6.
[141] M.Y. Pepino, O. Kuda, D. Samovski, N.A. Abumrad, Annu. Rev. Nutr. 34 (2014) 281–303, https://doi.org/10.1146/annurev-nutr-071812-161220.
[142] S.C.C. Huang, B. Everts, Y. Ivanova, D. O'Sullivan, M. Nascimento, A.M. Smith, W. Beatty, L. Love-Gregory, W.Y. Lam, C.M. O'Neill, C. Yan, H. Du, N. A. Abumrad, J.F. Urban, M.N. Artyomov, E.L. Pearce, E.J. Pearce, Nat. Immunol. 15 (2014) 846–855, https://doi.org/10.1038/ni.2956.
[143] P. Yang, H. Qin, Y. Li, A. Xiao, E. Zheng, H. Zeng, C. Su, X. Luo, Q. Lu, M. Liao, L. Zhao, L. Wei, Z. Varghese, J.F. Moorhead, Y. Chen, X.Z. Ruan, Nat. Commun. 13 (2022), https://doi.org/10.1038/s41467-022-33349-y.
[144] H. Wang, F. Franco, Y. Tsui, X. Xie, M.P. Trefny, R. Zappasodi, S.R. Mohmood, J. Fernández-garcía, C. Tsai, I. Schulze, F. Picard, E. Meylan, R. Silverstein, I. Goldberg, S. Fendt, J.D. Wolchok, T. Merghoub, C. Jandus, A. Zippelius, P. Ho, Nat. Immunol. 21 (2020) 298–308, https://doi.org/10.1038/s41590-019-0589-5.
[145] D.W. Dawson, S.F.A. Pearce, R. Zhong, R.L. Silverstein, W.A. Frazier, N.P. Bouck, J. Cell Biol. 138 (1997) 707–717, https://doi.org/10.1083/jcb.138.3.707.
[146] R. Simantov, M. Febbraio, R.L. Silverstein, Matrix Biol 24 (2005) 27–34, https://doi.org/10.1016/j.matbio.2004.11.005.
[147] V. Firlej, J.R.R. Mathieu, C. Gilbert, L. Lemonnier, J. Nakhlé, C. Gallou-Kabani, B. Guarmit, A. Morin, N. Prevarskaya, N.B. Delongchamps, F. Cabon, Cancer Res 71 (2011) 7649–7658, https://doi.org/10.1158/0008-5472.CAN-11-0833.
[148] J.F. Liu, C.W. Lee, M.H. Tsai, C.H. Tang, P.C. Chen, L.W. Lin, C.Y. Lin, C.H. Lu, Y. F. Lin, S.H. Yang, C.C. Chao, Biochem. Pharmacol. 155 (2018) 537–546, https://doi.org/10.1016/j.bcp.2018.07.024.
[149] J.C. Rodríguez-Manzaneque, T.F. Lane, M.A. Ortega, R.O. Hynes, J. Lawler, M. L. Iruela-Arispe, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 12485–12490, https://doi.org/10.1073/pnas.171460498.
[150] M. Streit, L. Riccardi, P. Velasco, L.F. Brown, T. Hawighorst, P. Bornstein, M. Detmar, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 14888–14893, https://doi.org/10.1073/pnas.96.26.14888.
[151] J.S. Hale, M. Li, M. Sinyuk, W. Jahnen-Dechent, J.D. Lathia, R.L. Silverstein, PLoS One 7 (2012), https://doi.org/10.1371/journal.pone.0040033.
[152] Y. Fang, Z.Y. Shen, Y.Z. Zhan, X.C. Feng, K.L. Chen, Y.S. Li, H.J. Deng, S.M. Pan, D.H. Wu, Y. Ding, Nat. Commun. 10 (2019) 1–16, https://doi.org/10.1038/s41467-019-11662-3.
[153] J.S. Hale, B. Otvos, M. Sinyuk, A.G. Alvarado, M. Hitomi, K. Stoltz, Q. Wu, W. Flavahan, B. Levison, M.L. Johansen, D. Schmitt, J.M. Neltner, P. Huang, B. Ren, A.E. Sloan, R.L. Silverstein, C.L. Gladson, J.A. Didonato, J.M. Brown, T. McIntyre, S.L. Hazen, C. Horbinski, J.N. Rich, J.D. Lathia, Stem Cells 32 (2014) 1746–1758, https://doi.org/10.1002/stem.1716.
[154] G. Pascual, A. Avgustinova, S. Mejetta, M. Martín, A. Castellanos, C.S.O. Attolini, A. Berenguer, N. Prats, A. Toll, J.A. Hueto, C. Bescós, L. Di Croce, S.A. Benitah, Nature 541 (2017) 41–45, https://doi.org/10.1038/nature20791.
[155] A. Ladanyi, A. Mukherjee, H.A. Kenny, A. Johnson, A.K. Mitra, S. Sundaresan, K. M. Nieman, G. Pascual, S.A. Benitah, A. Montag, S.D. Yamada, N.A. Abumrad, E. Lengyel, Oncogene 37 (2018) 2285–2301, https://doi.org/10.1038/s41388-017-0093-z.
[156] J. Pan, Z. Fan, Z. Wang, Q. Dai, Z. Xiang, F. Yuan, M. Yan, Z. Zhu, B. Liu, C. Li, J. Exp. Clin. Cancer Res. 38 (2019) 1–15, https://doi.org/10.1186/s13046-019-1049-7.
[157] J. Vera, R. Fenutria, O. Cañadas, M. Figueras, R. Mota, M.R. Sarrias, D. L. Williams, C. Casals, J. Yelamos, F. Lozano, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 1506–1511, https://doi.org/10.1073/pnas.0805846106.
[158] E. Burgueño-Bucio, C.A. Mier-Aguilar, G. Soldevila, J. Leukoc. Biol. 105 (2019) 891–904, https://doi.org/10.1002/JLB.MR0618-226R.
[159] M. Cristian, R.A. Baz, A.G. Stoica, M. Achie, M.M. Ghinea, M. Deacu, M. Booteanu, A.F. Mitroi, N. Dobrin, I.E. Iordache, G.I. Bălătescu, Med. (United States). 102 (2023) E33083, https://doi.org/10.1097/MD.0000000000033083.
[160] A. Tarakhovsky, W. Müller, K. Rajewsky, Eur. J. Immunol. 24 (1994) 1678–1684, https://doi.org/10.1002/eji.1830240733.
[161] A. Tarakhovsky, S.B. Kanner, J. Hombach, J.A. Ledbetter, W. Müller, N. Killeen, K. Rajewsky, Science 269 (1995) 535–537, https://doi.org/10.1126/science.7542801.
[162] G. Bikah, J. Carey, J.R. Ciallella, A. Tarakhovsky, S. Bondada, Science 274 (1996) 1906–1909, https://doi.org/10.1126/science.274.5294.1906.
[163] G. Dorothée, I. Vergnon, F. El Hage, B.L.M. Chansac, V. Ferrand, Y. Lécluse, P. Opolon, S. Chouaib, G. Bismuth, F. Mami-Chouaib, J. Immunol 174 (2005) 6888–6897, https://doi.org/10.4049/jimmunol.174.11.6888.
[164] F. Alotaibi, M. Rytelewski, R. Figueredo, R. Zareardalan, M. Zhang, P.J. Ferguson, S. Maleki Vareki, Y. Najajreh, M. El-Hajjar, X. Zheng, W. ping Min, J. Koropatnick, Eur. J. Immunol. 50 (2020) 695–704, https://doi.org/10.1002/eji.201948309.
[165] F.M. Alotaibi, W.P. Min, J. Koropatnick, Front. Immunol. 15 (2024) 1–10, https://doi.org/10.3389/fimmu.2024.1256766.
[166] G. Friedlein, F. El Hage, I. Vergnon, C. Richon, P. Saulnier, Y. Lécluse, A. Caignard, L. Boumsell, G. Bismuth, S. Chouaib, F. Mami-Chouaib, J. Immunol. 178 (2007) 6821–6827, https://doi.org/10.4049/jimmunol.178.11.6821.
[167] M. Tabbekh, K. Franciszkiewicz, H. Haouas, Y. Lécluse, K. Benihoud, C. Raman, F. Mami-Chouaib, J. Immunol. 187 (2011) 102–109, https://doi.org/10.4049/jimmunol.1004145.
[168] B. Thakral, L.J. Medeiros, P. Desai, P. Lin, C.C. Yin, G. Tang, J.D. Khoury, S. Hu, J. Xu, S. Loghavi, B. Hu, Y. Oki, S. Li, Eur. J. Haematol. 98 (2017) 415–421, https://doi.org/10.1111/ejh.12847.
[169] P. Zhao, L. Li, S. Zhou, L. Qiu, Z. Qian, X. Liu, B. Meng, H. Zhang, Hematol. Oncol. 37 (2019) 360–367, https://doi.org/10.1002/hon.2657.
[170] D. Korenfeld, L. Gorvel, A. Munk, J. Man, A. Schaffer, T. Tung, C. Mann, E. Klechevsky, JCI Insight 2 (2017), https://doi.org/10.1172/JCI.INSIGHT.96101.
[171] M. He, K. Roussak, F. Ma, N. Borcherding, V. Garin, M. White, C. Schutt, T. I. Jensen, Y. Zhao, C.A. Iberg, K. Shah, H. Bhatia, D. Korenfeld, S. Dinkel, J. Gray, A.U. Antonova, S. Ferris, D. Donermeyer, C.L. Arlehamn, M.M. Gubin, J. Luo, L. Gorvel, M. Pellegrini, A. Sette, T. Tung, R. Bak, R.L. Modlin, R.C. Fields, R. D. Schreiber, P.M. Allen, E. Klechevsky, Science (2023) 379, https://doi.org/10.1126/science.abg2752.
[172] H. Li, E. Burgueno-Bucio, S. Xu, S. Das, R. Olguin-Alor, C.A. Elmets, M. Athar, C. Raman, G. Soldevila, H. Xu, PLoS One 14 (2019) 1–19, https://doi.org/10.1371/journal.pone.0222301.
[173] A. Bhandoola, R. Bosselut, Q. Yu, M.L. Cowan, L. Feigenbaum, P.E. Love, A. Singer, Eur. J. Immunol. 32 (2002) 1811–1817, https://doi.org/10.1002/1521-4141(200206)32:6<1811::AID−IMMU1811>3.0.CO;2-G.
[174] M.H. Brown, E. Lacey, J. Immunol. 185 (2010) 6068–6074, https://doi.org/10.4049/jimmunol.0903823.
[175] M.E. Pitulescu, R.H. Adams, Genes Dev 24 (2010) 2480–2492, https://doi.org/10.1101/gad.1973910.
[176] M. Swidergall, N.V Solis, M.S. Lionakis, S.G. Filler, Nat. Microbiol. 3 (2018) 53–61, https://doi.org/10.1038/s41564-017-0059-5.
[177] M. Swidergall, N.V. Solis, Z. Wang, Q.T. Phan, M.E. Marshall, M.S. Lionakis, E. Pearlman, S.G. Filler, Cell Rep 28 (2019) 423–433, https://doi.org/10.1016/j.celrep.2019.06.020. .e5.
[178] T.J. Kottom, K. Schaefbauer, E.M. Carmona, A.H. Limper, J. Infect. Dis. 225 (2022) 525–530, https://doi.org/10.1093/infdis/jiab384.
[179] T. Xiao, Y. Xiao, W. Wang, Y.Y. Tang, Z. Xiao, M. Su, J. Hematol. Oncol. 13 (2020) 1–17, https://doi.org/10.1186/s13045-020-00944-9.
[180] Y. Zhou, H. Sakurai, Biol. Pharm. Bull. 40 (2017) 1616–1624, https://doi.org/10.1248/bpb.b17-00446.
[181] M. Zhang, L.C.M. Chiu, P.C.K. Cheung, V.E.C. Ooi, Oncol. Rep. 15 (2006) 637–643, https://doi.org/10.3892/or.15.3.637.
[182] Y.Bin Ji, C.F. Ji, H. Zhang, Molecules 17 (2012) 9947–9960, https://doi.org/10.3390/molecules17089947.
[183] Y. Zhang, Y. Liu, Y. Zhou, Z. Zheng, W. Tang, M. Song, J. Wang, K. Wang, Carbohydr. Polym. 267 (2021) 118154, https://doi.org/10.1016/j.carbpol.2021.118154.
[184] K. a Mohammed, X. Wang, E.P. Goldberg, V.B. Antony, N. Nasreen, Am. J. Cancer Res. 1 (2011) 419–431.
[185] D.H. Wang, Y.J. Zhang, S.B. Zhang, H. Liu, L. Liu, F.L. Liu, J. Zuo, Oncol. Rep. 32 (2014) 2429–2436, https://doi.org/10.3892/or.2014.3542.
[186] M. Tandon, S.V Vemula, A. Sharma, Y.S. Ahi, S. Mittal, D.S. Bangari, S.K. Mittal, J. Gene Med. 14 (2012) 77–89, https://doi.org/10.1002/jgm.1649.
[187] F.M. Siswanto, A. Tamura, R. Sakuma, S. Imaoka, Mol. Pharmacol. 101 (2022) 257–273, https://doi.org/10.1124/molpharm.121.000475.
[188] N. Sugiyama, E. Gucciardo, O. Tatti, M. Varjosalo, M. Hyytiäinen, M. Gstaiger, K. Lehti, J. Cell Biol. 201 (2013) 467–484, https://doi.org/10.1083/jcb.201205176.

[189] K.S. Boles, R. Barten, P.R. Kumaresan, J. Trowsdale, P.A. Mathew, Immunogenetics 50 (1999) 1–7, https://doi.org/10.1007/s002510050679.
[190] F. Li, H. Wang, Y.Q. Li, Y. Gu, X.M. Jia, Nat. Commun. 14 (2023) 1–17, https://doi.org/10.1038/s41467-023-42216-3.
[191] D.B. Rosen, W. Cao, D.T. Avery, S.G. Tangye, Y.J. Liu, J.P. Houchins, L.L. Lanier, J. Immunol. 180 (2008) 6508–6517, https://doi.org/10.4049/jimmunol.180.10.6508.
[192] C. Germain, A. Meier, T. Jensen, P. Knapnougel, G. Poupon, A. Lazzari, A. Neisig, K. Håkansson, T. Dong, N. Wagtmann, E.D. Galsgaard, P. Spee, V.M. Braud, J. Biol. Chem. 286 (2011) 37964–37975, https://doi.org/10.1074/jbc.M111.285312.
[193] V.M. Braud, A. Meghraoui-Kheddar, R. Elaldi, L. Petti, C. Germain, F. Anjuère, Front. Immunol. 13 (2022) 1–13, https://doi.org/10.3389/fimmu.2022.847576.
[194] A. Llibre, L. Garner, A. Partridge, G.J. Freeman, P. Klenerman, C.B. Willberg, F1000Research 5 (2016) 2929, https://doi.org/10.12688/f1000research.10009.1.
[195] H. Aldemir, V. Prod'homme, M.J. Dumaurier, C. Retiere, G. Poupon, J. Cazareth, F. Bihl, V.M. Braud, J. Immunol. 175 (2005) 7791–7795, https://doi.org/10.4049/jimmunol.175.12.7791.
[196] P. Roth, M. Mittelbronn, W. Wick, R. Meyermann, M. Tatagiba, M. Weller, Cancer Res 67 (2007) 3540–3544, https://doi.org/10.1158/0008-5472.CAN-06-4783.
[197] C. Germain, T. Guillaudeux, E.D. Galsgaard, C. Hervouet, N. Tekaya, A. S. Gallouet, J. Fassy, F. Bihl, G. Poupon, A. Lazzari, P. Spee, F. Anjuère, C. Pangault, K. Tarte, P. Tas, L. Xerri, V.M. Braud, Oncoimmunology 4 (2015), https://doi.org/10.1080/2162402X.2015.1026503.
[198] S.O. Mathew, P. Chaudhary, S.B. Powers, J.K. Vishwanatha, P.A. Mathew, Oncotarget 7 (2016) 68650–68661, https://doi.org/10.18632/ONCOTARGET.11896.
[199] J.D. Malaer, P.A. Mathew, Anticancer Res 40 (2020) 6613–6621, https://doi.org/10.21873/anticanres.14686.
[200] A.M. Marrufo, S.O. Mathew, P. Chaudhary, J.D. Malaer, J.K. Vishwanatha, P. A. Mathew, Am. J. Cancer Res. 8 (2018) 1050–1063.
[201] Y.G. Ma, M.Y. Cho, M. Zhao, J.W. Park, M. Matsushita, T. Fujita, B.L. Lee, J. Biol. Chem. 279 (2004) 25307–25312, https://doi.org/10.1074/jbc.M400701200.
[202] T. Fujita, Nat. Rev. Immunol. 2 (2002) 346–353, https://doi.org/10.1038/nri800.
[203] M. Matsushita, Y. Endo, S. Taira, Y. Sato, T. Fujita, N. Ichikawa, M. Nakata, T. Mizuochi, J. Biol. Chem. 271 (1996) 2448–2454, https://doi.org/10.1074/jbc.271.5.2448.
[204] M. Kuraya, Z. Ming, X. Liu, M. Matsushita, T. Fujita, Immunobiology 209 (2005) 689–697, https://doi.org/10.1016/j.imbio.2004.11.001.
[205] M.L. Jensen, C. Honoré, T. Hummelshøj, B.E. Hansen, H.O. Madsen, P. Garred, Mol. Immunol. 44 (2007) 856–865, https://doi.org/10.1016/j.molimm.2006.04.002.
[206] Y. Zhao, Y. Ren, X. Zhang, P. Zhao, W. Tao, J. Zhong, Q. Li, X.L. Zhang, J. Immunol. 193 (2014) 783–796, https://doi.org/10.4049/jimmunol.1302563.
[207] F. Luo, T. Chen, J. Liu, X. Shen, Y. Zhao, R. Yang, X. Zhang, Virol. Sin. 31 (2016) 406–414, https://doi.org/10.1007/s12250-016-3808-3.
[208] L.T. Wang, Q.L. Zeng, S.L. Jiang, Z.Y. Chen, X.L. Wang, L. Li, X. Li, Front. Oncol. 12 (2022) 1–19, https://doi.org/10.3389/fonc.2022.987481.
[209] T. Chen, Y. Hu, Q. Ding, J. Yu, F. Wang, F. Luo, X.L. Zhang, Virol. Sin. 30 (2015) 249–260, https://doi.org/10.1007/s12250-015-3605-4.
[210] A.S. Świerzko, M. Michalski, A. Sokołowska, M. Nowicki, A. Szala-Poździej, Ł. Eppa, I. Mitrus, A. Szmigielska-Kapłon, M. Sobczyk-Kruszelnicka, K. Michalak, A. Gołos, A. Wierzbowska, S. Giebel, K. Jamroziak, M.L. Kowalski, O. Brzezińska, S. Thiel, M. Matsushita, J.C. Jensenius, G. Gajek, M. Cedzyński, Cell Transplantations, Front. Immunol. 10 (2020) 1–11, https://doi.org/10.3389/fimmu.2019.03097.
[211] Q. Ding, Y. Shen, D. Li, J. Yang, J. Yu, Z. Yin, X.L. Zhang, Clin. Immunol. 183 (2017) 145–157, https://doi.org/10.1016/j.clim.2017.08.012.
[212] S. Bidula, D.W. Sexton, A. Abdolrasouli, A. Shah, A. Reed, D. Armstrong-James, S. Schelenz, J. Infect. Dis. 212 (2015) 234–246, https://doi.org/10.1093/infdis/jiv027.
[213] B. Beutler, Curr. Opin. Immunol. 12 (2000) 20–26, https://doi.org/10.1016/S0952-7915(99)00046-1.
[214] F. Peri, M. Piazza, Biotechnol. Adv. 30 (2012) 251–260, https://doi.org/10.1016/j.biotechadv.2011.05.014.
[215] N. Maeshima, R.C. Fernandez, Front. Cell. Infect. Microbiol. 4 (2013) 1–13, https://doi.org/10.3389/fcimb.2013.00003.
[216] F. Cochet, F. Peri, Int. J. Mol. Sci. 18 (2017), https://doi.org/10.3390/ijms18112318.
[217] H.Y. Hsu, K.F. Hua, C.C. Lin, C.H. Lin, J. Hsu, C.H. Wong, J. Immunol. 173 (2004) 5989–5999, https://doi.org/10.4049/jimmunol.173.10.5989.
[218] Y. Yang, X. Zhao, J. Li, H. Jiang, X. Shan, Y. Wang, W. Ma, J. Hao, G. Yu, Carbohydr. Polym. 191 (2018) 255–265, https://doi.org/10.1016/j.carbpol.2018.03.019.
[219] H. Guo, H. Wu, Y.B. Hou, P. Hu, J. Du, L. Cao, R. Yang, X. Dong, Z. Li, Int. J. Biol. Macromol. 249 (2023) 126039, https://doi.org/10.1016/j.ijbiomac.2023.126039.
[220] A. Murshid, J. Gong, T. Prince, T.J. Borges, S.K. Calderwood, PLoS One 10 (2015) 1–24, https://doi.org/10.1371/journal.pone.0122529.
[221] C.R. Stewart, L.M. Stuart, K. Wilkinson, J.M. Van Gils, J. Deng, A. Halle, K. J. Rayner, L. Boyer, R. Zhong, W.A. Frazier, A. Lacy-Hulbert, J. El Khoury, D. T. Golenbock, K.J. Moore, Nat. Immunol. 11 (2010) 155–161, https://doi.org/10.1038/ni.1836.
[222] E.M.Y. Moresco, D. LaVine, B. Beutler, Curr. Biol. 21 (2011) R488–R493, https://doi.org/10.1016/j.cub.2011.05.039.
[223] T. Kawai, S. Akira, Immunity 34 (2011) 637–650, https://doi.org/10.1016/j.immuni.2011.05.006.
[224] D.M. Underhill, A. Ozinsky, A.M. Hajjar, A. Stevens, C.B. Wilson, M. Bassetti, A. Aderem, Nature 401 (1999) 811–815, https://doi.org/10.1038/44605.
[225] G.D. Brown, J. Herre, D.L. Williams, J.A. Willment, A.S.J. Marshall, S. Gordon, J. Exp. Med. 197 (2003) 1119–1124, https://doi.org/10.1084/jem.20021890.
[226] B.N. Gantner, R.M. Simmons, S.J. Canavera, S. Akira, D.M. Underhill, J. Exp. Med. 197 (2003) 1107–1117, https://doi.org/10.1084/jem.20021787.
[227] K.M. Dennehy, G. Ferwerda, I. Faro-Trindade, E. Pyz, J.A. Willment, P.R. Taylor, A. Kerrigan, S.V. Tsoni, S. Gordon, F. Meyer-Wentrup, G.J. Adema, B.J. Kullberg, E. Schweighoffer, V. Tybulewicz, H.M. Mora-Montes, N.A.R. Gow, D.L. Williams, M.G. Netea, G.D. Brown, Eur. J. Immunol. 38 (2008) 500–506, https://doi.org/10.1002/eji.200737741.
[228] A. Ozinsky, D.M. Underhill, J.D. Fontenot, A.M. Hajjar, K.D. Smith, C.B. Wilson, L. Schroeder, A. Aderem, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 13766–13771, https://doi.org/10.1073/pnas.250476497.
[229] N.C. Rogers, E.C. Slack, A.D. Edwards, M.A. Nolte, O. Schulz, E. Schweighoffer, D. L. Williams, S. Gordon, V.L. Tybulewicz, G.D. Brown, C. Reis E Sousa, Immunity 22 (2005) 507–517, https://doi.org/10.1016/j.immuni.2005.03.004.
[230] B. Li, D.J. Allendorf, R. Hansen, J. Marroquin, C. Ding, D.E. Cramer, J. Yan, J. Immunol. 177 (2006) 1661–1669, https://doi.org/10.4049/jimmunol.177.3.1661.
[231] P.H. Kruse, J. Matta, S. Ugolini, E. Vivier, Immunol. Cell Biol. 92 (2014) 221–229, https://doi.org/10.1038/icb.2013.98.
[232] R. Pandey, C.M. DeStephan, L.A. Madge, M.J. May, J.S. Orange, J. Immunol. 179 (2007) 7385–7396, https://doi.org/10.4049/jimmunol.179.11.7385.
[233] B. Heit, H. Kim, G. Cosío, D. Castaño, R. Collins, C.A. Lowell, K.C. Kain, W. S. Trimble, S. Grinstein, Dev. Cell. 24 (2013) 372–383, https://doi.org/10.1016/j.devcel.2013.01.007.
[234] J.W. Hao, J. Wang, H. Guo, Y.Y. Zhao, H.H. Sun, Y.F. Li, X.Y. Lai, N. Zhao, X. Wang, C. Xie, L. Hong, X. Huang, H.R. Wang, C. Bin Li, B. Liang, S. Chen, T. J. Zhao, Nat. Commun. 11 (2020) 1–16, https://doi.org/10.1038/s41467-020-18565-8.
[235] J.J. Perez-Villar, G.S. Whitney, M.A. Bowen, D.H. Hewgill, A.A. Aruffo, S. B. Kanner, Mol. Cell. Biol. 19 (1999) 2903–2912, https://doi.org/10.1128/mcb.19.4.2903.
[236] C. Han, J. Jin, S. Xu, H. Liu, N. Li, X. Cao, Nat. Immunol. 11 (2010) 734–742, https://doi.org/10.1038/ni.1908.
[237] J.H. Reed, M. Jain, K. Lee, E.R. Kandimalla, M.H. Faridi, J.P. Buyon, V. Gupta, R. M. Clancy, J. Biol. Chem. 288 (2013) 9077–9083, https://doi.org/10.1074/jbc.M112.403303.
[238] J.W. Zimmerman, J. Lindermuth, P.A. Fish, G.P. Palace, T.T. Stevenson, D. E. DeMong, J. Biol. Chem. 273 (1998) 22014–22020, https://doi.org/10.1074/jbc.273.34.22014.
[239] E. Wakshull, D. Brunke-Reese, J. Lindermuth, L. Fisette, R.S. Nathans, J. J. Crowley, J.C. Tufts, J. Zimmerman, W. Mackin, D.S. Adams, Immunopharmacology 41 (1999) 89–107, https://doi.org/10.1016/S0162-3109(98)00059-9.
[240] K. Simons, E. Ikonen, Nature 387 (1997) 569–572, https://doi.org/10.1038/42408.
[241] L.J. Pike, J. Lipid Res. 44 (2003) 655–667, https://doi.org/10.1194/jlr.R200021-JLR200.
[242] D. Lingwood, K. Simons, Science 327 (2010) 46–50, https://doi.org/10.1126/science.1174621.
[243] H. Nakayama, F. Yoshizaki, A. Prinetti, S. Sonnino, L. Mauri, K. Takamori, H. Ogawa, K. Iwabuchi, J. Leukoc. Biol. 83 (2008) 728–741, https://doi.org/10.1189/jlb.0707478.
[244] S. Xu, J. Huo, M. Gunawan, I.H. Su, K.P. Lam, J. Biol. Chem. 284 (2009) 22005–22011, https://doi.org/10.1074/jbc.M109.009076.
[245] E.M. Carmona, T.J. Kottom, D.M. Hebrink, T. Moua, R.D. Singh, A.H. Limper, Am. J. Respir. Cell Mol. Biol. 47 (2012) 50–59, https://doi.org/10.1165/rcmb.2011-0159OC.
[246] K. Iwabuchi, I. Nagaoka, Blood 100 (2002) 1454–1464, https://doi.org/10.1182/blood.v100.4.1454.h81602001454_1454_1464.
[247] T. Sato, K. Iwabuchi, I. Nagaoka, Y. Adachi, N. Ohno, H. Tamura, K. Seyama, Y. Fukuchi, H. Nakayama, F. Yoshizaki, K. Takamori, H. Ogawa, J. Leukoc. Biol. 80 (2006) 204–211, https://doi.org/10.1189/jlb.0106069.
[248] A.K. Bhunia, T. Arai, G. Bulkley, S. Chatterjee, J. Biol. Chem. 273 (1998) 34349–34357, https://doi.org/10.1074/jbc.273.51.34349.
[249] M. Rajesh, A. Kolmakova, S. Chatterjee, Circ. Res. 97 (2005) 796–804, https://doi.org/10.1161/01.RES.0000185327.45463.A8.
[250] R. Pannu, A.K. Singh, I. Singh, J. Biol. Chem. 280 (2005) 13742–13751, https://doi.org/10.1074/jbc.M411959200.
[251] A. Filimoniuk, A. Blachnio-Zabielska, M. Imierska, D.M. Lebensztejn, U. Daniluk, Biomolecules 10 (2020) 1–9, https://doi.org/10.3390/biom10071083.
[252] P. Mingo-Casas, J. Sanchez-Céspedes, A.B. Blázquez, J. Casas, M. Balsera-Manzanero, L. Herrero, A. Vázquez, J. Pachón, M. Aguilar-Guisado, J.M. Cisneros, J.C. Saiz, M.A. Martín-Acebes, Emerg. Microbes Infect. (2023) 12, https://doi.org/10.1080/22221751.2023.2231556.
[253] T.T. Wei, W. Xu, B. Tu, W.X. Zhang, X.X. Yang, Y. Zhou, S.S. Zhang, J.L. Yang, M. Z. Xie, J. Du, W.W. Chen, Q.B. Lu, Curr. Med. Sci. 44 (2024) 121–133, https://doi.org/10.1007/s11596-024-2835-9.
[254] M. Kim, S. Jung, S.H. Lee, J.H. Lee, PLoS One 10 (2015) 1–15, https://doi.org/10.1371/journal.pone.0119519.
[255] R. Wang, R.Y. Chandawarkar, J. Surg. Res. 164 (2010) e273–e279, https://doi.org/10.1016/j.jss.2010.08.039.

[256] R. Bayarri-Olmos, N. Kirketerp-Moller, L. Pérez-Alós, K. Skjodt, M.O. Skjoedt, P. Garred, Front. Immunol. 9 (2018) 1–14, https://doi.org/10.3389/fimmu.2018.02238.
[257] Y.J. Ma, M.O. Skjoedt, P. Garred, J. Innate Immun. 5 (2013) 242–250, https://doi.org/10.1159/000345356.
[258] S.J. Jang, K. Ohtani, A. Fukuoh, T. Yoshizaki, M. Fukuda, W. Motomura, K. Mori, J. Fukuzawa, N. Kitamoto, I. Yoshida, Y. Suzuki, N. Wakamiya, J. Biol. Chem. 284 (2009) 3956–3965, https://doi.org/10.1074/jbc.M807477200.
[259] P. Kankkunen, L. Teirilä, J. Rintahaka, H. Alenius, H. Wolff, S. Matikainen, J. Immunol. 184 (2010) 6335–6342, https://doi.org/10.4049/jimmunol.0903019.
[260] N. Kalia, M. Kaur, S. Sharma, J. Singh, Front. Cell. Infect. Microbiol. 8 (2018) 1–20, https://doi.org/10.3389/fcimb.2018.00065.
[261] D.A. Patten, S.K. Kamarajah, J.M. Rose, J. Tickle, E.L. Shepherd, D.H. Adams, C. J. Weston, S. Shetty, Sci. Rep. 7 (2017) 1–15, https://doi.org/10.1038/s41598-017-17928-4.
[262] M.J. Alkhatatbeh, A.K. Enjeti, S. Acharya, R.F. Thorne, L.F. Lincz, Nutr. Diabetes. 3 (2013) e59, https://doi.org/10.1038/nutd.2013.1. -7.
[263] G.D. Ross, V. Větvicka, Clin. Exp. Immunol. 92 (1993) 181–184, https://doi.org/10.1111/j.1365-2249.1993.tb03377.x.
[264] G.D. Ross, V. Větvicka, Clin. Exp. Immunol. 92 (1993) 181–184, https://doi.org/10.1111/j.1365-2249.1993.tb03377.x.
[265] R.L. Silverstein, M. Febbraio, Sci. Signal. 2 (2009), https://doi.org/10.1126/scisignal.272re3.