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Research progress of polysaccharide structure-activity relationship

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ABSTRACT

The biological activities of polysaccharides are affected by a variety of factors such as monosaccharide composition, molecular weight, glycosidic bond type, branching degree, molecular conformation and functional groups, and are closely related to structural features. In order to clarify the structure of polysaccharides as much as possible, it is necessary to characterize and simulate the structure of polysaccharides based on primary structure characterization, and further describe or visualize the three-dimensional structure of polysaccharides. A large number of studies have shown that polysaccharides from different sources and structures participate in or directly exert their activities in the fields of anti-tumor, anti-oxidation, and immune regulation related to immunology, anticoagulation, hypoglycemia, lipid-lowering, anti-fatigue, and other activities. The structural modification/modification of polysaccharides provides the possibility to improve the activity, efficiency, or functional specificity of polysaccharides. Due to the diversity and complexity of the structure of polysaccharides, the structural prediction is not complete and of high accuracy, and the functional prediction is limited by the diversity of binding receptors, so the downstream pathways involved cannot be accurately located. Therefore, it is necessary to consider the comprehensive results from multiple perspectives in the study of the mechanism of exerting biological activity. Structural detection and analysis of polysaccharides are inextricably linked to the development of polysaccharide biological activities, which can be easily predicted through structural analysis and summarization of structural patterns.

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1. Introduction

Determination and resolution of polysaccharide structure is a core issue in polysaccharide research, and according to existing studies, both primary structure (e.g., monosaccharide composition, molecular weight, type of glycosides bonding, degree of polymerization, etc.[1]) and senior structure, such as conformation[2], are related to the biological activities of polysaccharides. For example, low molecular weight polysaccharides tend to be oriented towards antitumor[3], hypoglycemic[4] or antioxidant effects[5]; higher galactose content may be associated with antitumor activity[6], whereas a high proportion of α-galactoside bonds tends to have better hypoglycemic activity[7]. However, due to the limited means of structural detection, if the structure of polysaccharides needs to be further investigated, it is necessary to combine the extraction method of polysaccharides with the selection of suitable analytical means, according to the structural characteristics of polysaccharides to further detect and analyze them in a purposeful manner, in order to maximize the structural precision and accuracy of polysaccharide analysis[8]. However, this strategy requires a large amount of crude polysaccharide as the basis for separation and obtains high purity polysaccharides at the cost of low yield, so it is necessary to optimize the upstream separation and purification process in the structural analysis of polysaccharides to obtain polysaccharides with both high yield and high purity as the basis for structural detection. On the basis of high purity polysaccharides, it is necessary to improve the accuracy and

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reproducibility of polysaccharide structure analysis, and combine with the downstream analysis and prediction of polysaccharide structure to provide a comprehensive description of the structure[9]. Therefore, the structural study of polysaccharides is actually based on the optimization of the whole system of polysaccharide isolation and purification as well as analysis and even prediction, and the basis of this study is the means of polysaccharide structure detection.

As mentioned above, the structure of polysaccharides is complex and diverse, and the structure-function relationship of polysaccharides is not one-to-one correspondence[6]. Compared with small molecule active substances, the extremely wide molecular weight distribution allows polysaccharides to have both safety and good biological activity. Existing studies have shown that the activity of polysaccharides is not specific, from binding receptors to participating pathways, but shows a cross-linking/cascade state of mutual influence[10]. For example, polysaccharides with antioxidant activity may have anti-tumor activity due to scavenging free radicals or increasing the expression of antioxidant enzymes[11]. Similarly, polysaccharides with immunomodulatory activity may participate in anti-tumor processes by activating non-specific immune cells or promoting cytokine expression. Polysaccharides that play a role in oxidative protection may also enhance the activity of isomerases such as glycosidase to participate in metabolic pathways, while exhibiting metabolic regulatory effects such as hypoglycemic activity[12]. Therefore, for the functional study of polysaccharides, on the one hand, the biological activity of polysaccharides should be described as comprehensively as possible on the basis of the comprehensive structural characteristics of polysaccharides based on the structural changes of polysaccharides. On the other hand, it is necessary to integrate the results of a large number of researches on the biological activity mechanism of polysaccharides of the same kind, and improve the downstream mechanism of polysaccharide to exert biological activity as comprehensively as possible. On the basis of the above, the functional prediction based on polysaccharide structure is possible.

2. Research progress in structure of polysaccharides

2.1 Preliminary structure of polysaccharides

2.1.1 Molecular weight

Molecular weight is an important factor affecting the biological activity of polysaccharides, in the primary structure of the monosaccharide species, proportion, type of glycosides bond, etc. can affect the distribution of the molecular weight of polysaccharides[13], large molecular weight polysaccharides tend to have high viscosity and low water solubility, and these characteristics undoubtedly limit the bioavailability and bioactivity of large molecular weight polysaccharides[14]. Current studies have shown that molecular weight and molecular weight distribution are closely related to polysaccharide antiviral effects[15], antioxidant activity[16] and immune-enhancing function[17]. For example, heparin is clinically used for the treatment of venous thrombosis, and clinical data show that low molecular weight heparin is more effective than high molecular weight heparin in the treatment of thrombosis[18]. Li et al.[19] found that the molecular weights and antioxidant activities of four *Auricularia* polysaccharides were directly proportional to the antioxidant activities of the polysaccharides obtained. According to the correlation law between molecular weight and biological activity revealed in the existing polysaccharide studies, the molecular weight can be used as part of the basis for the separation to obtain polysaccharides with different activities. Li et al.[20] extracted and isolated polysaccharides with different molecular weights from *Cordyceps sinensis* and analyzed their physicochemical properties and antitumor activities, from which the molecular weights ranging from 3 000 to 10 000 kDa were screened and obtained with best antitumor activity. On the other hand, from the research of synthetic polysaccharides, specific molecular weight chitin can be biosynthesized by engineered bacteria and has good antimicrobial activity[21]. The correlation between different biological activities and different molecular weights is indisputable from both natural and synthetic polysaccharides studies (Table 1).

In addition, the influence of molecular weight on biological activity is also reflected in the polydispersity coefficient, which is determined by high performance liquid chromatography (HPLC) or gel-penetration chromatography (GPC) coupled with a multi-angle light scattering detector (MALS) to determine the molecular weight of the sample by means of the logarithmic average molecular weight (Mn), the weight-average molecular weight (Mw), and the z-averaged molecular weight (Mz). Mn, Mw and Mz are determined and calculated, and the degree of polymerization (DP) of the polysaccharide can be calculated. For example, in the study of inulin and fructan, Tang et al.[32] showed that long-chain inulin with DP values between 23–25 was able to maintain blood glucose homeostasis better than short-chain inulin with DP = 4–5, and that long-chain inulin (DP = 3–60) produced more intestinal short-chain fatty acids than short-chain inulin with a DP below 20. Tawfick et al.[33] studied the metabolome of inulin from intestinal microecological perspective. Fructan with high degree of polymerization promoted an increase in the α-diversity of gut microbes, and that polysaccharides with higher degree of polymerization may have a better role in promoting gut microbes. As a primary structural feature of polysaccharides, the link between the molecular weight of polysaccharides and the senior structure of polysaccharides is a fundamental part of the study of polysaccharide structure and even polysaccharide conformational relationships.

With the deepening of the study on the conformational relationship of polysaccharides, the detection of single molecular features is no longer suitable for the investigation of polysaccharide structure[34]. Therefore, the detection of molecular weight of polysaccharides is not only limited to HPLC, but also the combination of multiple assays, which can provide a comprehensive description of polysaccharidemolecules as much as possible and provide more structural information.

2.1.2 Monosaccharide composition

The determination of monosaccharide composition is currently classified into high-performance gel-permeation chromatography (HPGPC) and high-performance size-exclusion chromatography (HPSEC) according to the different columns. As one of the basic features for describing the structure of polysaccharides, it has been shown through a number of studies that polysaccharides obtained from different sources or different extraction methods may have significant differences in their monosaccharide fractions and ratios due to differences in their monosaccharide environments. For example, comparing the polysaccharide extracted from brown algae (*Coccophora langsdorfii*) by Imbs et al.[34] with the polysaccharide

Table 1
Relationship betweeen molecular weight and activity.

Mw (kDa)	Polysaccharides resource	Extraction	Molecular weight/DP	Activities	References
< 10	*Tremella fuciformis*	Water extraction-acid hydrolysis	3.896 kDa	Antioxidant capacity	[22]
	Poria cocos	Water extraction-enzymatic hydrolysis	6.21 kDa	Anti-inflammatory and Anti-lung cancer activities	[23]
	Stemona tuberosa Lour	Alkali extraction	1.819 kDa/DP = 1.02	Anti-inflammatory	[24]
	Dendrobium officinale	Enzymatic hydrolysis	3.489 kDa	Anti-tumor effects	[25]
	Tremella fuciformis	Water extraction-US/H_2O_2 degradation	12.7 kDa	Scavenging free radical	[26]
	Cordyceps sinensis	Water extraction-enzymatic hydrolysis	39.09 kDa/DP = 1.148 2	Hypolipidemic activity	[20]
10–100	*Ziziphus jujuba* cv. Muzao	Ultrasound-H_2O_2/Vc degradation	62.73 kDa	Antioxidant activity	[27]
100–1 000	*Plumula nelumbinis*	Microwave-assisted water extraction	11.6 kDa	Antioxidant and anti-inflammatory	[28]
	Tremella fuciformis	Water extraction-US/H_2O_2 degradation	814 kDa	Antioxidant activity	[26]
	Auricularia cornea	Water extraction-enzymatic hydrolysis	720 kDa	Antibacterial and anti-inflammatory	[19]
	Auricularia auricula		740 kDa		
	Mulberry ungus		690 kDa		
	Antrodia cinnamomea	Enzymatic hydrolysis-potassium sulfate fractionation	231.6 kDa	Anti-inflammatory	[29]
		Enzymatic hydrolysis-ammonium sulfate fractionation	133.60 kDa	Anti-inflammatory	
1 000–10 000	*Tremella fuciformis*	Water extraction	2 238 kDa	Antioxidant capacity and immune activity	[22]
		Water extraction-enzymatic hydrolysis	5 800 kDa	Antioxidant capacity	[30]
	Auricularia polytricha	Water extraction-enzymatic hydrolysis	1 260 kDa	Hypolipidemic activity and immunomodulatory	[19]
	Lentinula edodes	Ultrasonic extraction	4 610 kDa	Regulation of intestinal metabolism	[31]

obtained from kelp (*Laminaria japonica*) by Esim et al.[35], the major monosaccharide fractions of the former at ratios of fucose:galactose:mannose = 45.0:18.0:16.2, and those of the latter were galactose:mannose:glucose = 50.6:17.33:32.06; whereas polysaccharides from the same source present a certain degree of species-specific monosaccharide repeating units due to similar monosaccharide occupancies, thus possessing similar biological activities. For example, the kelp polysaccharides obtained by acid digestion combined with hydroalcohol precipitation by Li et al.[36] had the same 5 polysaccharides with similar proportions of higher content compared with the kelp polysaccharides obtained by Park et al.[37]. However, due to the structural properties of the monosaccharides themselves, high proportions of specific monosaccharides may exhibit significant rigidity or flexibility. For example, xylose (Xyl), rhamnose (Rha) and mannose (Man) have relatively stable structures, and high aggregation is more likely to form rigid structures, which indirectly leads to the formation of relatively stable crosslinked structures in the polysaccharide space[38]; whereas a high proportion of monosaccharides such as arabnose (Ara), galactose (Gal) and glucose (Glc) are more likely to aggregate and form flexible sugar chains, which in turn form polymer or helices, and are more likely to spread chains in solvents, especially in high polymer polysaccharides, whose spatial structures are more varied, making the differences in biological activities more obvious[39]. This difference in the nature of the glycosides caused by the composition of monosaccharides, and thus the difference in spatial structure may be one of the reasons for the difference in activity. For example, Qi et al.[40] showed that the monosaccharide composition of *Polygonatum sibiricum* polysaccharides greatly affected their antioxidant activities, with both hydroxyl radical scavenging and ABTS scavenging abilities being inversely proportional to the Man molar ratio and positively proportional to the Ara molar ratio. The results suggest that the composition of monosaccharides, in addition to being an indicator of polysaccharide homogeneity, also has the potential to be used as an indicator of the structure-specificity of polysaccharides, and that, due to the nature of monosaccharides and the differences in chain formation, their types and ratios can also indirectly affect the formation of glycosidic bonds and spatial structure formation (Tables 2 and 3).

2.1.3 Functional groups

The study of polysaccharide functional groups mainly focuses on the directed modification or modification of polysaccharides, which is currently the more concerned structural feature in polysaccharide activity studies. The modified polysaccharides are often structurally characterized before and after modification by infrared (IR) characterization of the changes in the moiety and the aforementioned structural assays[57]. In application, for example, due to the lack of fluorescent and UV groups, polysaccharides cannot be detected by fluorescence or UV detectors, and polysaccharides exist in a certain molecular weight distribution, which makes mass spectrometry detection and analysis extremely difficult[58]. In order to achieve the tracing of polysaccharides, the fluorescent labelling

method based on the terminal active groups of polysaccharides has emerged. If polysaccharides have more amino and hydroxyl groups and weaker intermolecular hydrogen bonding, it is conducive to their biological activity, and it is easy to trigger amination and nucleophilic addition reaction with FITC and other markers containing isothiocyanic acid groups (N=C=S), to achieve the fluorescent labelling of polysaccharides[59]. Meanwhile, in terms of polysaccharide activity, a higher proportion of hydroxyl groups facilitates free-radical scavenging. For example, it may be precisely due to the exposure of hydroxyl groups that polysaccharides of *Sargassum fusiforme* are enzymatically digested, which is favourable for the exposure of hydrogen atoms and the immobilization of superoxide anion, resulting in a significantly better scavenging of superoxide anion in the degraded polysaccharide of *S. fusiforme* than that of brown sugar (brown algae)[60]. Similarly, *β*-glucan obtained from oats has a good ability to chelate metal ions due to the exposure of more hydroxyl groups[61]. However, the role played by active functional groups in polysaccharides is limited by the number and spatial structure, making it often impossible to form an accurate correspondence between the activity and the predicted structure. Therefore, in order to further deepen the structure-function relationship of polysaccharides, in addition to the study of the role of active functional groups, researchers have also paid more and more attention to the physicochemical properties and structural differences brought about by the differences in the types and quantities of functional groups. Feng et al.[62] through the study of polysaccharides of *Sagittaria sagittifolia* L., found that the ultrasonic degradation of the polysaccharide with increase in the polar groups, the water solubility increased. In the study of Cheung et al.[63], curdlan was also degraded by ultrasound, the more hydroxyl groups were exposed, the higher the mass-to-charge ratio and the stronger the corresponding charge effect, which reduced the formation of the gel state in a neutral environment, and the water solubility was significantly enhanced. However, in natural polysaccharides, there is also the formation of smaller particles bound to water molecules due to the exposure of hydroxyl groups[64]. It suggested that there are differences in the role of homologous functional groups in contributing to the structure (Tables 2 and 3).

In addition to the above mentioned differences in physicochemical properties due to active functional groups and functional group-influenced structures, functional groups also have an effect on polysaccharide branching and cross-linking degree. For example, Fang et al.[65] showed that kelp polysaccharides with abundant sulfate groups are more likely to form highly complex cross-linked structures and express higher bile acid binding capacity. Also, the presence of high abundance of sulfate groups correlates with high branching degree and tends to have better anti-tumor activity[66]. Due to the direct correlation between functional groups and biological activities, in the study of polysaccharide conformational efficiency, on the one hand, we can combine the composition of monosaccharides and the types and proportions of glycosides bonds, and simulate the structure of the sugar chain through the proportion, distribution and spatial relationship of functional groups, so as to achieve the prediction and simulation of the three-dimensional structure of polysaccharides; on the other hand, based on the nature of the functional groups, we can make use of the differences in the activity of functional groups before and after modification to annotate the polysaccharide activity, which can further deepen the research on the conformational relationship of polysaccharide.

2.1.4 Glycosides

As polysaccharides are macromolecules, the linkage between monosaccharides can actually serve as a link between the primary and higher structures of the polysaccharide chains, so the type of glycoside bond and the linkage mode are of great significance to the structure analysis of polysaccharides. Due to the complexity of the polysaccharide structure, the current study basically chooses to combine chemical and instrumental analyses to speculate the partial structure of polysaccharides, which is different from the structure analysis of proteins through multiple instrumental tests and software simulations[67]. Currently, the detection of glycosides bonds mainly relies on monosaccharide composition analysis, methylation and gas chromatography to depict the linkage of glycoside residues; two-dimensional nuclear magnetic resonance (NMR) analysis to analyze the heterodimeric carbon-hydrogen configuration, the

Table 2
Polysaccharides with different glycosidic bonds participate in the same functional pathway.

Resource	Extraction	Monosaccharide and ratio	Glycosides	Groups/ Terminal glycoside	Senior structure	Mechanism	Receptor	References
Nostoc commune Vaucher	Ultrasonic assisted-water extraction	Man:Ara:Glc = 0.30:6.84:2.81	→3)-Rha*p*-(1→, →4, 6)-Glc*p*-(1→, →6)-Glc*p*-(1→, →4)-Glc*p*-(1→, →3)-Glc*p*-(1→,	Glc; Xyl ;Gal	*α*-(1→4)-*D*-glucans with higher proportion of branch chain	MAPK and TLR4-IRF7	TLR4 and TLR7/8	[41-42]
	Water extraction	Glc:Xyl:Gal:Ara:Man:GlcA:Rha = 42.6:23.61:17.68:2.19:1.6:7.78:2.60	→4)-*α*-*D*-Gal*p*-(1→, →4)-*β*-*D*-Glc*p*-(1→, →4)-*α*-*D*-Xyl*p*-(1→, → 4,6)-*β*-*D*-Glc*p*-(1, *α*-*D*-Manp-(1→,→3,4)-*α*-*D*-Xyl*p*-(1→	–OH/ Man;Glc;Ara	*α*-(1→4)-*D*-Gal*p*-(1→	TLR7-IRF7, MAPK and PI3K-Akt	TLR2, TLR4-MD2	[43]
	Water extraction	Rha:Man:Glc:Gal = 0.65:0.55:2.91:2.73	→3)-Glc*p*-(1→, →4)-Glc*p*-(1→, →2-Gal*p*-(1→, →2, 6)-Gal*p*-(1→, →6)-Glc*p*-(1→, →6)-Gal*p*-(1→	Glc; Xyl; Gal	1→3-Man*p* with branching chains			[42]

Table 3
Polysaccharides with similar glycosidic bonds but different in senior structures are involved in different pathways.

Resource	Extraction	Monosaccharide and ratio	Glycosides	Groups/ Terminal glycoside	Senior structure	Mechanism	References
Gastrodia elata Blume	Water extraction	Fru:Man:allose:Glc:Gal:isomaltose : maltose:cellobiose:kojibiose	→4)Glc*p*(1→,→6)Glc*p*(1→, →4,6)Glc*p*(1→	Glcp	Flexible single chains and the porous stable conformation	MAPK, mTOR, JNK-1, ATF-2, c-Jun, PPAR, AMPK, and NF-κB	[44]
	Enzymatic hydrolysis				Flexible polysaccharide prone to inter-chain crosslinking		[45]
Catharanthus roseus	Water extraction	Man:Rha:GlcA:Glc:Gal:Ara = 1.56:1.71:1.00:1.62:8.04:8.97.	→5)-*α*-*L*-Ara*f*-(1 → 3,5)-*α*-*L*-Ara*f*- (1 → 3)-*α*-*L*-Ara*f*- (1 → 3,5) -*α*-*L*-Ara*f* -(1 → 3)-*α*-*L*-Ara*f*-(1 → 3,4)-*α*-*L*-Rha*p*-(1 → 3)-*α*-*D*-Gal*p*-(1 → 3,4)-*α*-*D*-Gal*p*-	–OH	3 side chains	TLR2 and TLR4	[46]
	Water extraction	Man:Rha:GlcA:GlcNAc:Glc:Gal:Ara:Fuc = 4.19:4.78:1.61:1.00:1.44:7.41 4.72:1.15	→3)-*α*-*D*-Gal*p*-(1 → 3,4)-*α*-*D*-Gal*p*-(1 → 3)-*α*-*D*-Gal*p*-(1 → 3,4)-*α*-*D*-Gal*p*-(1 → 6)-*β*-*D*-Man*p*-(1 → 5)-*α*-*L*-Ara*f*-(1 → 3,5)-*α*-*L*-Ara*f*- (1 → 3)-*α*-*L*-Rha*p*-(1 → 3,4)-*α*-*L*-Fuc*p*-(1→	–COOH	4 side chains	MAPK/Akt/NF-κB	[46]
	Water extraction	Man:Rha:GalA:Glc:Gal:Ara = 1.00:2.59:12.15:2.60:3.07:4.54			With a high branching degree	Alter the gut microbiota and metabolites (e.g., SCFAs) to alleviate hyperglycemia and tissue impairment, and to inhibit cognitive impairment.	[47-48]
		Rha:Ara:Xyl:Man:Glc:Gal = 0.3:0.6:1.0:1.0:12.1:1.7			Rotation = + 140°, big flake-like structures with a small portion of baculiform surface		
		Rha:Ara:Xyl:Man:Glc:Gal = 0.3:0.6:0.7:1.0:15.1:2.5			Rotation = + 140°, big flake-like structures with a small portion of baculiform surface	Higher branched degree result in the stronger antitumor activity *in vitro*.	[49-50]
		Rha:Ara:Xyl:Man:Glc:Gal = 0.6:0.8:0.7:1.0:12.3:2.0			Rotation = + 156°, cross-linked chains		
	Water extraction-alkaline hydrolysis	Glc:Gal:Ara:GalA:Xyl = 10:1.3:1.7:0.95:1			*β*-Glucans	↑CD4, CD3, CD19 and CD8 lymphocytes; ↑p53, Bax and Caspase-3; ↓ Bcl-2.	[51-52]
Astragalus membranaceus	Water extraction-enzymatic hydrolysis	Rha:GalA:Gal:Glc:Ara = 0.1:0.39:13.4:17.2:1				Low-Mw and high branching exert better immunomodulatory.	[53]
		Rha:GalA:Gal:Glc:Ara = 0.14:0.14:9.6:24.04:1					
		Rha:GalA:Gal:Glc:Ara = 0.375:0.375:18.8:90.5:1			Triple helix	→4)-*α*-*D*-Glu-(1→ enhance both specific and non-specific immunity.	
		GlcA:Rha:GalA:Glc:Gal:Ara = 0.32:0.56:1.70:79.85:3.86:13.71				The more chain breaks, the higher the water solubility; but monosaccharide or disaccharide alone has no significant effect on immune cells.	
		GlcA:Rha:GalA:Glc:Gal:Ara = 0.25:0.30:1.58:93.70:1.40:2.76				NF-κB and MAPK	[54-56]
		GalA:Glc:Gal:Ara = 0.33:98.18:0.20:1.29			*α*-(1→4)-*D*-glucans	ERK/JNK	
		GalA:Glc:Gal:Ara = 0.48:98.38:0.56:0.58				JAK-STAT signaling,	
		GalA:Glc:Gal:Ara = 0.29:98.88:0.02:0.81			*α*-(1→4)-*D*-glucans with higher proportion of branch chain	Toll signaling	
		GlcA:Rha:GalA:Glc:Gal:Ara = 0.24:0.63:3.86: 85.67:3.88:5.72			1→2,4-Glc*p*, 1→4,6-Glc*p* indicated high degree of branching chains	IMD	

Note: Gul, *D*-Gulose; Fru, *D*-Fructose; Rib, *D*-Ribose; Rha, *L*-Rhamnose; Fuc, *L*-Fucose ; GlcA, *D*-Glucuronic acid; GlcN, *D*-Glucosamine.

sequence of glycoside residues in the polysaccharide repeating units, and the substituents of the pyranose or furanose, and ultimately integrate the multiple results to speculate on glycosides bonding modes[68].

Based on the structural analyzes and biological activities of polysaccharides from natural sources, the biological activities exhibited by polysaccharides obtained by different extraction methods may be linked to the type of glycoside bonds[69]. For example, Liao et al.[70] used hot water extraction, ultrasonic-assisted extraction and enzyme-assisted extraction of ginger (*Zingiber officinale* Roscoe) polysaccharides to obtain 5 purified polysaccharides, and after comparison, it was found that the 5 polysaccharide fractions had similarities, but among them, EGP2 and UGP1 were mainly polymerized with *β*-(1→6)-*D*-Gal*p*, and UGP2 was mainly polymerized with *α*-(1→3)-*L*-Ara*p*, and in combination with the results of the analysis of antitumor activity, the polymerization of the *β*-(1→6)-*D*-Gal*p* bond-linked polysaccharides had better antitumor activity. Further, it has been shown that linear *β*-(1→3)-*D*-glucan main chain admixed with an appropriate proportion of (1→6)-Glc short chain has better potential for antitumor development than *β*-(1→6)-*D*-glucan structure[71]. Similarly, Tian et al.[72] explored the relationship between antioxidant activity of mushroom polysaccharides and glycosides bonds with the help of multiple linear regression and found that Ara-(1→4)-Man-(1→2) glycosides bonds were significantly correlated with the reducing capacity, whereas -Glu-(1→6) and -Ara-(1→4) glycosides bonds were associated with DPPH radical scavenging capacity[72]. The correlation between specific glycosides bond types and biological activities may be related based on the interactions between chain residues or the spatial structure formed by the branched chains. For example, the *β*-(1→3) glycosides bond in yam polysaccharides plays a key role in the expression of immune-enhancing activity, which is influenced by the antitumor, anti-inflammatory and immunomodulatory functions through *β*-linked mannose residues or *α*-glycosidic bonds bound to the ends of branched chains[73]. Similarly, xylose residues on arabinoxylan are linked through *β*-(1→4) glycosides bonds, and part of the xylose residues can be obtained by substitution of arabinose residues by *α*-(1→2) glycosides bonds, which have good antioxidant activity[74]. The role of inulin in maintaining blood glucose homeostasis, in addition to the previously mentioned molecular weight, has also been shown to be related to the *β*-(2→1) glycosides bond connected between fructose, and terminal Glc can be connected to the polysaccharide chain through the *α*-(1→2) glycosides bond, thus increasing the reactivity[75]. Moreover, with reference to this, it actually suggests that from a biochemical point of view, different glycoside bonds may have some receptor or reaction directivity. For example, dextran has been shown to activate specific receptors including nuclear factor kappa-light-chain-enhancer of activated B Cells (NF-κB) receptor tyrosine kinase axis and exert relevant biological activities[76]. In addition to this, for example, in a variety of polysaccharides isolated from *Ganoderma tsugae* Murr, unlike the peptide-*β*-(1→3)-glucan structure of several other polysaccharides, in which 2 polysaccharides have the same amount of proteins in their fractions, which are linked to gluco-galactosaccharides *via* fucose or mannose, are able to activate the secretion of the dimerized soluble cytokine interferon-γ (IFN-γ) and the production of the inflammatory factor interferon-inducible protein 10 (IP-10)[77]. Therefore, in fact, the relationship between the structure and biological activity of glycosides bonds shows a certain degree of regularity with the depth of research (Tables 2 and 3). Considering the importance of glycosides bond in polysaccharide structure and the regularity shown in biological activity studies, the role of glycosides bond can be explored in further studies by combining the 2 aspects of polysaccharide high-level structure and the mechanism related to biological activity in a reverse direction.

2.2 Senior structure of polysaccharides

The conformation of polysaccharides based on the primary structure is directly related to the mechanism of their biological activities, it can be regarded as the node linking the structure and activity of polysaccharides. With the updating of instruments and diversification of detection methods, cryoelectron microscopy can show the fine polysaccharide chain structure as much as possible from the molecular point of view[78]; circular dichroism (CD) can make use of the chiral structure of the polysaccharide molecules to influence the rotational direction of the circularly polarized light, so as to analyze the secondary structure of the polysaccharide, and to speculate the information about the spatial structure of the polysaccharide and the intermolecular interactions[79]; atomic force microscopy (AFM) can be used to analyze the structure of the polysaccharide and the interactions between the polysaccharide molecules[80]. It can show the state of polysaccharide extended chain under appropriate concentration, and combined with transmission electron microscope (TEM), the spatial structure of polysaccharides can be compared with that of polysaccharides in extended and aggregated states, so as to analyze and speculate the structure of polysaccharides[34].

In addition to the updating of advanced structure investigation methods, the primary structure basis for the formation of advanced structures and the resulting differences in biological activities are also worth investigating. For example, molecular weight is the most basic primary structure of polysaccharides, but with the use of MALs, data such as Mw or Mn can be obtained, and the ratio of Mw to Mn, which is defined as the degree of branching (DB), is related to the polysaccharide conformation[81]. Polysaccharides with high molecular weights are more inclined to form more complex spatial conformations[82], whereas too low molecular weights imply the presence of fewer reactive groups in the structure, making it difficult to form reactive spatial structures[83]. Similarly, monosaccharide composition also exerts different biological activities by affecting the higher conformation of polysaccharides. For example, 2 water extracted polysaccharides of *Gentiana crassicaulis*[84], GCP-I-I and GCP-II-I, both have a similar conformation to pectin polysaccharides and are active in binding to complement. However, GCP-I-I expresses higher complement binding activity, and based on the comparison of the results of the monosaccharide composition of the 2, it was found that the former contains a higher proportion of type II arabinogalactan, which may be structurally more prone to forming dextran-like triple helices, with the ability to accommodate highly flexible side-chain moieties such as *β*-*D*-Gal-1,6-*β*-*D*-Gal, thus presenting multiple conformational states that are capable of better binding to complement. Moreover, the polysaccharides of *Pleurotus ferula*, which were extracted and isolated in the previous studies of our group[85], were observed in their spatial conformation by AFM. It was found that PFPS was mostly in a flexible chain-like stretching

conformation at low concentrations, and some polymerized chains could also be observed. As the concentration of PFPS increased, the sugar chains of PFPS formed aggregates. However, in addition to structural features related to biological activity, such as three-stranded helical conformation, homogeneity is also one of the indicative features of conformation. With reference to *C. sinensis* mycelium[14] both the hot water extract WIPS and the alkaline extract AIPS showed irregularly coiled structures, but AIPS was more homogeneous, and the results in terms of antitumor activity indicated that AIPS had higher immune-enhancing activity. In addition to inferring the higher structure from the primary structure basis, the spatial structure activity caused by the primary structure can also be utilized in reverse for polysaccharide synthesis[86]. For example, the results of Yao et.al.[21] demonstrated that site-specific fucosylation could achieve chemical-enzymatic catalyzed self-synthesis of 108 sugars with uniform spatial structure and good stability, and indicated that the spatial conformation of the polysaccharide backbone played a key role in the action. The type and ratio of glycosides bonds, as the connection point between the monosaccharide composition and the higher structure, also have an important influence on the formation of the spatial structure. For example, Wu et al.[87] found that *C. sinensis* polysaccharides with *β*-1,6 glycosides bonds are more likely to form hyperbranched and globular conformations, and have better immunomodulatory activities than those with single chain structures; even the simpler glucan structures have similar patterns, such as Chen et al.[88] confirmed that highly branched *β*-1,3-*D*-glucans and *β*-1,6-*D*-glucans are more likely to form hyperbranched and globular conformations than those with single chain structures. And a *β*-1,6-*D*-glucan branched chain with at least one side chain based on a *tris*-Glc residue, the polysaccharide backbone composed of these 2 structures has a stronger immune-enhancing activity than the straight or less branched *β*-1,3-*D*-glucan chain. Thus, on the basis of the primary structure of polysaccharides, the differences in the advanced structure of polysaccharides mainly affect the molecular dynamics, thus showing different biological activities. To improve the development efficiency of active polysaccharides, on the one hand, it is necessary to advance the research on the conformational relationship of polysaccharides, and on the other hand, it is necessary to shorten the cycle of polysaccharides collection and structural analysis, and to improve the prediction ability, so the structural analysis and prediction of polysaccharides also need to be further developed in the same direction.

2.3 Structural analysis and prediction

In previous studies, the collected primary institutional features of polysaccharides were often summarized and cross-linked based on relevant data such as monosaccharide composition, glycosides bond type and ratio, NMR spectroscopy correspondence results, monosaccharide composition and IR detection results, to obtain a variety of putative structures of polysaccharides, and then screened based on the primary structural features of polysaccharides, respectively, to ultimately obtain one or more possible structures, which would then serve as a structural basement for activity investigation[89]. However, as far as the existing studies are concerned, there is no obvious and stable correlation between a specific structure and a specific activity of polysaccharides, which suggests that this conventional structural analysis may only be applicable to homogeneous polysaccharides with simple monosaccharide composition, limited types of glycosides bonding, or low degree of branching[90]. For the more common macromolecular polysaccharides in natural products, this method depends more on the experience of the analyst and the limited precision of the instrument, and does not have good stability and accuracy. Moreover, for the limited types of possible structures obtained from the speculation, the subsequent activity verification is limited by the structural basis and the means of verification, and therefore the final conformational relationship does not have a good general applicability[91].

In order to improve the completeness of the postulated structures and based on the above mentioned important impact of polysaccharide senior structure on function, there are 3 main new approaches to polysaccharide structure research. The first is computer-guided liquid NMR/mass spectrometry, where high-resolution NMR provides precise mass information, and complex planar and stereo structural information can be obtained by tandem mass spectrometry. To ensure the accuracy of the structure of polysaccharides by detecting and predicting the structure of polysaccharides on the basis of as comprehensive as possible, the development of many computer-assisted structure elucidation (CASE) software has also provided the possibility of structure integration and screening, such as ACD/Structure Elicitor, Bruker CMC-SE and Mestrelab MNova Structure Elicitor, etc.[92], which cover aspects such as database searching and spectral data-assisted analysis, and can improve the efficiency of de-duplication and structure construction.

Next is the glycoprotein structure simulation strategy based on protein structure, which speculates the structural domains of bound polysaccharides through the vacuum region of the protein simulated structure; it integrates the structural information of the polysaccharides so as to describe the conformations of bound polysaccharides[93]. This method makes use of the well-developed protein structure analysis and simulation software, and with the high accuracy of protein simulation, it inverts the vacuum region of bond energy calculation to circle the possible distribution region of the binding polysaccharide structure in known glycoproteins, so as to speculate the binding polysaccharide structure. However, this method is limited by the lack of bond energy calculation terms and verification software[94], and the selection of research targets also has many difficulties, such as the collection of bound polysaccharides, the incompleteness of the primary structure information and the influence of the advanced structure, so this research method needs a new way of thinking.

Finally, the reverse polysaccharide synthesis strategy applies to polysaccharides with high repetitive units. Based on the results of polysaccharide structure detection, the rapid synthesis of polysaccharide fragments with the help of a photocatalytic system/one-step synthesis authenticates reverse polysaccharide structure and verifies polysaccharide activity differences, to describe the polysaccharide senior structure through the differences[95]. However, natural polysaccharides are much richer than synthetic polysaccharides in terms of structural information, such as monosaccharide composition, branches, and primary-advanced structural relationships, and this strategy has more reference than practical significance in the study of conformational relationships of natural polysaccharides. In the final analysis, the structural analysis of natural polysaccharides relies on the integration of structural information, but in terms of simulation and prediction, in addition to the development of software, a variety of new

ideas are needed to improve the credibility of the primary-senior structure relationship, the completeness of the simulated structure, and the diversity of the screening-verification means, to further improve the accuracy of the structural analysis and prediction of polysaccharides[96].

In summary, the basis of polysaccharide structure and prediction is actually computer molecular structure simulation and molecular dynamics simulation. The development of software with high accuracy, high fitness, and effective validation is the key to the study of polysaccharide structures and conformational relationships (Fig. 1).

3. Functional progress of polysaccharides

3.1 Study on the biological functions of polysaccharides and modified polysaccharides

The biological activity of polysaccharides is related to physicochemical properties of polysaccharides, bioavailability and binding sites, etc. The former 2 structural characteristics of polysaccharide, such as molecular weight, branching degree, uronic acid content and conformation, can affect the function[97] of polysaccharides, while the latter is reflected in the diversity of polysaccharide binding to receptors and the diversity of receptors and downstream pathways. In recent years, the focus of polysaccharide research is not only the structural analysis of polysaccharides, but also the modification of polysaccharides[98]. With the deepening of the research on the structure activity of polysaccharides, the modification of polysaccharides actually provides a new way to further study the structure activity relationship of polysaccharides.

3.1.1 Immunological activity

Immune regulatory function is one of the most significant biological functions of natural polysaccharides[99]. Currently available studies have confirmed that immune-enhancement polysaccharides can activate non-specific immune cells including macrophage (Mφ) and dendritic cell (DC) directly or indirectly through the complement system. It affects the expression of cytokines and promotes the proliferation and differentiation of lymphocytes[100]. It can also regulate T cell proliferation[101], differentiation by participating in macrophage polarization[102] or regulating cytokine secretion at the same time, so as to achieve bidirectional immune regulation.

Previous studies have shown that the effects of polysaccharides on macrophages often depict bidirectional characteristics. *Lycium bararum* polysaccharides (LBP)[103] and tea polysaccharides (TPS)[104] enhanced the phagocytosis ability of macrophages and promoted inflammatory mediators such as TNF-α, IL-1β, and IL-6 to improve the immune response. However, when combined with other polysaccharides, it can inhibit inflammatory mediators[105], mainly through the downstream pathway[106] or by regulating the transformation of M1/M2 macrophages[103] to achieve the inhibition of excessive immune response. Structurally, it is believed that the branched-chain structure may be the key to stimulating macrophages. Peng et al.[107] characterized the multi-branched chain LBP with *β*-(1→3)-gal as the main chain and a large amount of galactose or arabinose structure at C6. After degrading the main branch chain, the more side chains with high arabinose and galactose content were exposed, the greater the effect on stimulating macrophage proliferation displayed. At the same time, higher content of glucuronic acid means the presence of more sulfuric acid groups and stronger solubility[108], which is positively correlated with the activation of macrophages to a certain extent[109]. However, when the polysaccharide skeleton is glucuronic acid, the structure of arabinogalactan may negatively regulate or suppress immune activity based on the actions of acetyl group or blocking carboxyl group[110]. This bidirectional regulatory relationship with structure is difficult to predict the function of polysaccharides, and is widely found in the study of the biological activity of polysaccharides.

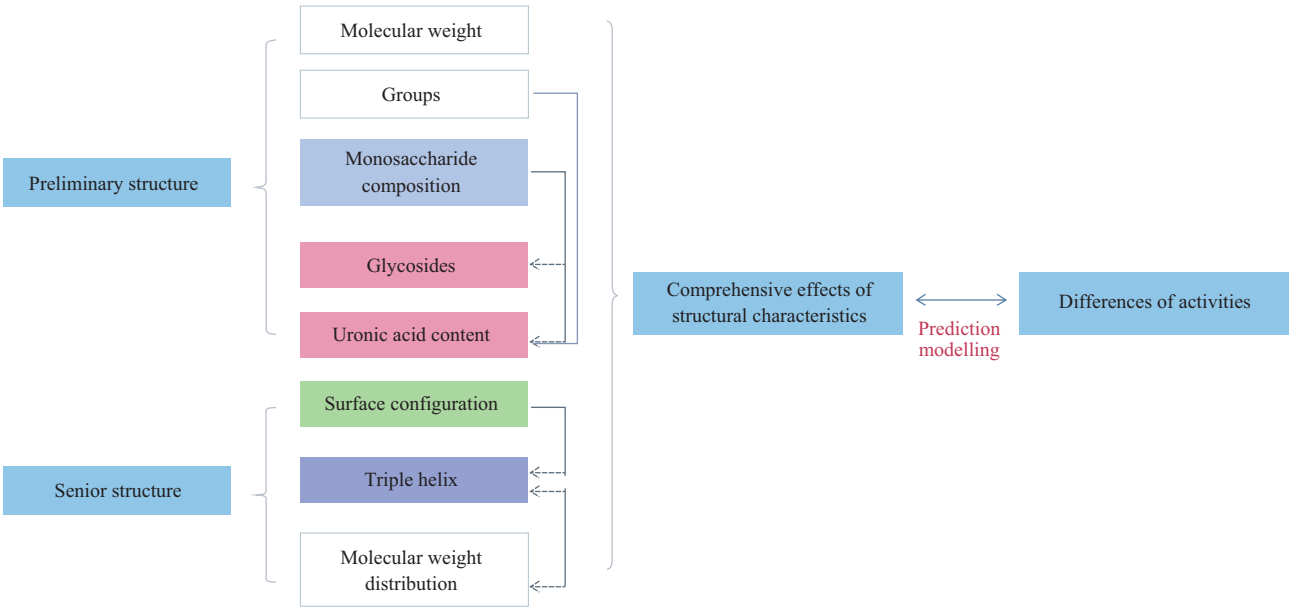

Fig. 1 Relationship between structures.

The stimulatory effect of polysaccharide on DC is similar. As antigen-presenting cells, DC is involved in regulating innate and adaptive immune responses[111], integrating signals through surface molecules and other related molecular patterns to ultimately determine the direction of regulatory action. Zhao et al.[112] characterized the structure of *Panax ginseng* polysaccharide (GPS) and found that the main chain is composed mainly of arabinose and galactose. Ara-*α*-(1,3,5)-, Gal-*β*-(1,3,6)-, Rha-*α*-(1,2,4)- can form dihedral angles of the main chain, and further aggregate through non-covalent bonding, which can promote the expression of CD86, CD40, and MHC-II on the surface of DC, secreting cytokines IL-12 and TNF-α, activating $CD4^+$ T cells to secrete IFN-γ, and promoting $CD4^+$ T cell proliferation[113]. The stimulating effect of polysaccharides on DC is often related to the main branched chain characteristics brought about by the type and proportion of glycoside bonds. For example, the polysaccharides of *Ganoderma lucidum* polysaccharide (GLP) are mainly linked by *α/β*-(1,3)/(1,4)/(1,6) glucoside bonds, which can stimulate the proliferation[114] of Th17 cells, but have no significant effect on the expression of IL-12. However, polysaccharides with *β*-1,3-glucan as the skeleton and *α*-1, 2-Fuc as the terminal glucoside can activate DC through TLR4 and up-regulate the expression of cytokines such as IL-12, TNF-α, IL-6, and IL-10[115]. For polysaccharides with immune activity, some of their structural features are often related to the proliferation or activation of immune cells, and participate in the up-regulation of the expression of various cytokines. Some of the structural features are involved in inhibiting excessive immune response and maintaining homeostasis.

In addition, studies on modified polysaccharides suggest that the degree and type of modification can affect the direction of action through structural changes, and support the immunomodulatory effects of different structural characteristics. For example, the sulfated polysaccharide[116-117] of *Cyclocarya paliurus* can promote the proliferation and phagocytosis of RAW264.7 cells, and increase the expression levels of TNF-α and IL-6 cytokines. When the degree of substitution was 0.45, it tended to promote the proliferation of T lymphocytes, and when the degree of substitution was 0.15, it tended to promote the proliferation of B lymphocytes. For selenizingly modified polysaccharides, the proportion of Se to polysaccharide content could affect its immune-enhancing activity. For example, when the selenium content of lily polysaccharide[118] is 39.78 mg/g and the total sugar content is 72.49%, the levels of IL-2, IL-6 and IFN-γ are higher, the proliferation of lymphocytes is promoted, and the serum antibody titer is significantly increased. In addition, the regulation of the modified polysaccharide on immune activity is also reflected in overcoming immunosuppression. For example, phosphorylated *Cyathula officinalis* Kuan polysaccharide can promote the proliferation of spleen cells[119], promote phagocytosis of peritoneal macrophages, increasing the proportion of T cell subpopulation and IgG concentration, so as to overcome the cyclophosphamide-induced immunosuppression. These immune reactions are often cross-linked with anti-tumor or antioxidant activities, so it is necessary to explore the immunological activity of polysaccharides in conjunction with other biological activities to improve the description of the structure-immunological activity relationship of polysaccharides.

3.1.2 Anti-tumor activities

The action mechanism of polysaccharides with anti-tumor activity is usually concentrated in 2 aspects: indirect activation of immune response and direct induction of tumor cell differentiation or apoptosis[120]. As mentioned above, LBP has a good immune-enhancing effect. The glycoside structure composed by *β*-(1-4)/(1-6)-Gal of main chain and by *β*-(1-3)-Ara/Gal or *α*-(1-4)-Gal of branched chain[121]. It can induce DC maturation by activating TLR4-MyD88-NF-κB signal transduction[122] or promote T cell proliferation by increasing cytokine levels such as IFN-γ or IL-12[123]. Marine algae polysaccharides (MAP) can exert anti-tumor effects by inhibiting tumor cell proliferation, inducing tumor cell apoptosis and cell cycle arrest, inhibiting tumor tissue angiogenesis and metastasis, clearing reactive oxygen species (ROS), inducing immune response, and regulating intestinal microbiota, etc.[124]. Studies on the relationship between the structure of various polysaccharides and anti-tumor have shown that structural characteristics, including molecular weight and monosaccharide composition, can affect anti-tumor activity, but in the study of improving anti-tumor activity by modifying polysaccharides, groups and the specific monosaccharide component subunits related to them are more critical, and can have a greater impact on anti-tumor activity by affecting spatial structure and other aspects[125].

Since the physicochemical properties of the modified polysaccharides, such as water solubility and substitution degree, which are directly or indirectly related to the change of anti-tumor activity[126]. In most studies, the modification method or process directly affects the structural change, and then affects the way to exert anti-tumor activity. Taking LBP as an example, its terminal glucoside is *α*-(1→3)/(1→5)-Ara or *β*-(1→3)-Rha, which can significantly improve immune activity after sulfation modification, and different modification methods cause differences in the degree of substitution (DS). Finally, the antitumor activity showed differences[127-128]. From the perspective of indirectly activating the immune system, the type and proportion of glucosides bond are more critical when polysaccharides with high abundance of glucuronic acid or acetyl group, which are directly related to anti-tumor activity, are removed. For example, the glucan with *β*-1,3/1,6- as the main glucoside bond extracted from Antarctic brown algae by Su et al.[129] can play an anti-cancer role by promoting phagocytosis of macrophages and increasing the secretion of pro-inflammatory cytokines such as IL-1β, TNF-α, IL-2, IL-12p70, CXCL1 and IFN-γ. However, with the increase of the content of sulfuric acid group or glucuronic acid, it often shows a more direct tumor killing effect on the basis of indirectly promoting immune response. For example, the inhibitory effect of polysaccharides on tumor is proportional to the proportion of sulfuric acid groups[130]. *Monostroma nitidum* polysaccharide with high uronic acid content can stimulate the production of NO and PGE2 in mouse macrophages, and have direct cytotoxic effects on AGS human gastric cancer cells and HeLa human cervical cancer cells[131]. Similarly, after selenyl modification, TPS can reduce the levels of IL-6 and TNF-α in spleen, up-regulate the expression level of nuclear factor E2-related factor 2 (Nrf2), and significantly improve the activity of NK cells[132]. Based on this, for polysaccharides with certain immune activity, the modification towards anti-tumor activity focuses more on preserving immune activity while increasing the killing effect on tumor cells.

Some polysaccharides have direct tumor inhibition effect. For example, *Morus alba* L. polysaccharide has a concentration-dependent inhibitory effect on SGC-7901 and HeLa cells, and it can induce cell apoptosis and cell cycle arrest at the S phage in the SGC-7901 cells[133]. Fucoidan inhibited the proliferation and colony-forming ability of HT-29 cells at a concentration of 200 μg/mL[134]. Based on the glycoside composed of (1→3)- and (1→4)-*α*-*L*-fucopyranyose, after sulfation and acetylation, melanoma cell colony formation can be significantly inhibited by modified *Coccophora langsdorfii* polysaccharide at low concentrations[35]. For polysaccharides that have no significant tumor inhibition effect, on the one hand, polysaccharides within a specific molecular weight range can be obtained by adjusting the extraction and purification methods, so as to develop anti-tumor effects[135]. On the other hand, studies have shown that polysaccharides with low molecular weight and a high proportion of sulfuric acid groups can increase the probability of contact with tumor cells, inhibit the occurrence and development of tumor cells by inducing apoptosis, blocking cell cycle, or indirectly by anti-oxidation, inhibition of angiogenesis and other ways, and improve anti-tumor activity[136]. For example, negatively charged phosphate groups can be highly bound to the surface receptors of immune cells and effectively activate the immune response. *Eucommia ulmoides* polysaccharide has no strong tumor inhibition effect, but after phosphoryl modification, it can significantly promote the apoptosis of MCF-7 and B16 cells[137]. Similarly, sulfuric acid groups can bind to immune cell receptors through hydrogen bonding and electrostatic interaction, thereby enhancing the immune response and inhibiting angiogenesis in the tumor microenvironment. Sulfated *Phellinus ribis* polysaccharide inhibited vascular endothelial growth factor (VEGF) and significantly reduced the microvascular density in tumor tissue[138]. In addition, acetylated *Ophiopogon japonicus* galactan induced the proliferation of PANC-1 and Bx PC-3 cells, and the apoptosis induced by selenium-modified polysaccharide was enhanced compared with that before the modification[139]. In fact, the status of the tumor is related to both the oxidation and immune status of the body. Therefore, the development of anti-tumor activity of polysaccharides can be evaluated by the anti-tumor activity of polysaccharide groups or monosaccharide subunits. For polysaccharides with complex composition and high molecular weight, the influence of group modification on anti-tumor activity is mainly reflected in the indirect effect of enhancing immune response. For polysaccharides with structural characteristics such as composition close to glycan or low molecular weight, group changes are more reflected in the direct tumor inhibition effect. Accordingly, as a biological function to undertake immune response and antioxidant action, the difference in anti-tumor activity can also add evidence to the structure-activity relationship of polysaccharides.

3.1.3 Oxidative protection

When the oxidative and antioxidant defense systems are unbalanced, the chain reaction in mitochondria is terminated, such as pyridine triphosphate nucleotides, nitric oxide synthase, cyclooxygenase, lipoxygenase and cytochrome P450 participate in the production of ROS, and ultimately lead to the accumulation of ROS, which destroys the structure and function of DNA, cell membranes and proteins and inducing the production of excess free radicals to further cause oxidative damage[140]. As mentioned above, polysaccharide itself generally has good safety, and can achieve regulatory balance due to its bidirectional regulatory effect. Therefore, polysaccharide, which can reduce the level of oxidative stress and reduce side effects, has gradually attracted the attention of researchers. Polysaccharides mainly achieve antioxidant stress by scavenging free radicals, promoting antioxidant oxidase activity and/or regulating antioxidant signaling pathways[141].

The structural characteristics of polysaccharides, such as group, molecular weight and side chain, can affect the scavenging activity of polysaccharides. Similar to polysaccharides with direct anti-tumor activity, the structural characteristics of low molecular weight and shorter side chains tend to have a larger space, which is conducive to the contact between groups and cells. Polysaccharides modified by groups can also achieve effective free radical scavenging through structural changes such as steric hindrance. For example, *Sargassum tenerrimum* polysaccharide (SP) has the activity of scavenging ABTS· and DPPH. After sulfate modification, it is found that the sulfated polysaccharide of SP with lower molecular weight shows higher scavenging ability of DPPH·, OH– and O_2–[142]. Furthermore, SP exhibited cytoprotective activity through ROS scavenging activity and inhibited ROS generation and cell death in the hydrogen peroxide induced oxidative stress. In *S. sagittifolia* L., the water-soluble non-starch neutral polysaccharides showed higher DPPH·, OH· and ABTS· scavenging activities than other water-soluble polysaccharides from the same source[143]. Compared with nature polysaccharides, the sulfated polysaccharides showed a lower Mw and considerably higher radius of gyration suggesting that the sulfated polysaccharides may become more extended. Interestingly, the inhibitory activity toward cancer cell growth was enhanced by the sulfated polysaccharides, and the sulfated polysaccharides also showed a stronger immunomodulatory activity through increasing the levels of NO, IL-1 and TNF-α. In further studies, the types and sites of modified groups can also change the free radical scavenging ability through directional changes in polysaccharide structure. For example, selenium is the active site component of many enzymes in human body, and polysaccharide selenide has the dual activity of selenium and polysaccharide. Appropriate modification methods can improve the availability of polysaccharide on the basis of retaining the activity of polysaccharide. The selenylation of *Suillellus luridus* polysaccharide[144] was located at the C-4 site of (1-6)-*β*-*D*-Glc*p* and the glycosides bond junction site C-3, and its scavenging ability on DPPH·, ABTS· and O_2– was superior to that of polysaccharide without modification. The study of Hou et al.[118] found that there was no significant difference in the content of uronic acid between the polysaccharidesand its selenated polysaccharides, but the modified polysaccharides had stronger free radical scavenging ability. It induced higher levels of macrophage proliferation and phagocytosis, as well as stimulated higher NO production. Phosphorylation changes the molecular weight of polysaccharides through phosphoric acid groups or enhances the electronegativity of polysaccharides, which affects the conformational structure of polysaccharides. For example, after phosphorylation, the total sugar content of *Cucurbita moschata* polysaccharide decreased, reducing ability decreased, and showed strong OH– and O_2– scavenging ability[145]. The modification of *Auricularia polytricha* polysaccharide[146] by phosphate method can enhance the scavenging ability of OH– and O_2– by increasing the electronegativity of polysaccharide, but weaken the scavenging ability of DPPH·.

The derivatives could inhibit H_2O_2-induced cell death and cell apoptosis on thymic lymphocyte and the derivatives presented higher protective effects. Meanwhile, the acetylation modification of polysaccharides is based on the introduction of acetyl groups into the branch chain of the molecule, which promotes the full development of the branch chain and exposes more hydroxyl or carboxylic groups. On the one hand, it can enhance the scavenging ability of free radicals such as OH– and DPPH[147]; on the other hand, it can improve the solubility of the polysaccharide, the ability to reduce cellular oxidative damage was found with the addition of groups, thus changing its antioxidant activity[148]. In addition to the anti-tumor potential, sulfated modification also has a good prospect for the development of antioxidant effects. For example, *Mesona chinensis* benthas polysaccharide itself has good antioxidant activity, and after sulfate modification, it can obtain stronger scavenging ability of OH–, DPPH· and other free radicals[149], and it had potential effects reflected by reducing lipid accumulation, preventing oxidative stress, improving inflammatory symptoms, and alleviating liver functions by histopathologic observation, etc.

In terms of the development of antioxidant activities, it is necessary to adjust the modification methods to achieve targeted modification. In addition to scavenging free radicals, polysaccharides can also stabilize excess electron free radicals by promoting the activity of antioxidant enzymes, thus slowing down oxidative damage in the process of antioxidant stress. The neutral polysaccharide extracted from *Pleurotus geesteranus* can significantly improve the activities of superoxide dismutase (SOD), total antioxidant capacity (T-AOC), catalase (CAT), and glutathione peroxidase (GSH-Px) in the liver tissue of aged mice, and reduce the content of malondialdehyde (MDA), thereby alleviating oxidative damage[150]. In addition to removing ROS, the modifications such as selenization and sulfation can also improve the activity of antioxidant enzymes. Combined with the modification groups with antioxidant activity, such as selenyl LBP[151] and *Paeonia suffruticosa* seed meal polysaccharide, the results showed that the modified polysaccharide could significantly reduce the ROS level in macrophages after oxidative damage, and increase the activities of SOD and GSH-Px in the cells[152]. In addition to the function of the groups, the side chain of the polysaccharide is also one of the influencing factors. Main chain composed as →6)-*α*-*D*-Gal*p*-(1→ and →3)-*β*-*D*-Glc*p*-(1→, and branching chain composed as *β*-*D*-Glc*p*-(1→4/6)-*β*-*D*-Glc*p*-(1→ and *α*-*L*-Fuc*p*-(1→2/6)-*α*-*D*-Gal*p*-(1→. Such the structure of GLP towards to improve in the liver and serum SOD and GSH-Px enzyme activity and lower MDA level[153-154]. As mentioned above, the antioxidant activity of polysaccharide is affected by its chemical composition, molecular weight and other structures, and it shows strong reducing ability, chelating ability and scavenging free radicals[155]. Lower molecular weight, specific groups and higher DB of polysaccharides may link various biological activities through the improvement of bioavailability, and the enhancement of oxidative protection is often accompanied by the enhancement of anti-tumor activity or immune activity. Therefore, targeted or broad-spectrum activity screening and development can be realized according to the structural characteristics of polysaccharides and the correlation between biological activities.

3.1.4 Others

As mentioned earlier, polysaccharide activity is often not specific due to the complexity of receptors and pathways involved. Polysaccharides with immunostimulatory activity can interact directly or indirectly with the immune system, triggering cellular/molecular events while activating the immune system and exhibiting biological functions other than immune activity[156]. For example, polysaccharides with the structure of (1→4) *D*-mannan, arabinoxan, (1→4) *D*-glucan (C3 junction (1→6) *D*-Glc), (1→3) *D*-mannan (including (1→6) *D*-Gal*p* as side chain)[157] can enhance the phagocytosis function of macrophages and promote the production of ROS and NO biogenesis activates downstream signaling pathways and participates in many other biological processes. For example, *Schisandra chinensis* Fructus polysaccharide (SCP) can regulate the release of IL-1β, IL-6 and TNF-α in serum and brain of elderly mice and activate MAPK signaling pathway, thereby improving cognitive decline[158]. In the inflammatory environment, polysaccharides can play an anti-inflammatory role by reducing the level of pro-inflammatory cytokines and inhibiting related signaling pathways[159]. For example, *Crataegus pinnatifida* polysaccharides and *Aureobasidium pullulans* can inhibit LPS-induced NO production, *iNOS* mRNA expression and the expression of pro-inflammatory cytokines TNF-α and IL-6[160-161]. In LPS-induced RAW264.7 cells, *Lycium ruthenicum* can reduce the levels of p-NF-κB p65, phosphorylated IκBα and TLR4, and can improve inflammation by inhibiting the TLR4/NF-κB signaling pathway[162]. Furthermore, given the association of chronic inflammation with diseases such as type 2 diabetes, cardiovascular disease, and obesity, polysaccharides with immunologic properties may also be suitable for participating in the treatment or repair of damage in these diseases[163-164]. Polysaccharide can inhibit the release of inflammatory cytokines (such as TNF-α, IL-1β and IL-6), and can be used to repair pathological lesions of colon in DSS induced IBD model. *Nitraria tangutorum* Bob polysaccharide can also inhibit the release of inflammatory cytokines and reduce the level of TLR-4 associated with NF-κB signaling pathway[159]. In addition, *Morinda citrifolia* polysaccharide significantly inhibited NF-κB, IκBα, Iκκ α/β and their phosphorylated products in high-fat treated mice[165], and participated in the repair or reduction of tissue damage. Studies such as these on the biological activity of polysaccharide "niche" suggest that polysaccharides with immune activity can actually add evidence to the structure-activity relationship of polysaccharides by improving the biological function of anti-inflammatory and anti-neurodegenerative diseases.

Similarly, oxidative stress has been shown to play a key role in the pathogenesis of diseases of the respiratory system, digestive system, urinary system, and nervous system[166]. For example, excessive oxidative stress can cause mitochondrial dysfunction and produce excess ROS in the liver, leading to liver damage and liver-related diseases, such as liver fibrosis, alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), etc.[167]. Water-soluble non-starch polysaccharides can slow down the oxidation process by regulating antioxidant enzymes (such as CAT, SOD, GSH-Px), and significantly reduce the liver injury induced by CCl4[168]. Excessive ROS will activate the death receptors on the surface of skin cell membrane, and eventually lead to a large number of apoptosis of skin cells, thus causing skin diseases (such as epidermal tumors and inflammatory skin diseases, etc.)[169]. *Annona muricata* leaves

(ALP) protects epidermal keratinocytes from radiation damage by inhibiting oxidative stress by increasing the expression of SOD and CAT[170]. In addition, oxidative stress induced by high lipids enhances lipid peroxidation, leading to liver fat deposition[171]; Increase plasma lipids, chemokines, lipid peroxidation, and adhesion molecules, inducing atherosclerotic plaque formation and plasma lipid levels[172]. Various polysaccharides extracted from *Opuntia macrorhiza* show strong reducing ability and antioxidant activity, which can significantly inhibit lipid peroxidation[173].

Similar activity principles are also applicable to the treatment of diabetes mellitus and its complications. Enzymes related to glucose metabolism are the targets for polysaccharides to achieve hypoglycemic or protective effects. For example, TPS regulates liver glucose metabolism by improving glucokinase (GK) activity[174]. *Dipsacus asper* polysaccharide (DAP) reduces the production of lipid peroxides and improves blood glucose control by regulating the activity of antioxidant enzymes such as SOD, GSH and CAT[175]. In addition, studies have shown that by reducing molecular weight[176] and under the action of phosphorylation modification[177], polysaccharides presents a curly triple helix structure and improves its hydrogen supply capacity, which can reduce the blood vessel remodeling induced by ROS and low density lipoprotein (LDL) peroxidation while gaining stronger hypoglycemic ability.

In addition, the chain reaction of free radicals induces the production of glycosylation end products in nucleic acids, proteins and lipids. Downstream products such as NOS and iNOS can down-regulate the expression of monocarboxylate transporter 1, leading to mitochondrial dysfunction, activation of glial cells, amyloid beta deposition and plaque formation, leading to neurodegenerative diseases[178]. For example, pathological iron accumulation exists in the dense part of substantia nigra in PD patients, and iron overload causes Fenton and Hubervez reactions to generate a large number of hydroxyl radicals. Meanwhile, the reduction of antioxidant enzymes reduces the ability of neurons to clear free radicals, aggravating cell damage[179]. Polysaccharide extracted from *Morchella importuna* (MIP) reduces oxidative stress by increasing the expression of antioxidant enzymes, activating Caspase-3, and effectively alleviating H_2O_2-induced cell damage[180]. In the study on the role and mechanism of *D*-Gal in inducing AD, *Flammulina velutipes* polysaccharide (FVP) normalizes the biological parameters of SOD, CAT and GSH-Px in rats with *D*-Gal induced memory impairment, and protects the brain by inhibiting MDA[181]. LBP extended the average life span of *Drosophila melanoglypha* by increasing CAT and SOD activities[182], revealing that polysaccharides with antioxidant activity also have potential in anti-aging.

On the one hand, polysaccharides with anti-tumor activity can enhance humoral and cellular immune response[183], and show antiviral effects[184]. Clinical and pharmacological studies have shown that letinan (LNT) with β-(1→3) *D*-glucan as the main chain and β-(1→6)-Glc as the branch chain can specifically stimulate T cells, up-regulate the expression of NLRP3 transcription factor in $CD4^+$ T cells, improve CTL response, NK cell activity and IFN-γ level[183]. Significantly enhance the action of anti-hepatitis C virus vaccine. On the other hand, it blocks cell membrane oxidation and other processes through the above-mentioned anti-oxidative stress to prevent the virus from destroying the immune system. In summary, it is necessary to broaden the scope of activity exploration in the functional study of polysaccharides; And with the development of extensive and in-depth research, polysaccharides with corresponding activities can indicate the direction of investigation for specific structure and activity in subsequent studies.

In fact, few current studies have relatively complete and specific descriptions of the relationship between the structure and function of polysaccharides, and more of them are based on empirical speculation in existing studies. Therefore, it is necessary to establish a concept of "Customization" on the description of the structure-activity relationship of polysaccharides, so as to characterize the structure of polysaccharides in detail. In the functional exploration, both bidirectional activity and cross-linking of related signaling pathways should be considered. On this basis, it is expected to establish specific and universal structure-activity relationship, and finally realize the prediction of polysaccharide function.

3.2 Study on the mechanism of polysaccharide action

As mentioned above, the diversity of the structure-activity relationship of polysaccharides is due to the complexity of polysaccharide structure and the bidirectional regulation through the receptor and downstream signaling pathway. That is also a difficulty in the study of polysaccharide function. Due to the cross-linked and complex action pathways, the related activities of polysaccharides show superposition, antagonism or synergy with the change of structure, concentration and even action target, and finally show the comprehensive activity of polysaccharides. Currently studied polysaccharide receptors are mainly divided into mannose receptor (MR) and Toll-like receptor family (TLR), scavenger receptor (SR) and complement receptor 3 (CR3). Following the Nrf2-ARE (NF-E2-related factor antioxidant response element) pathway, MAPK pathway, PI3K/Akt pathway and NF-κB pathway regulate a variety of signals to produce different biological activities (Table 4).

3.2.1 Binding receptors of polysaccharides

3.2.1.1 MR Receptors that bind polysaccharides

MR, which is highly expressed on macrophages, immature DC and endothelial cells, has multiple domains, and C-type lectin domain-4 (CTLD) has binding specificity to different structures[207]. For polysaccharides, multiple Man or Man-Glc tandem glycoside chains and sulfated polysaccharide structures usually have higher CTLD binding potential. CTLD4 has more extensive binding properties, such as Fuc, GalNAc, Gal and Man. *Rheum tanguticum* polysaccharide and *C. sinensis* polysaccharide with a high proportion of Man, Gal and Glc bind to CTLD, induce macrophages to secrete IFN-γ[208], transform M2 macrophages into M1 macrophages through NF-κB signaling pathway, and increase the secretion of TNF-α, IL-12 and NOs[209]. In addition to the role of monosaccharides, the type and proportion of glucosides bonds are equally important. For example, *Polygonatum sibiricum* polysaccharide with β(2→1/6) as the main link is more inclined to NLRP3-related pathway,

Table 4
Relationship betweeen comprehensive receptor and mechanism.

Resource	Glycosides	Receptors	Activity	Mechanism	References
Inula japonica	→5)-*α*-*L*-Ara*f*-(1→, →3,5)-*α*-*L*-Ara*f*-(1→, →2,3,5)-*α*-*L*-Ara*f*-(1→, →2,5)-*α*-*L*-Ara*f*-(1→, *α*-*L*-Ara*f*-(1→	TLR-4	Antitumor	P*D*-1/VEGF/TLR-4	[185]
Panax ginseng	*α*-Glc*p*-(1→, →4)-*α*-Glc*p*-(1→, →4,6)-*α*-Glc*p*-(1→, →3,4)-*α*-Gal*p*-(1→, *α*-Glc*p*-(1 →	TLR-2/4	Anti-inflammatory	PI3K/Akt TLRs/NF-κB	[186-187]
Astragalus	→3)-*β*-*D*-Gal*p*-(1→, *D*-Glc*p*-(1→, →4)-*α*-*D*-Glc*p*-(1→ and →4,6)-*α*-*D*-Glc*p*-(1→	TLR3/7/9	Reduced cellular inflammatory response	NF-κB-MAPK; TLRs/NF-κB/TNF-*α*	[188-189]
Monascus purpureu	Linear *α*-(1→4)-Glc*p*, 5-*β*-*D*-Gal*f* and 2-*β*-*D*-Man*p*	TLR4	Immunomodulatory	MAPK/NF-κB	[190]
Lycium barbarum	1,3-*β*-*D*-galactopyranosyl residues, 1,3-*β*-Gal*p*; 1,6-*β*-Gal*p*; 1,4-*α*-Glc*p*; 1,6-*α*-Glc*p*; 1,4-*α*-Gal*p*A	TLR-2/4;CR3	Reversed the oxidative injury and inflammatory response. Anti-aging	TLRs/NF-κB	[191]
Pleurotus eryngii	3-*O*-methylated mannogalactan, (1→3)/(1→6)-*β*-*D*-glucans, (1→3)-*α*-*D*-glucan and (1→2)-*α*-*D*-mannan	TLR2-TLR6;Dectin-1/2	Immunomodulatory Anti-inflammatory	TLR-4/MyD88/NF-κB	[192]
Ganoderma lucidum	(1→3)-*β*-*D*-glucuronic acid, *β* (1→3), *β* (1→ 4), and *β* (1→6)-*D*-glucan	Dectin-1	Antitumor Antioxidant Antidiabetic	JAK-1/STAT-3 TLR-4/MyD88/NF-κB Keap1-Nrf2/ARE	[193]
Dictyophora indusiate	(1→2,6)-*α*-*D*-Glc, (1→6)-*β*-*D*-Gal, (1→6)-*β*-*D*-Man, (1→6)-*β*-*D*-Glc, (1→3)-*α*-*L*-Man	Dectin-1 CR3	Immune enhancement activities	PI3K/Akt/MAPK/NF-κB TLR4/NF-κB	[194-195]
Xanthoria parietina	*α*-*D*-Glc*p*-(1→[→[4)-*α*-*D*-Glc*p*-(1]$_2$→[6)-*α*-*D*-Glc*p*-(1]$_3$→ 4)]$_n$ (1,4)- and (1,6)-*α*-*D*-Glc*p* →[6)-*α*-*D*-Man*p*-(1 →[2,6)-*α*-*D*-Man*p*-(1]$_2$→[2)-*α*-*D*-Man*p*-(1]$_2$→]$_n$, (1,3)-*β*-*D*-Gal*f*-(6→2)-*α*-*D*-Man*p*-(1→	Dectin-2	Anti-inflammatory	MAPK/NF-κB	[196]
Lentinus edodes	→2,6)-*α*-*D*-Gal*p*-(1→ and →6)-*α*-*D*-Gal*p*-(1→, *β*-*D*-Glc*p*-(1→, →3)-*β*-*D*-Glc*p*-(1→ and →2,6)-*α*-*D*-Gal*p*-(1→, and →3,6)-*β*-*D*-Glc*p*-(1→ and →3,6)-*β*-*D*-Glc*p*-(1→, *β*-*D*-Glc*p*-(1→2)-*α*-*D*-Gal*p*-(1→6)-*β*-*D*-Glc*p*-(1→6)-*β*-*D*-Glc*p*-(1→	Dectin-1	Immunomodulatory Antidiabetic	Dectin-1/Syk NLRP3/Caspase-1/GSDMD	[197-199]
Cordyceps militaris	(1→3)-*β*-*D*-glucans	Dectin-1	Hypoglycemic Immunomodulatory Antitumor	PI3K/Akt IκB-NF-κB	[200]
Angelica gigas	(1→4)-Gal*p*-(1→3- and (1→6- and (1→4,6- and (1→3,4,6-branching	CR3	Immunomodulatory	MAPK/NF-κB	[201]
Taraxacum platycarpum Dahlst.	(→1)-, (1→2)-, (1→4)- and (1→2,4)-galactopyranose	TLR2/4 CR3	Immunomodulatory	MAPK/NF-κB	[202]
Curcuma longa	Rhamnogalacturonan, RG-I	TLR2/4 CR3/SR	Immunomodulatory	P38/JNK/NF-κB	[203]
Suaeda maritima	Ara*f*-(1→, Man*p*-(1→, Glc*p*-(1→, →4)-Glc*p*-(1→3/4)-Gal*p*-(1→3)-Man*p* (1→, →6)-Gal*p*-, →4,6)-Gal*p* (1→, →3,6)-Man*p*-(1→	SR	Immunomodulatory	MAPK/NF-κB	[204]
Saussurea laniceps	→3,6)-Gal*p*-(1→, →4)-Gal*p*A-(1→, →6)-Gal*p*-(1→, →4, 6)-Gal*p*-(1→, →2,4)-Rha*p*-(1→, →4)-Gal*p*-(1→, T-Gal*p*-(1→, →3)-Gal*p*-(1→, T-Rha*p*-(1→, T-Ara*f*-(1→, →5)-Ara*f*-(1→, T-Glc*p*-(1→, →4)-Xyl*p*-(1→ and →4)-Man*p*-(1→	TLR2/4 SR	Immunomodulatory Antiviral Anticancer	MAPK/NF-κB JAK/STAT	[205-206]

regulating the activation of MAPK and NF-κB, mediating the release of IL-1β and IL-18, and participating in inflammation[210]. Another with →4)-*β*-*D*-Gal*p*-(1→ and →4,6) -*β*-*D*-Gal*p*-(1→ as the main glucosidic bond can bind to a variety of ligands, including MR, promote the secretion of IL-1β, TNF-α, and IFN-γ, and play an immunomodulatory role[211]. At present, the endocytosis of MR is generally believed to be due to low-affinity interactions with various ligands. MR relies on network proteins to mediate the continuous cycle of endocytosis between the early endosomal compartment and the plasma membrane[212]. Among them, CTLD binds to the structure of oligosaccharides containing mannosan, sulfate groups interact with the cysteine region[213], collagen structure can bind to the FnII domain[214], and lipoarabinomannan (LAM) structure can be internalized through MR receptors[215]. Therefore, the multi-branched polysaccharide with the above structure is more inclined to MR and its downstream pathway in receptor selection, so as to participate in biological processes such as immune regulation or antioxidant.

3.2.1.2 TLR receptors that bind polysaccharides

Compared with MR, which has certain structural feature selectivity, the current study focuses more on the membrane receptors TLR2 and TLR4. The binding of TLR to the majority of high molecular weight polysaccharides with *α/β*-(1→3/4/6) glucoside bond has been confirmed in immune-related studies. For example, *Angelica dahurica* polysaccharide with →3)-Man*p*/Glc*p*-(1→,→4,6)-Gal*p*-(1→,→2/4)-Gal*p*-(1→ and →5)-Ara*f*-(1→) promotes DC maturation through TLR4 activation of MAPK and NF-κB signaling pathway, and expresses CD86, MHCII and TNF-α. IL-12 and IL-1β[216] to activate NK cells and splenic lymphocytes, and shows inhibitory effect on H22 cells[169]. Its pathway is mainly dependent on MAPK and NF-κB signaling pathways, which increase cytokine production and NO secretion[217], and expand the inflammatory response. For example, *Prunella vulgaris* Linn polysaccharide can enhance phagocytic function of RAW264.7 cells through TLR receptor pathway through *α*(1→3) and *β*(1→3,4) glucoside linkage, and promote the secretion of NO, IL-6, and TNF-α, and increase mRNA expression of *iNO*, *IL-6*, and *TNF-α*[218]. The acidic heteropolysaccharide isolated from the fruit of *Physalis alkekengi* L. has a main chain consisting of (1→5)-Ara and (1→3/6)-Gal/GalA, branching attached to O-3 of (1→6)-Gal and ending in Gal or Gal-Glc; All Glc and most GalA are distributed in branches, branch residues are composed of (1→3)-GalA, (1→4)-Gal, (1→4)-Glc or (1→4,6)-Glc, and some branches contain small amounts of (1→3)-Gal and (1→3)-GalA. The expression of TLR 2 and TLR 4 on the cell surface can be regulated to activate DC cells. It can also improve the clearance rate of DPPH· and ABTS·[219-220]. In addition to the MyD88-dependent signaling pathway, TLR4 can also mediate the MyD88 independent signaling pathway. Such as *Saposhnikovia divaricate* polysaccharide[221], its main chain composed with →{[4)-*α*-*D*-GalA*p*-(1→5)-*α*-*L*-Ara*f*-(1→4)*α*-*D*-GalA*p*-(1→5)-*α*-*L*-Ara*f*-(1→6)-*β*-*D*-Gal*p*-(1]8→3,6)-*α*-*D*-Man*p*-(1→3)-*β*-*D*-Man*p*-(1→4,6)-*β*-*D*-Glc*p*-(1}23, C6 and C4 sites has branched chain →3,6)-*D*-Man*p*-(1→,→4,6)-*β*-*D*-Glc*p*-(1→ and →5)-*α*-*L*-Ara*f*-(1→, C5 connected with terminal glycoside *β*-*D*-Gal*p*-(1→ and *β*-*D*-GalA*p*-(1→. Such a structure binds to the TLR4 receptor and activates the TIR domain adaptor protein (TRIF)[221-222], which significantly inhibits the protein expression of MMP2/9 and enhances the protein expression of TIMP-1/2. Decreased the protein expression of TLR4-NF-κB signaling pathway in rats, thereby reducing the secretion of inflammatory factors IL-6 and TNF, and alleviating the damage of knee joint and ankle joint in rats with rheumatoid arthritis[221-222]. TLR can be regarded as the primary binding receptor for polysaccharide to exert immune activity, and it is indispensable in the exploration of polysaccharide function.

3.2.1.3 Binding CR3 receptor of polysaccharides

Polysaccharides with *β*-glucan or similar structures are more likely to bind to CR3 receptors, and the downstream signaling pathway can be roughly divided into 3 types: spleen tyrosine kinase (Syk) classical/non-classical pathway and non-Syk-dependent pathway[223]. The classical Syk pathway is similar to the signaling pathway mediated by TLR receptor. Polysaccharides with *β*-glucan structure bind to the Dectin-1 receptor and promote the transition of early phagosomes containing *β*-1,3-glucan to mature phagolysosomes[224], which inducing the phosphorylation of IκB protein and activation of the subunits C-Rel, P50 and P65 of NF-κB. For example, LNT with *β*-1,3-glucan structure was labeled by Cy7 and 5-DTAF and proved *in vitro* that the structure promoted lysosome maturation through Dectin-1/Syk signaling pathway and mediated phagocytosis and degradation of LNT. The polysaccharide of *Lentinula Edodes*[225] and *Ficus carica*[226] have similar *β*-1,3/6-glucan structure, which can promote the secretion of TNF-α and NO through Dectin-1/Syk pathway, and enhance the phagocytosis function of RAW264.7. It can also promote the expression of CD40, CD80, CD86 and MHCII on the surface of DC, increase the secretion of IL-12, IL-23, IL-6 and IFN-γ, and promote the maturation of DC.

However, non-Syk-dependent pathways are more likely to activate innate immune function by overlapping different signaling pathways. For example, the polysaccharide structure is glycan and contains a certain proportion of mannose or terminal mannose, which is more inclined to bind Dectin-2 and Dectin-3[227]. Similarly, the (1→3) *D*-glucan structure interacts with Dectin-1 when it is in the granular/aggregated state. The synthesis of NF-κB is regulated by Src family kinases phosphatidylinositol 3 kinase (PI3K) and proteinkinase B/Akt. When in a soluble state, it interacts with CR3, focal adhesion kinase, Syk, PI3K, Akt, p38 mitogen activated proteinkinase, phospholipase C (PC) and proteinkinase C (PKC) activated Iκκα to phosphorylate P100 and transform it into p52, thus initiating gene transcription[76]. For example, *Pleurotus eryngii* polysaccharide, with *α*-(1→3)-Man and *β*-(1→3)-Glc as its main structure, promotes NO secretion through Dectin 2-Syk signaling pathway and up-regulates the levels of TNF-α, IL-1β and IL-6[228]. Interestingly, when the proportion of Man or Fuc increases, as a mannan or fucosan involved in the immune response, it is through the co-action of CR3 receptor and TLR receptor. MAPK and glycogen synthase kinase 3 mediate the production of TNF-α, which enhances the phagocytosis of phagocytes and enhancing the immune function[99].

The non-Syk-dependent pathway is mainly activated directly by polysaccharide such as C-lectin or PRR in the tyrosine non-phosphorylated state, carbonhydrate recognize domain (CRD), activate Ras protein and Raf kinase, activate MAPK and NF-κB signaling pathway to promote cytokine secretion and mediate innate immune response[229-230]. Structurally, polysaccharides or oligosaccharides with multiple branched chains have a higher probability of binding to CRD and function as glycosyl[231-232].

3.2.1.4 Binding to SR receptors of polysaccharides

SR receptors are often associated with polysaccharides from microorganisms, and the main influencing factors are polysaccharide Mw and monosaccharide type. Fermentation and other means not only change the physical and chemical properties of polysaccharides, but also affect the polysaccharide-receptor binding and the direction of downstream signaling pathway[233]. As the model receptor on the surface of *M*φ, the types of "non-self" ligands identified are extremely diverse. Highly polymerized polysaccharides with LPS-like structure or high anionic ligands such as dextran sulfate[234-235] are more likely to increase the expression of surface molecules and cytokines through SR recognition, thus playing a role in immune response. For example, fucoidan is mediated by Class A SRs (SR-A) and induces iNOS activation and NO production in RAW 264.7 cells through a NF-κB dependent pathway[236]. It can also inhibit the binding of LOX-1 (Class E SRs) to outer membrane protein A[237]. In contrast,

the negatively charged chondroitin sulfate and heparin also have immunomodulatory activities, but do not bind to SR[238-239]. In addition, depolymerized fucoidan (DFPS) from the same source showed a strong ability to promote NO secretion based on the structure of low sulfate group content[234], suggesting that the structural heterogeneity of polysaccharides may be an important factor in the activation of immunomodulatory response through SR.

There are 2 main types of signaling pathways that bind to SR: PTK(Src)/Rac1/PAK/JNK and PTK(Src)/Rac1/PAK/p38 pathway[240]. In terms of immunomodulatory activity, SR is not the only target. Fucoidan has been reported to enhance macrophage function even when SR-A is absent[241]. It has been reported to activate TLR4 and synergistically regulate SR-A levels through TLR2 and TLR4 mediated by the p38 signaling pathway[242]. In addition, SR-A is activated by TLR4-MAPK-ERK and JAK-STAT pathways, and CD36 is activated by TLR4-JAK-STAT pathway[243]. Therefore, in the case that non-SR-A ligand from the same source of fucoidan can up-regulate SR-A and TLR4 at the same time, it can be inferred that fucoidan with glycan form can be recognized by TLR4, activate the downstream MAPK-ERK and JAK-STAT pathways, and activate SR-A. In general, polysaccharides with low molecular weight and high heterogeneity have a higher possibility of binding to SRs and promoting its expression, while polysaccharides with glycan structure may indirectly promote SRs expression by acting on other receptors (such as TLR4). Similar thinking may be the key to elucidating the polysaccharide-targeting receptor and downstream pathway.

3.2.2 *Signaling pathways related to polysaccharide function*

Although the biological activity of polysaccharides in most studies did not fully describe the details of all the relevant signaling pathways and/or identify the transcription factors involved, the downstream pathways involved in the currently known immunomodulatory, antioxidant and anti-tumor activities are basically composed of the following pathways, which are induced by the binding of the above-mentioned receptors, and finally show comprehensive activity. A brief relationship diagram is shown in Fig. 2.

3.2.2.1 *NrF2-related signaling pathways*

Nrf2 plays a key role in oxidative stress and inflammation induced by LPS or *D*-GalN, and is one of the important regulatory factors of cellular oxidative stress[244]. Inactivated Nrf2 is retained in the cytoplasm by Kelch-like ECH-associated protein-1 (Keap-1),

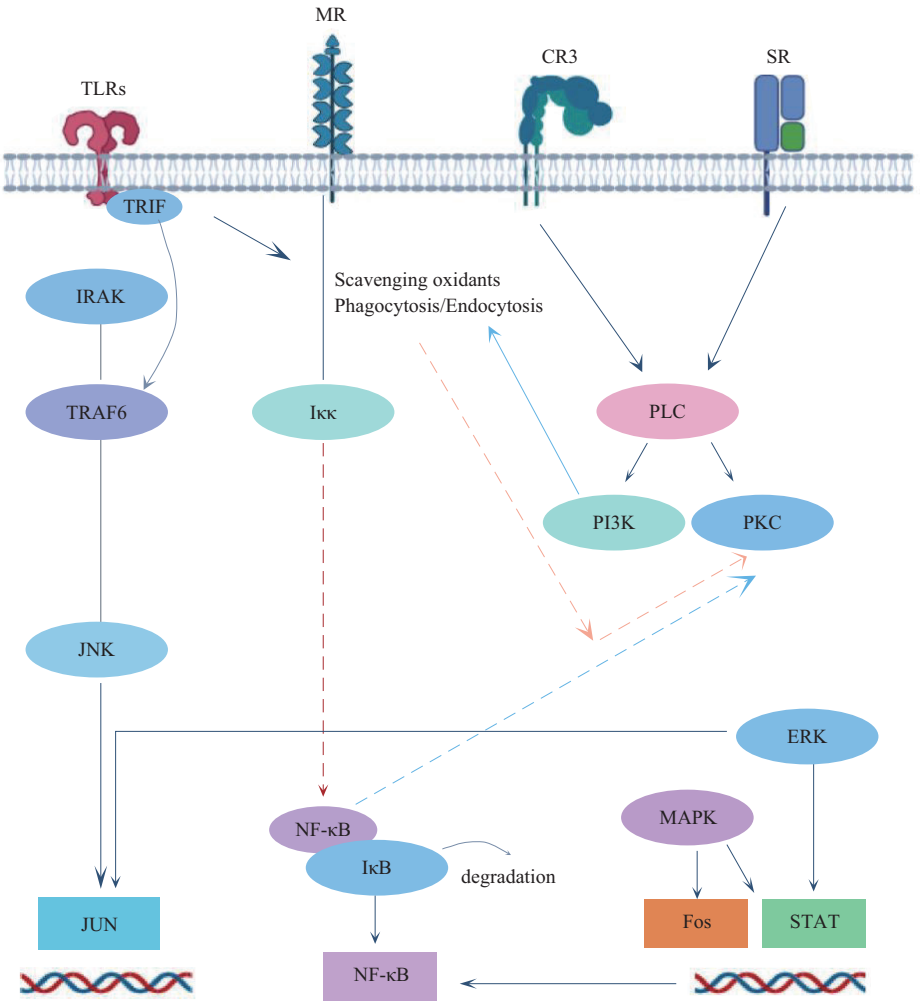

Fig. 2 Relationship between receptors and mechanism.

which plays an important negative regulatory role on Nrf2. Under oxidative stress or inflammation, polysaccharides stimulate lysine on Keap1 to phosphorylate Nrf2 and separate it from Keap1. The Nrf2/ Keap-1 complex is dissociated[245], and Nrf2 is translocated into the nucleus. Interacts with the antioxidant reaction element (ARE) in the antioxidant enzyme promoter and other bZIP proteins (such as JunD, cJun and ATF4, etc.[246]) to form heterodimers, and then produce Heme oxygenase (HO-1), SOD, GSH-Px, NAD(P)H dehydrogenase quinone 1 (NQO1) and other antioxidant enzymes[247]. For example, polysaccharide from *Hippophae rhamnoides* L. can regulate the cytoplasmic expression of Keap-1, promote nuclear translocation of Nrf-2, inhibit phosphorylation of JNK, reduce the expression of Bax, and correspondingly increase the ratio of Bcl-2/Bax. The activity of SOD was increased and the expression of NO and iNOS was inhibited through non-metabolic interference pathway, thus alleviating the oxidative stress and nitrogen stress induced by acetaminophen[248]. Interestingly, polysaccharides can cross-link the PI3K/Akt or MAPK pathway and Nrf2-ARE signaling pathway in a dose-dependent manner to reduce oxidative damage. For example, *Morchella esculenta* polysaccharide can alleviate lung cell damage through PI3K/ Akt-mediated Nrf2-ARE pathway and play an antioxidant role[249]. In addition, the NRF2-related signaling pathway is also involved in the expression of other related activities. For example, *Codonopsis lanceolate* polysaccharide (CLPS) improves HFD-induced insulin resistance by activating the Nrf2-ARE signaling pathway, which provides potential for the treatment of various metabolic diseases such as T2DM and NAFLD[250]. *Astragalus* polysaccharide can inhibit H_2O_2-induced oxidative damage of HUVECs by activating Nrf2 signaling pathway. Nrf2-related signaling pathway provides a new idea and target for the study of polysaccharide function.

3.2.2.2 NF-κB related signaling pathway

NF-κB, as an important regulator of oxidative stress and immune response, is mainly mediated by TLR receptors, and the β unit of IK-β kinase IκκB complex (IκκB) is activated when stimulated by polysaccharide[251]. NF-κB inhibitors (IκB) are phosphorylated with the catalyzation of IκB, dissociated from NF-κB and transported into the nucleus to form dimers with specific sequences and initiate the expression of target genes[252]. For example, *Potentilla chinensis* polysaccharide can promote the pintocytosis activity of *M*φ through NF-κB/p65 and promote NO release in a dose-dependent manner[253]. *Sarcodon aspratus* can activate the TLR-mediated NF-κB and MAPK pathways, stimulate the production of NO, ROS and cytokines TNF-α and IL-6, and enhance the phagocytosis capacity of RAW264.7 cells[212]. At the same time, since TNF-α is also involved in the activation of TNF signaling pathway, IL-6 can activate JAK-STAT signaling pathway. Therefore, polysaccharides that activate macrophages and participate in antioxidant or anti-tumor processes often have the potential to promote DC maturation. The expression of cytokines in the signal network stimulated by polysaccharides is the key to cross-linking.

3.2.2.3 MAPK-related signaling pathway

MAPK signaling cascade is involved in oxidative stress and immune regulation[254]. Under polysaccharide stimulation, one pathway points to MAPK cascades of extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinase (JNK) and p38, phosphorylated transcription factors produced by MAPK that are activated by phosphorylation enter the nucleus to regulate transcription of related genes[255]. For example, *P. ferulae* polysaccharides (PFPS) activated the MAPK signaling pathway through TLR4, which enhanced the expression of DC surface molecules CD40 and CD86 and the secretion of cytokines IL-12p40 and TNF-α, inducing Th1 immune response[256]. Another pathway suggests that MAPK stimulates other signaling pathways such as Nrf2 or NF-κB to exert anti-oxidation or further induce tumor cell apoptosis through the production of NO, ROS and cytokines[257]. For example, *Floccularia luteovirens* polysaccharide can activate MAPK, stimulate the secretion of sIgA and cytokines, trigger the Nrf2/Keap1 pathway and improve the activity of antioxidant enzymes to inhibit oxidative stress. By up-regulating the expression of Occludin and ZO-1, it can enhance the immunomodulatory activity and enhance the intestinal physical barrier function. Chitosan oligopolysaccharides repair H_2O_2-induced oxidative damage of human keratinocytes through the MAPK and Nrf2 pathways[258]. In addition, referring to the aforementioned biological activities and the relationship between related pathways, for example, *L. japonica* polysaccharide can inhibit the MAPK signaling pathway in mice to reduce oxidative damage, thereby inhibiting the formation of atherosclerotic plaque and plasma lipid level induced by HFD[259]. *Schisandra chinensis* Fructus polysaccharide alleviated oxidative damage by activating MAPK pathway and improved cognitive decline in AD rats, which may provide a new idea and method for clinical treatment of AD[158,260]. LBP can bind to TLR 2/4 on the surface of macrophages, stimulate signal proteins such as TIR domain-containing adaptor (TRIF) and MyD88, and further activate signal pathways such as MAPK and NF-κB. On the one hand, it induces macrophages to secrete TNF-α, IL-1, IL-6 and other inflammatory factors[261]; on the other hand, it enhances the expression of MHC II on the surface of DC and promotes the production of IL-12p40, thus activating DC[262]. As a key point of crosslinking oxidative stress and immune regulation, MAPK pathway provides proof for the hypothesis of "multi-receptor consensus-multi-pathway synergism" of polysaccharides.

3.2.2.4 PI3K/Akt-related signaling pathway

As an important signal transduction pathway, PI3k/Akt plays a key role in antioxidant, immune regulation, apoptosis, and other biological processes. When polysaccharide binds to IRα receptor, it mediates Pl3k to promote cascade reaction and Akt phosphorylation, exerting antioxidant activity[176]. This signaling pathway often plays an important role in the resistance to ROS-induced oxidative damage. For example, the polysaccharide of Ficus pumila L. can resist excessive accumulation of ROS through IRα/IRβ-IRS-1-PI3K/Akt pathway and alleviate hyperglycemia caused by damage of pancreatic islet β cells[263]. Polysaccharide extracted from *Ostrea rivularis* can inhibit proliferation, migration, invasion and angiogenesis of EA.hy926 cells through PI3K/Akt signaling pathway, showing anti-angiogenic activity, reduce the formation of cellless capillaries in retinal tissue, and improve retinal damage in *db*/*db* mice. *Fructus mori* polysaccharide cleared ROS through Pl3k/Akt-Nrf2-ARE pathway to protect alveolar epithelial cells and was able to resist idiopathic pulmonary fibrosis[264]. The signaling pathway was also involved in immune regulation. For example, *Glycyrrhiza uralensis*

polysaccharides (GUPS) promoted DC maturation by activating the Pl3k/Akt signaling pathway through TLR4[265]. Acidic polysaccharides of *Panax quinquefolius* L. and *Dendrobium officinale* in granules of Tiepishihu Xiyangshen (TXG) can increase the levels of serum TNF-α, IL-6 and IFN-γ, and improve the imbalance of intestinal microbial community[266-267]. GLP can enhance the activities of antioxidant enzymes such as GSH, SOD, and CAT, and has a protective effect on CTX-induced immunosuppression[268]. In this light, studies have proved that TXG may achieve immune regulation by regulating TLR4/MAPKs and PI3K/Akt/FOXO3a signaling pathways[269]. As a key signal transduction pathway, PI3K/Akt is a critical node of the downstream signaling pathway.

4. Future perspectives

Based on the existing studies, the primary structural characteristics of polysaccharides (e.g. molecular weight, monosaccharide composition and functional groups, etc.) can directly or indirectly affect the formation of the advanced structure of polysaccharides (branching degree, spatial configuration, etc.); whereas, the biological activity of polysaccharides is often related to the physicochemical properties of the polysaccharides, their bioavailability, and their binding sites, etc.[270]. Understanding the structural features of polysaccharides is important for understanding their regulatory mechanisms and developing polysaccharide drugs with specific activities. Based on the establishment of polysaccharide structure-function relationships, polysaccharide structure analysis can be combined with polysaccharide structure analysis to predict the biological activities of polysaccharides, which can be helpful for the design and development of polysaccharide vaccines, immunoadjuvants, or other therapeutic drugs[271].

However, the accuracy of polysaccharide structure analysis and modelling needs to be further improved due to the limited detection means and the structural complexity of natural polysaccharides, and consequently, the certainty of polysaccharide structure-function relationships is greatly reduced. Therefore, in order to establish a clear conformational relationship of polysaccharides, in addition to the necessary structural tests, it is necessary to combine computer science with more efficient simulation and screening to further advance the study of the conformational relationship of polysaccharides[272]. With the in-depth study of polysaccharide conformational effects, the functional changes of the corresponding polysaccharides before and after the structural changes actually offer the possibility of further clarifying the relationship between specific structures and functions, and more structure-function data can be used to explore the possibility of polysaccharide structure-activity relationships with the support of libraries and software development applications, and can even be combined with the extraction method of polysaccharides, the environmental conditions of monosaccharides, or optimal polysaccharide structure design, to a certain degree. The structure prediction and functional screening of polysaccharides aiming to achieve specific biological functions can be accomplished by combining the polysaccharide extraction method, monosaccharide environmental conditions or the optimal polysaccharide structure design to a certain extent, which can greatly save the development efficiency of natural polysaccharides.

From the classical antitumor, antioxidant and immunomodulatory activities to the emerging anticoagulant and antifatigue activities, the corresponding relationship between the structure and specific activities of polysaccharides has been supported by a large number of research results, but there is still no relatively clear corresp onding relationship, which is directly related to the cross-linking of polysaccharide functions. The cross-linking of functional relationships is mainly achieved through the co-mediation of multiple receptors and the tandem multi-signaling pathways of signal molecules such as cytokines[273]. Therefore, according to the existing studies, the four types of receptors MR, SR, CR3 and TLRs, as well as the four key pathways Nrf2, NF-κB, MAPK and PI3K/Akt, which play a major role in polysaccharide stimulation, were described as objects, and the biological activity was associated with the signaling pathway through the different signaling pathways involved in polysaccharides from different sources and the same polysaccharide. It was confirmed that polysaccharides play biological functions through multi-receptor co-mediation-multi-pathway synergism[274]. In combination with summary of the law of polysaccharide structure, the binding receptor situation can be roughly predicted by the structural characteristics of polysaccharides, and the final activity can be predicted by the downstream signaling pathway, so as to clarify the functional differences of the same polysaccharide and the commonality of the functions of different polysaccharides.

In the absence of high-precision structural prediction and accurate localization of acceptor-pathway, structural modification of polysaccharides can be combined[34], which on the one hand provides the possibility to improve the availability of polysaccharides, and on the other hand comprehensively evaluates the results of activity changes before and after the structural change of polysaccharides from multiple perspectives, so as to provide information for the exploration and integration of biological activity mechanism of the same polysaccharide. In the future, functional prediction based on polysaccharide structure can be realized from the point and the surface.

5. Conclusion

There is a complex and close relationship between the structure and activity of polysaccharides, and the detection and analysis of their structure is the basis for the development of polysaccharide biological activity. In addition to the structural complexity of polysaccharides, the relationship between biological functions of polysaccharides also adds complexity to the study of the structure-activity relationship of polysaccharides. Briefly, polysaccharides with mannosan-like structure or with abundant sulfated groups tends to bind MR receptors and participate in various responses, including anti-inflammatory, oxidative clearance, and immune enhancement, through signaling NF-κB-MAPK pathways and so on. Polysaccharides with *α/β*-(1→3/4/6) glucoside structures tend to bind to TLR-like receptors, *via* the TRIF/MyD88 activation pathway, to participate in biological activities such as immune enhancement, anti-inflammation, anti-tumor, etc.. Polysaccharides with *β*-1,3-glucan-like structures tend to bind to Dectin-1/2 and other CR3 receptors, *via* Syk or non-Syk-dependent pathways, to participate in immune responses. Non-aggregated, oligomeric polysaccharides tend to associate with SR receptors *via* a pathway similar to TLR4,

activating JAK-STAT signaling and participating in antioxidant, anti-aging, etc. biological processes.

Through comparison and screening, this paper describes the related activities and principles of polysaccharides on the basis of classical biological functions, and describes the relationship between the functions of polysaccharides as evidence of extension and functional cross-linking in the emerging activity research field.

Declaration of interest statement

All authors declared they have no conflict.

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