多糖调控巨噬细胞免疫应答机制的研究进展

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摘要 多糖是一类来源广泛且具有多种生物学活性的天然大分子物质, 能增强机体先天性和适应性免疫系统。近来研究发现, 生物活性多糖能通过巨噬细胞表面多种受体诱导复杂而又交叉的信号转导, 调控细胞功能和相关细胞因子的表达, 但对于相关的研究缺乏系统的归纳分析。该文综述了生物多糖对巨噬细胞的免疫调节作用、刺激信号通路以及多糖结构与受体关系, 旨在为相关领域的研究提供参考。

关键词 多糖; 巨噬细胞; 免疫; 受体; 信号通路

1 引言

天然多糖主要来源于微生物(细菌和真菌)、藻类和高等植物等的组织中, 具有复杂的结构并表现出多样的功能活性, 如免疫调节、抗肿瘤、抗炎症、抗病毒及抗氧化等, 是一种有效的生物应答调节剂(biological response modifier, BRM)[1]。先天免疫系统的调节, 是保护人体健康的重要策略[2], 也一直是多糖生物活性研究的热点。在机体的先天免疫体系中, 巨噬细胞是最有效的吞噬细胞, 其功能活性还在一定程度上影响适应性免疫系统。能够刺激巨噬细胞免疫应答的生物多糖主要可分为β-葡聚糖和高支化度的杂多糖两大类(部分见表1), 其中, β-葡聚糖主要来源于细胞壁或储备于真菌细胞质, 而杂多糖主要为高等植物的果胶物质[3]。Schepetkin等[4]对不同来源多糖对巨噬细胞的免疫调节作用加以分类综述, 并归纳了多糖激活巨噬细胞的潜在信号通路。之后, 谢燕霞等[5]报道了不同受体介导植物多糖对巨噬细胞的激活作用, 巫光宏等[6]也从蛋白激酶活化和TLR4 (Toll-like receptor 4)介导两种途径阐述了真菌类多糖刺激巨噬细胞的信号通路。然而, 目前对生物活性多糖激活巨噬细胞及相关机制的报道仍缺乏系统的归纳整合。本文对近年来有关多糖刺激巨噬细胞免疫应答机制的研究加以综述, 从细胞的免疫应答、信号转导途径、多糖与细胞受体的构效关系等方面进行系统地阐述, 以期为相关研究的开展提供参考。

2 多糖对巨噬细胞的免疫调节作用

2.1 对NO生成的影响

NO广泛参与了包括免疫应答在内的机体多系统的生理和病理过程, 其合成是巨噬细胞非特异性免疫涉及细胞溶解/细胞生长抑制的重要机制[7]。NO由一氧化氮合酶(nitricoxide synthase, NOS)催化L-精氨酸转变为L-瓜氨酸而生成[8]。诱导型NOS (iNOS)的合成则是对巨噬细胞中产生的特异性信号的应答反应, 不依赖胞质内钙离子[9]。多糖能刺激巨噬细胞的呼吸爆发, 催化活性氧簇(ROS)和NO的释放[10], 表1中列举的大多数活性多糖都能刺激巨噬细胞NO的生成和iNOS的表达。腹膜巨噬细胞释放活性氮介质只对IFN-γ产生应答, iNOS的诱导表达引发IFN-γ依赖性NO的产生[11-12]。对于巨噬细胞中iNOS基因的表达, IFN-γ刺激初级信号反应, 而多糖(如脂多糖或甘草多糖)或致炎(炎症前)细胞因子则刺激二级信号反应[13-15]。

2.2 对细胞因子分泌的影响

巨噬细胞能够极化为M1 (classically activated macrophage)和M2 (alternatively activated macrophage)[16]。M1细胞表现为促炎症反应, 维持Th1依赖性免疫反应, 产生炎症介质(如IL-1、IL-6、IL-12、NO、TNF-α), 对微生物或感染/变异细胞表现出较高的吞噬能力。M2细胞表现为抗炎症活性, 抑制Th1应答, 促进Th2应答, 释放出抗炎症因子(IL-10、

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表1 多糖对巨噬细胞的免疫调节作用

Table 1 Immunomodulatory effects of polysaccharides on macrophages

来源 Source	结构特征 Strusture feature	细胞类型 Macrophage type	剂量 Dose (μg/mL)	蛋白 Protein	内毒素 Endotoxin	作用 Effect	介导受体/通路 Mediated receptor/pathway	方法 Method
Acanthopanax senticosus[22]		MPM	3~100	—	×	↑ NO, iNOS, IL-1β, IL-6, TNF-α	TLR4/TLR2→MAPKs/NF-κB	A, C
Aloe vera[3]	50~10 000 kDa β-(1,4)-D-Man	MPM	100~500	—	×	↑ Migration, endocytosis, phagocytosis, cytotoxicity, MHC-II, NO, TNF-α	FcγR	
Angelica gigas[83]		RAW264.7	1~100	—	×	↑ iNOS	CD14/CR3→p38MAPK →NF-κB	A, C
Astragalus membranaceus[19]	3.5~1 580 kDa Rha, Xyl, Glc, Gal, Man, Fru	MPM, THP-1	100	×	×	↑ IL-1β, TNF-α	TLR4	A, B, C
Carthamus tinctorius[20]	>100 kDa Glc, Gla, Ara, Xyl, Rha,Man	MPM	0.000 1~100	<3%	×	↑ INF-γ, IL-12, TNF-α	TLR4→NF-κB, but not TLR2	
Cordyceps sinensis[105]	82 kDa Glc, Man, Gal	NR8383	6.25~100	<1%	—	↑ Phagocytosis	Acid phosphatase	A
Fucoidan[63]		MPM, RAW264.7	50	—	—	↑ NO, iNOS, iNOS promoter	SR→p38MAPK→AP-1, SR→NF-κB	A, C
Ganoderma lucidum[31-32]	585 kDa L-Fuc, D-Xyl D-Man, D-Gal, D-GlcNAc, D-Glc	MPM, THP-1	0.01~100	<6.5%	×	↑ IL-1β, IL-6, IL-12, IFN-γ, TNF-α,	GM-CSF, G-CSF, M-CSF TLR4→PTK (Src)→PLCγ1 →PKC→MEK1→ERK, TLR4→PTK (Src)→Rac1 →PAK→p38, TLR4→ PTK→Rac1→PAK→JNK, ribosomal protein S7, transcriptional coactivator	A, B, C, D
Opuntia polyacantha[10]	168~733 kDa Gal, Xyl, Ara, Rha	THP-1, J774.A1	25~800	—	×	↑ NO, IL-6, TNF-α	NF-κB	
Paenibacillus polymyxa[54]	β-glucans	RAW264.7	3~300	—	—	↑ NO	MAPKs, NF-κB, AP1	A
Platycodon grandiflorum[21,26-27]	Inulin-type polyfructose	RAW264.7	1~100	—	×	↑ NO, iNOS, TNF-α	TLR4→MAPKs→AP-1, TLR4→ NF-κB, CD14, CD11b	A, C
Polyporus umbellatus [23,25]	160 kDa D-Glc, D-Gal, D-Man	MPM	12.5~100	—	<0.4 μg/g	↑ NO, IL-1β, TNF-α	TLR4→NF-κB, but not TLR2 and CR3	A, C
Rheum tanguticum[106]	60~80 kDa Man, Ara, Glc	RPM	200 mg/kg	—	—	↑ IFN-γ (*in vivo*)	MR	B
Silene vulgaris[89]	Acidic arabinogalactan	RPM	15 150	—	—	↑ Phagocytosis	Ca^{2+}-dependent myeloperoxidase	
Streptococcus pnemoniae[36]	D-GlcUA, D-Glc, L-Rha	MPM	5~50	×	—	↑ NO, TNF-α, cytotoxicity	CD14-dependent, TLR2	A
Trametes versicolor[24]	Glc, Man	J774.A1, MPM	62.5~1 000	—	×	↑ IL-6, TNF-α.	TLR4, but not dectin1	A, C

×: 未检出或可忽略; — : 未检测; ↑: 增强或促进。MPM: 小鼠腹腔巨噬细胞; RPM: 大鼠腹腔巨噬细胞; TLR2/4: Toll样受体2/4; SR: 清道夫受体; MR:甘露糖受体; CR-3: 补体受体3; MAPK: 细胞分裂素活化蛋白激酶; AP-1: 活化剂蛋白-1; SAPK/JNK: 应激活化蛋白激酶/c-Jun氨基端激酶; MHC-II: 主要组织相容性复合物II; PKC: 蛋白激酶C; PTK: 蛋白酪氨酸激酶。A: 已知受体的抗体或已知激酶的抑制剂的阻断作用; B: 已知受体多糖的竞争结合作用; C: 特定受体突变体和野生体的作用比较; D: 多糖作用受体的分离鉴定。

×: not detected or negligible; — : not tested; ↑: increased. MPM: mouse peritoneal macrophage; RPM: rat peritoneal macrophage; TLR2/4: Toll-like receptor-2/4; SR: scavenger receptor; MR: mannose receptor; CR-3: complement receptor-3; MAPK: mitogen-activated protein kinases; AP-1: activator protein-1; SAPK/JNK: stress-activated protein kinases/jun N-terminal kinase; MHC-II: major histocompability complex-II; PKC: protien kinase C; PTK: protein tyrosine kinase. A: inhibition of receptor/kinase by specific antibody/inhibitor; B: competitive binding of receptor by reported saccharide ligand; C: resulting comparision between definited mutant and its wild-type; D: affinity adsorption and identification of polysaccharide's receptor.

IL-1受体抗体、TGF-β), 分泌精氨酸酶1, 产生Th2细胞化学引诱物[16]。目前, 文献报道的大多数生物活性多糖表现为促进巨噬细胞M1极化[3,10,16,19-27], 可以刺激巨噬细胞IL-1、IL-6、IL-12和/或TNF-α的表达, 促进Th1导向的适应性免疫应答, 抑制Th2应答。醋酸杆菌属β-(1→4)-D-葡聚糖能在体外刺激巨噬细胞IL-12的分泌, 在小鼠体内通过诱导IgE生成抑制Th2细胞免疫应答, 且能增强对单核细胞增多性李司忒(氏)菌响应的Th1反应[17-18]。此外, M1巨噬细胞通过iNOS代谢精氨酸为NO, 而M2巨噬细胞通过精氨酸酶将L-精氨酸转变为尿素和鸟氨酸, 故这类多糖还可能降低细胞核精氨酸酶活性抑制巨噬细胞的M2极化。与之相反, 新型隐球菌多糖能通过激活M2巨噬细胞而诱导Th2反应[28]。桧属多糖不仅能促进炎症介质的表达, 还能增强抗炎症因子IL-10的分泌[29], 潜在的作用机制还不明确。

人参多糖S-IIA能促进THP-1细胞中IL-8的分泌, 且伴随*IL-8* mRNA的增量表达。同时还能增强IL-1β和TNF-α诱导的IL-8表达。S-IIA可能先诱导IL-1的增量表达, 再协同刺激IL-8的生成[30]。此外, 灵芝多糖还能诱导小鼠腹腔巨噬细胞和THP-1细胞中IFN-γ、GM-CSF、G-CSF和M-CSF等细胞因子的表达[31-32]。

2.3 对细胞受体表达的影响

人参根部提取的酸性多糖能增加小鼠腹腔巨噬细胞CD14的表达, 同时降低CR3的水平[33]。而从其叶部提取的含鼠李半乳糖醛酸II的果胶则能上调巨噬细胞Fc-受体的水平[34]。同样, 柴胡属果胶能通过Ca^{2+}/钙调节蛋白依赖性通路刺激腹腔巨噬细胞Fc-受体的表达, 而不涉及蛋白激酶A或蛋白激酶C通路[35]。芦荟多糖能同时上调小鼠腹腔巨噬细胞MHC-II和Fcγ-受体的表达[3]。

2.4 对其他功能的影响

BALB/c小鼠通过腹腔注射芦荟多糖和酵母多糖能够显著增加巨噬细胞向腹膜腔的迁移, 刺激4天后分离得到的腹腔巨噬细胞数增加了约5倍, 与4%硫胶质肉汁的作用相当[3]。荚膜多糖[36]和芦荟多糖[3]能够分别在体外和体内增强巨噬细胞吞噬作用及对肿瘤靶细胞的毒性。白及多糖经N, N'-carbonyldiimidazole (CDI)/ethylenediamine修饰后, 产生核苷酸亲和力, 能有效结合DNA形成纳米级的紧密而又稳定的复合体, 促进寡聚脱氧核苷酸的转染, 并可能通过甘露糖受体(mannose receptor, MR)和β-葡聚糖受体来介导寡聚脱氧核苷酸的定向呈递[37]。值得注意的是, 还有个别多糖对巨噬细胞活性表现出抑制的作用, 如雷公藤多糖能抑制THP-1细胞中TNF-α的生成和黏附分子(CD11c、CD18、CD14和CD54)的表达[38], 以及川续断蛋白多糖能抑制巨噬细胞的吞噬功能(抑制因子为结合蛋白)[39]。

3 多糖刺激巨噬细胞免疫应答的信号通路

免疫活性多糖的报道逐年增加, 越来越多的研究转入对多糖免疫调节作用分子机制的探讨。细胞中识别并接受活性多糖分子的蛋白包括模式识别受体和原浆蛋白[1]。多糖能通过与各类模式识别受体结合, 引发胞内一系列的信号级联反应, 诱导转录激活和炎症相关因子的表达[4]。目前关于多糖刺激巨噬细胞信号通路的研究方法主要可归纳为4种: 通过已知受体的抗体或已知激酶的抑制剂来阻断细胞信号通路, 从而推测该受体或激酶是否参与多糖的免疫调控过程; 通过已知受体多糖的竞争结合作用推测另外一种多糖是否也是通过该受体介导活性; 特定受体突变体和野生体的作用比较; 多糖作用受体的分离鉴定(表1)。

3.1 TLR2/4介导

目前, 共发现有13种TLRs, 其中TLR1/2/4/5/6/10分布于巨噬细胞表面, TLR7-9/11分布于其细胞间隙[40-41]。但只有TLR2/4能结合糖基配体, 其胞内接合体主要为含有Toll/IL-1同源性受体(TIR)衔接蛋白的髓样分化因子(myeloid differentiation factor 88, MyD88)、MAL (MyD88 adaptor-like)、TRIF (TIR-domain-containing adapter-inducing interferon-β)和TRAM (TRIF-related adaptor molecule)[41]。TLR2/4识别保守的病原相关分子模式(pathogen associated mo1ecular pattems, PAMPs), 刺激细胞因子生成, 上调吞噬细胞中共刺激分子表达, 在先天性免疫与获得性免疫间建立一个紧密相连的桥梁。研究发现, 多糖刺激巨噬细胞免疫应答均涉及TLR4下游MAPKs (mitogen-activated protein kinase)和NF-κB的活化, 而这两条途径相对独立[20-23,25-27]。

3.1.1 NF-κB信号转导途径　由均一或杂的Rel族蛋白通过二聚作用形成的NF-κB, 在静息状态下与抑制蛋白IκB结合, 并在细胞质中呈惰性。NF-κB转导的细胞信号途径可分为MyD88依赖性和非MyD88依

赖性(即TRIF/TRAM途径)途径(图1)。MyD88依赖性途径表现为: (1) 多糖直接与TLR4结合[19,32], 或借助CD14、RP105或MD-2等分子作为桥梁间接与TLR4结合[42-44]; (2) TLR4通过TIR与衔接蛋白MyD88结合, MyD88再由死亡结构域与丝氨酸/苏氨酸激酶IRAK结合; (3) 结合后的IRAK通过补充衔接蛋白TRAF6激活IκB激酶复合体IKKc (IKKα/IKKβ/IKKγ)催化IκB分子中两个特定丝氨酸磷酸化反应; (4) 磷酸化后的IκB被遍在蛋白化, 并触发26S蛋白酶体的降解作用; (5) 游离出的早期活化NF-κB进入细胞核内, 结合特定基因的κB序列启动基因转录, 并诱导炎症因子的表达[4,45-48]。而TRIF/TRAM途径一方面通过刺激干扰素调节因子3 (IRF3)调节相应基因转录, 另一方面通过TRAF6激活NF-κB并诱导IFN-β的表达[4,47-49]。细胞经刺激后, 随着IκB的磷酸化和降解, 会重新合成新的IκB蛋白进入细胞核, 再次结合钝化DNA上游离出的NF-κB[49]。

3.1.2 MAPKs信号转导途径 MAPKs是一类高度保守的丝/苏氨酸蛋白激酶, 是与细胞增殖、分化或凋亡密切相关的胞内信号转导酶类。哺乳动物细胞中的MAPKs主要有ERKs (extracellular signal-regulated kinase)、JNKs/SAPKs (c-Jun NH_2-terminal kinase/stress-activated protein kinase)和p38MAPK三种亚类, 其上游激酶分别是MEK1/MEK2、MKK4/MKK7和MKK3/MKK6。SAPK/JNK和p38MAPK是应激诱导基因表达的重要调节剂, 致炎细胞因子所诱导的基因表达大部分由SAPK/JNK和p38MAPK介导(ERK1/2未参与LPS刺激RAW264.7细胞中NOS的表达)[50-53]。SAPK/JNK和p38MAPK是桔梗多糖诱导RAW264.7细胞中iNOS和TNF-α表达的重要调节剂, 而ERKs的上游激酶MEK1仅涉及TNF-α的表达[27]。但ERKs、SAPK/JNK和p38MAPK转导的通路对灵芝多糖和多粘类芽孢杆菌多糖刺激的巨噬细胞免疫应答有相近的贡献[31,54]。生物活性多糖经TLR4诱导MAPKs的磷酸化, 通过增强AP-1的DNA结合活力促进基因转录, 调节多种炎症介质(iNOS、TNF-α、IL-1β)的基因表达[22,27,54], 其中JunB和Fos-related antigen 1 (Fra-1)是涉及AP-1活化的主要成分, 可能不涉及STAT1和载体DNA[27,54]。此外, Chen等[31]推测灵芝多糖对巨噬细胞ERKs、JNKs和p38MAPK的激活可能受上游PTK(Src)、PKC和PTK的影响。

红花多糖能够通过TLR4诱导多种类型巨噬细胞中IκBα的快速降解, 激活转录因子NF-κB, 而TLR2不涉及其信号转导过程[20]。在*TLR4*基因缺失

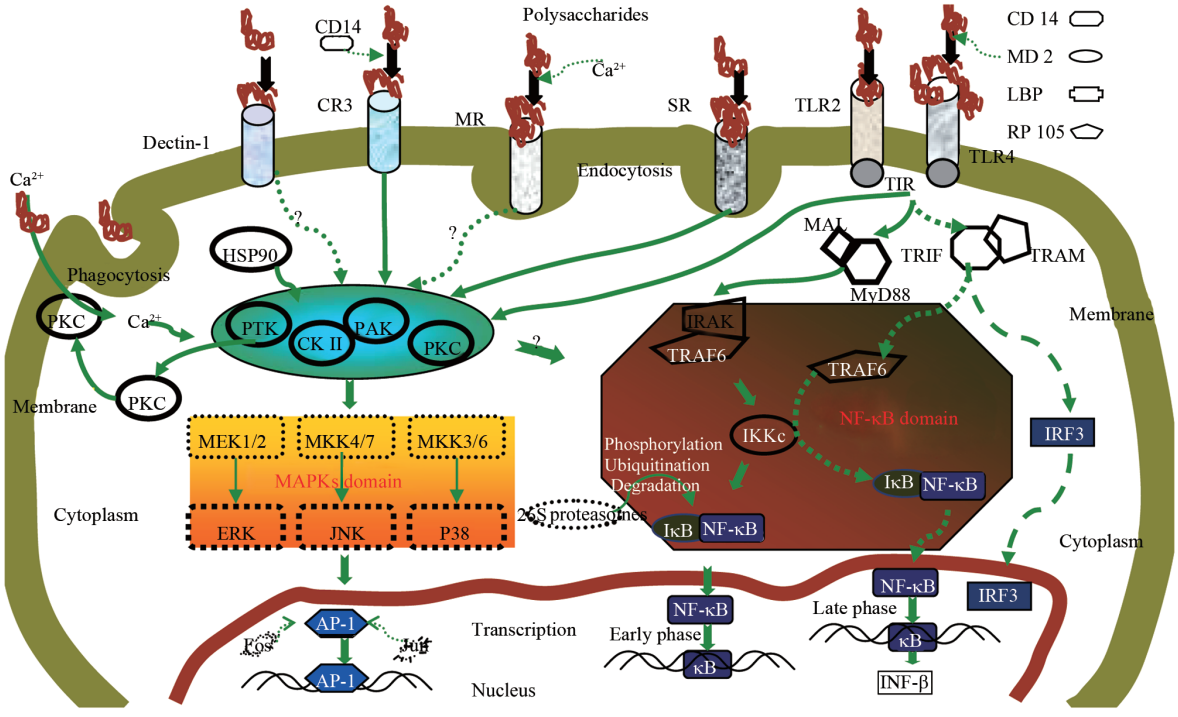

图1 多糖刺激巨噬细胞免疫应答的信号通路(根据参考文献[4]修改)

Fig.1 The signaling pathways of macrophage stimulated by polysaccharides (modified from reference [4])

小鼠免疫细胞中, TLR2可能与其他TLRs形成二聚体或低聚物, 转导刺五加多糖的刺激信号。TLR2/4抗体可能通过空间位阻等机制干扰TLRs二聚体或低聚物的形成, 从而阻断多糖的刺激信号[22]。猪苓多糖对巨噬细胞的刺激作用也与TLR4、TLR2和CR3等有密切关联[23]。TLRs介导一系列的免疫应答反应, 但其信号通路的过度活化可能导致组织损伤, 产生炎症和自身免疫性疾病, 如Crohn's病、炎性肠疾病和TLR4依赖性败血症性休克[55-56]。

3.2 SR介导

SR是具有多区域和多配位子的受体, 能够识别内源性配体维持组织内环境稳定, 识别外源性配体发挥防御性免疫[57]。根据结构特点, SRs可分为A型SRs (SR-A1、SR-A2和MARCO)、B型SRs (SR-B1和CD36)和果蝇C型(*Drosophila* Class C SR)[58], 而它们的共同点是能够结合化学改性的低密度脂蛋白[59]。研究发现, 由三个糖基化蛋白链构成的多区域性的三聚体SR-A具有广泛的配体选择性, 可以与甲基化牛血清白蛋白(mBSA)、双链DNA分子、双链RNA分子、脂膜酸和其他多种阴离子化合物结合, 主要通过胞吞作用依赖性诱导巨噬细胞不同模式的基因表达[59-62]。墨角藻聚糖是典型的SR-A糖配体, 能够通过SR-A介导PKC、PAK (p21-activated kinase)和MAPKs的活化, 诱导iNOS启动子的表达和NO的生成, 以及引发炎症因子的分泌和尿激酶型纤维蛋白酶原激活剂的表达[63-65]。酪氨酸磷酸化和MAPKs的激活则是SR-A介导的信号传导级联的关键单元[66], 可能与下游NF-κB和AP-1调控基因表达有关。然而, Kim等[67]通过对比墨角藻聚糖刺激*SR-A*缺陷型和其野生型小鼠巨噬细胞中TNF-α表达和含酪氨酸蛋白的磷酸化作用发现, SR-A并未参与信号转导, 而产生的免疫应答很大程度上是由CD14介导的。也有文献报道SR-B能部分介导墨角藻聚糖的免疫刺激作用[68]。当*SR-A*缺陷时, 墨角藻聚糖在特定的环境中与其他辅助因子结合, 通过其它膜受体协同刺激细胞并引发胞内信号级联反应, 或通过胞内吞作用触发免疫信号, 从而弥补SR-A介导的信号途径。

热休克蛋白90 (HSP90)是ATP依赖性肽链分子装配陪伴蛋白, 它能通过影响酪氨酸激酶v-Src和Lck、丝氨酸/苏氨酸激酶Raf-1和酪蛋白激酶II等多种信号分子活性调节p38MAPK和NF-κB通路信号的转导[69]。Nakamura等[63]也证实HSP90处于p38MAPK的上游, 当巨噬细胞体系中加入HSP90抑制剂后, NO生成和iNOS启动因子活性都受到抑制。 除墨角藻聚糖外, β-葡聚糖能够体内增强大鼠巨噬细胞SR对内毒素的清除作用, 抑制TNF的产生[70]。

3.3 甘露糖受体介导

作为C型凝集素样受体家族重要成员的MR, 是主要由巨噬细胞表达的一种跨膜糖蛋白, 能够经细胞膜实现快速内吞作用, 通过披网格蛋白小泡呈递抗原至胞内体系[71]。MR受体能同时介导糖结合/包裹颗粒的吞噬作用和可溶性糖配体的内吞作用[72], 这一特性与阳离子的存在有密切的联系, 具体表现有: (1) 在EDTA (螯合的二价阳离子)存在的条件下, MR还能介导巨噬细胞贴壁功能[73]; (2) MR通过Ca^{2+}依赖性优先结合含有末端甘露糖残基、岩藻糖残基或N-乙酰基葡萄糖残基的糖基配体[74]; (3) 含甘露糖残基的阳离子聚合物(如甘露糖基化的聚赖氨酸和壳聚糖)能作为载体呈递基因至巨噬细胞中[75-76], 而阳离子化的白及多糖也可能通过MR和β-葡聚糖受体来实现寡聚脱氧核苷酸的定向呈递[37]。含多个重复配位体的多糖可与MR在细胞表面上形成交联, 并刺激细胞内吞、免疫应答、吞噬作用、癌症转移和调节血清蛋白平衡[77-78]。含有近50%甘露糖的当归多糖和含有N-乙酰葡糖胺残基的大黄多糖能通过MR介导大鼠腹腔巨噬细胞TNF-α的分泌, 而对IL-4的表达无影响[79]。此外, 多糖与MR结合也可能干扰抗原的内吞作用[80]。

3.4 其他受体介导

CR3 (CD11b/CD18)是由α和β两条肽链以非共价键结合而构成的异二聚体糖蛋白, 能识别细胞间粘附分子-1 (ICAM-1)、fixed iC3b和β-葡聚糖[81], 并且与二价阳离子依赖性的巨噬细胞贴壁功能有密切联系[82]。当归多糖能通过CR3和CD14刺激RAW264.7细胞中p38MAPK的磷酸化, 诱导NF-κB/Rel的活化, 从而调控相关基因的表达[83]。桑黄多糖对巨噬细胞NO生成和细胞表面分子表达的刺激作用也是由CR3介导的[84]。含蛋白的茯苓杂甘露聚糖通过CR3、CD14和TLR4经p38MAPK途径刺激小鼠巨噬细胞中NF-κB/Rel的激活和iNOS的表达[85]。

B-葡聚糖受体/dectin-1能特异性结合β-(1→3)-D-葡聚糖[86], β-葡聚糖对多糖受体的亲和力大小依次为: 小核菌葡萄聚糖>裂殖菌多糖>昆布多糖>磷酸

化葡聚糖>硫酸化葡聚糖[4]。小核菌葡萄聚糖通过dectin-1介导J774A.1细胞中TNF-α的表达, 而不受TLR4影响[24]。

肺炎链球菌多糖可能通过CD14依赖性途径促进巨噬细胞NO生成和TNF-α的表达[87]。而CD14和CD11b可能都是桔梗多糖刺激巨噬细胞免疫应答的细胞结合位点, 其抗体都能显著降低多糖诱导的NO生成[21]。血脂多糖结合蛋白(LBP)和可溶性CD14与桔梗多糖刺激巨噬细胞中NO的生成有关[26]。

3.5 Ca^{2+}调控

酵母多糖能够诱导NR8383肺泡巨噬细胞中Ca^{2+}内流, 当PKC活性经Caiphostin和Bisindolymalcimide抑制后, Ca^{2+}内流显著降低, 且多糖与PKC激活剂表现出相似的作用。酵母多糖的刺激作用依赖于PTK活性, 促进PKC从细胞质向细胞膜转移, 从而引起Ca^{2+}内流[88]。麦瓶草果胶能够增强大鼠腹腔巨噬细胞的吞噬功能及髓过氧化酶活性, 且在一定程度上表现出Ca^{2+}依赖性, 但却对二价阳离子依赖性的CR3和SR介导的巨噬细胞贴壁作用无影响[73,82,89]。弱酸性的麦瓶草阿拉伯半乳聚糖C1在无钙溶液环境下能刺激巨噬细胞溶酶体的分泌, 且钙依赖性凝集素(甘露糖和半乳糖的特异性受体)未涉及C1的刺激作用, 果胶C1与细胞受体的结合可能依赖胞外钙离子[89]。

4 多糖结构与受体的关系

多糖凭借特定的结构特征与巨噬细胞受体结合, 进而触发一系列的免疫应答反应。结构上的差异可能主要表现为不同的受体亲和力。β-葡聚糖(包括小核菌葡萄聚糖、裂殖菌多糖和昆布多糖等)的大分子组分具有相对较高的受体亲和力, 呈现出较强的免疫刺激活性[4]。从桧、仙人掌、猪苓、芦荟、艾菊和苦艾等植物组织中分离得到的不同多糖组分, 其巨噬细胞免疫刺激活性也与分子量呈现一定的正相关性[10,12,29,90-93]。高分子量多糖表现出更高的免疫活性, 可能部分依赖于能交联结合受体或其它膜靶点的高度重复结构特点。而葡聚糖含有两个侧链分支可能是最适的巨噬细胞受体识别结构, 主链中含有过多的葡萄糖残基或较多的侧链分支会阻碍聚合物形成适当的折叠[94-95]。

研究发现, 鼠李半乳糖醛酸II型结构区域可能是麦瓶草多糖[89]和婆婆纳多糖[96]调节巨噬细胞免疫活性的关键, 且该结构区域中含有同为LPS组成的2-酮-3-脱氧辛酸[97]。故鼠李半乳糖醛酸II可能是TLR4受体结合多糖的特异性结构区域。此外, 鼠李半乳糖醛酸II的阿拉伯半乳聚糖侧链对于婆婆纳多糖的免疫调节活性也不可或缺[96]。而阿拉伯半乳聚糖II型结构区域(高支化度且主要由β-(1,3)-半乳聚糖主链和含有阿拉伯糖和半乳糖的侧链构成)可能是果胶刺激巨噬细胞活性的重要单元[29,93,96]。

5 小结

活性多糖刺激巨噬细胞内的信号转导主要涉及MAPKs区和NF-κB区的激活。MAPKs区主要受PTK、PKC和PAK等激酶刺激活化, 而NF-κB区主要由IKKc和TRAF6调控。这些胞内激酶是多糖刺激信号转导途径中的信使, 对于MAPKs区上游激酶是否参与NF-κB的激活尚不确定。TLR2/4、CR3和SR能介导细胞内激酶对MAPKs的活化, 而MR和Dectin-1介导免疫调节的潜在作用机制鲜见报道, 可能仍与某些蛋白激酶有关。此外, 生物多糖通过巨噬细胞激活的方式发挥其免疫调节作用, 相关的作用机制的解析已到达分子水平。但相比多糖本身的认知程度却有所欠缺, 远不及蛋白质和核酸, 多糖的构效关系一直是研究的瓶颈。

生物多糖的抗肿瘤和免疫调节活性一直是药理学研究的热点, 它们除了表现出优异的生物活性外, 来源广泛和对机体低毒害等特点更是其他化学合成药物所不能媲美的。许多多糖的毒理学实验都未表现出任何毒副作用[19,54]。目前, 香菇多糖、云芝糖肽、裂殖菌多糖和一些蛋白多糖已经用于临床肿瘤免疫治疗[1]。而且临床试验证实这些活性多糖能延长癌症患者的寿命, 改善癌症患者的身体状况[98-103]。多糖也可以作为理想的抗肿瘤因子载体, 通过吞噬/内吞作用介导巨噬细胞相关的免疫治疗[104]。生物多糖作为免疫调节剂有着广阔的发展和临床应用前景。随着系统化研究的深入, 多糖免疫调节作用的机理会得到更加明确的阐释, 越来越多的活性多糖会被开发利用, 并以保健品和药品的形式融入人们的生活中。

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Immunostimulating Mechanisms of Polysaccharides on Macrophages

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Abstract　As widely distributed natural macromolecules, polysaccharides exhibit a number of biologic activities, especially immunopromoting effects on immune system. Bioactive polysaccharides can stimulate multiple signaling pathways via macrophage receptors followed by improving the secretion of cytokines, and finally enhance the cellular immune function. The present review focuses on the immunostimulating effects, potential mechanisms and structure-receptor relationship of polysaccharides on macrophages, which purposes to provide the basic information of polysaccharide-induced macrophage activation for related researches.

Key words　polysaccharide; macrophage; immune; receptor; signaling pathway

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