巨噬细胞真菌多糖受体研究进展

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摘要 大型真菌多糖能够调节免疫应答、细胞代谢、细胞癌变等多项生命活动。大型真菌多糖不仅能影响免疫器官, 还能激活巨噬细胞、淋巴细胞、树突状细胞等免疫细胞。研究表明, 巨噬细胞表面存在特异性真菌多糖受体, 该类受体能够与真菌多糖结合, 激活巨噬细胞, 发生免疫反应。目前已发现的真菌多糖受体包括Toll样受体(Toll-like receptors, TLRs)、树突状细胞相关C型凝集素-1(dendritic cell-associated C-type lectin-1, Dectin-1)、甘露糖受体和补体受体3等。在免疫应答的最初阶段, 巨噬细胞通过识别外部真菌多糖配体被活化, 启动胞内的信号转导途径, 最终发生吞噬能力增强, 促进一氧化氮(nitrogen monoxide, NO)产生和细胞因子分泌等一系列免疫反应。然而, 真菌多糖刺激巨噬细胞表面受体作用机制的研究有待进一步深入, 这些研究将帮助我们更好地理解免疫反应精细调控机制, 寻找新型天然免疫调节剂。

关键词 巨噬细胞; 真菌多糖; 多糖受体; 免疫调节

Progress on Macrophages Receptors of Fungus Polysaccharide

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Abstract The large edible fungus polysaccharide is closely related to the immune response, cell metabolism, cell carcinogenesis, and so on. It can not only affect the immune organs, but also activate the immune cells, such as macrophages, lymphocytes, dendritic cells and so on. There is a specific receptor on the surface of macrophages, which can bind to fungus polysaccharides, activate macrophages, and produce immune responses. It has been found that the fungus polysaccharide receptors including Toll-like receptors (TLRs), dendritic cell-associated C-type lectin-1 (Dectin-1), mannose receptor, complement receptor 3 and so on. The activation of intracellular signal transduction pathways by the recognition of external fungus polysaccharide ligands at the initial stage of the immune response, the eventual enhancement of phagocytosis, the promotion of NO production and cytokine secretion and a series of immune responses. However, the study of the mechanism of the effect of fungal polysaccharides on macrophage surface receptors needs to be further studied. These studies will help us to better understand the fine regulation of immune response mechanisms and find a new type of natural immune modulators.

Keywords macrophages; fungi polysaccharide; polysaccharide receptors; immunomodulatory

多糖(polysaccharide)是一种大分子活性物质, 具有多种生物活性和功能, 除了主要的免疫调节活性外, 还具有抗氧化、抗肿瘤、抑菌等作用。许多研究表明, 多糖能够有效提高机体免疫力[1]。多糖

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是由多个单糖构成的糖类物质, 这些单糖通过糖苷键连接在一起, 形成直链或者有分支的长链[2]。糖类是四大类生物大分子之一, 与蛋白质、核酸和脂质共同组成生命体的分子基础, 其中多糖具有种类众多、来源广泛、结构复杂等特点[3]。许多关于多糖免疫调节作用的研究表明, 多糖可以通过刺激巨噬细胞(macrophages, MΦ)表面受体, 如Toll样受体4(Toll-like receptors 4, TLR4)、Toll样受体2、甘露糖受体(mannose receptor, MR)、树突状细胞相关C型凝集素-1(dendritic cell-associated C-type lectin-1, Dectin-1)和补体受体3(complement receptor 3, CR3)等激活巨噬细胞, 引起胞内信号转导, 产生相应免疫反应。被激活的巨噬细胞通过分泌一氧化氮(nitrogen monoxide, NO)及细胞因子, 如肿瘤坏死因子-α(tumor necrosis facter-α, TNF-α)、白介素(interleukin, IL)等进一步调节机体免疫, 实现免疫功能[4]。

1 真菌多糖免疫调节概况

多糖因其生物活性作用已成为食品、生命和医药等科学领域研究的热点之一[5-7]。研究表明, 多糖广泛的分布在微生物和植物的细胞壁及动物的细胞膜中, 可分为真菌多糖、细菌多糖、植物多糖和动物多糖[8]。大量研究证实, 真菌多糖与细胞代谢、病毒感染、免疫应答、细胞癌变等密切相关, 其中免疫调节是其最主要的作用[9]。当机体处于正常生理情况下, 由先天性免疫和适应性免疫共同发挥免疫作用, 调节机体的生理功能, 使其保持在相对稳定的状态[10]。真菌多糖对两种免疫都有调节作用, 多糖不仅能影响免疫器官, 还能激活巨噬细胞、T淋巴细胞、B淋巴细胞、NK细胞和树突状细胞等免疫细胞[11]。真菌多糖能够提高巨噬细胞吞噬能力, 刺激NO生成, 并且通过引起胞内信号通路变化促进免疫因子分泌, 从而增强免疫功能[12]。大型真菌多糖即从大型肉质或胶质子实体真菌中提取的多糖, 表1主要针对近年来研究发现的大型真菌多糖对巨噬细胞的免疫调节作用进行概述。

关于真菌多糖如何激活巨噬细胞并引起一系列免疫反应, 有研究已表明, 巨噬细胞表面存在特异性真菌多糖受体, 该类受体能够与真菌多糖结合, 引起胞内各种信号转导途径发生变化, 从而促进细胞因子或抗体的生成[4]。

2 巨噬细胞真菌多糖受体

真菌多糖结构复杂且具有多变性, 单糖组成、糖苷键、分子量和分支化程度等均可以通过影响多糖结构继而影响多糖活性。所以, 确定真菌多糖的作用机理和明确其信号转导途径存在较大困难[24]。从目前的研究推断来看, 真菌多糖对巨噬细胞的活化是通过识别其表面真菌多糖特异性受体并与之结合而实现的。在机体做出免疫应答的初始阶段, 这些受体识别到其外部配体后被活化, 启动巨噬细胞内的信号转导途径, 最终发生一系列的免疫反应[25]。真菌多糖通过对免疫功能的调节, 可以减缓某些免疫相关疾病, 如慢性炎症、感染、过敏等, 同时对肿瘤的发生和发展也有一定的抑制作用[26]。目前已发

表1 大型真菌多糖对巨噬细胞的免疫调节作用

Table 1 Immune regulation of large edible fungi polysaccharides on macrophages

多糖 Polysaccharide	对巨噬细胞的影响 Effects on macrophages	参考文献 Reference
Auricularia auricular polysaccharide	Phagocytic enhancement	[13]
Sagittaria sagittifolia polysaccharide	Improve macrophage function	[14]
Ganoderma applanatum polysaccharides	Stimulate production of TNF-α	[15]
Collybia albuminosa polysaccharides	Increased phagocytic rate and phagocytic index	[16]
Cordyceps militaris polysaccharides	Promote NO production	[17]
Agaricus blazei Murrill polysaccharides	Promote the proliferation of mouse macrophages and the release of NO and iNOS	[18]
Coprinus comatus polysaccharides	Produce NO by concentration dependent manner	[19]
Auricularia polytricha polysaccharides	Stimulate production of TNF-α, IL-1 and IL-6	[20]
Cordyceps sinensis polysaccharides	Induce TNF-α production	[21]
Trametes versicolor polysaccharides	Increase the amount of cytokines such as TNF-α and IL-1	[22]
Flammulina velutipes polysaccharides	Synthesis and secretion of TNF-α increase	[23]

现的真菌多糖受体包括TLRs、CR3、Dectin-1、MR等[27]。

2.1　Toll样受体(TLRs)

TLRs是一种跨膜受体, 由介导识别病原体相关分子模式(pathogen-associated molecula pathogen-associated molecular patterns, PAMPs)的I型跨膜蛋白、跨膜结构域和胞质Toll白细胞介素(IL)-1受体结构域三部分共同组成。TLRs主要表达于巨噬细胞和树突状细胞等吞噬细胞[28]。巨噬细胞主要存在TLR2和TLR4, 与炎症及免疫调节关系最为密切, 其配体包括多糖、糖蛋白、脂蛋白等。在巨噬细胞上TLRs与配体结合后, 通过激活与受体相应的信号通路, 诱导产生大量的活性因子从而导致炎症和免疫反应的发生[29]。

Li等[30]研究发现, 猪苓多糖(*Polyporus umbellatus* polysaccharides, PPS)能够显著上调巨噬细胞NO产生量和细胞因子的分泌量, 使用TLR4功能性抗体处理巨噬细胞, 则PPS介导的TNF-α和IL-1β的产生被显著抑制, 而TLR2功能性抗体不具有此作用, 这说明PPS通过TLR4/NF-κB(nuclear factor-κB)信号通路发挥作用。但使用蛹虫草发酵液多糖刺激巨噬细胞发现, TLR4和TLR2均可以被激活, 进而活化下游MAPKs(mitogen-activated protein kinases)/NF-κB信号通路诱导NO的产生[31]。Yu等[32]发现, 黑灵芝多糖通过TLR4/ROS(reactive oxygen species)/PI3K(phosphatidylinositol 3 kinase)/Akt(protein kinase B)/MAPKs/NF-κB信号通路激活巨噬细胞, 促进TNF-α的产生。白灵菇多糖可以明显改善巨噬细胞吞噬功能, 刺激细胞因子TNF-α、IL-6和IL-10的产生及其mRNA的表达[33]。Zhang等[34]发现, 黑灵芝多糖通过TLR4/MAPKs/NF-κB通路启动细胞因子TNF-α和IL-1β的释放, 这与Yu等[32]的发现相似。综上所述, 真菌多糖可以增强巨噬细胞吞噬功能, 并通过激活TLR4、TLR2/MAPKs/NF-κB信号通路促进细胞因子的释放及上调其mRNA的水平。

2.2　补体受体3(CR3)

CR3(CD11b/CD18)属于白细胞整合蛋白β2家族中的一员, 巨噬细胞膜上模式识别受体之一, 介导细胞黏附和信号转导[35]。CR3是一种高度糖基化的异二聚体, 其CD11b亚基中存在一个可以结合不同配体的共同结合位点[36]。巨噬细胞CR3的配体为补体和β-葡聚糖, 与配体的结合引起胞外域构象变化并通过细胞膜传输胞外信号, 激活相应的信号转导通路, 导致肌动蛋白重塑, 吞噬颗粒脱落, 并使细胞因子的产生发生变化[37]。

在通常情况下, CR3在活化巨噬细胞信号转导通路中与CD14协同并和其他多种受体(如Dectin-1、TLRs)形成信号转导复合体, 进行跨膜信号的转导[38]。多糖的生物活性主要来自于其分支(1,3)-β-D-葡聚糖, 其可能是通过CR3受体结合的多糖[39]。Zheng等[40]已经证实, 酵母葡聚糖为线性β-(1,3)-葡聚糖, 它通过CR3激活巨噬细胞, 诱导TNF-α和单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)的释放以及下游信号通路NF-κB p65的核易位。免疫实验发现, 竹荪多糖上调巨噬细胞NO、TNF-α和IL-1的分泌。进一步实验证明, CR3为竹荪多糖的膜受体之一, 并且PI3K/Akt/MAPK/NF-κB信号通路参与到这一免疫反应中[41]。Wang等[42]发现, 紫芝多糖通过与CR3等模式识别受体结合激活巨噬细胞, 同时开启下游信号通路包括脾脏酪氨酸激酶(spleen tyrosine kinase, Syk)、MAPKs和NF-κB, 导致TNF-α的产生。

2.3　甘露糖受体(MR)

MR也是巨噬细胞上一种跨膜受体, 其功能的发挥是钙依赖性的。MR在胞外有三个结构域, 分别为富含亮氨酸的CR结构域、II型纤维连接蛋白结构域、八个串连的C型凝集素样结构域, 膜上存在跨膜结构域, 胞内含有短尾巴结构域。MR具有内外源性配体双重识别功能, 三个胞外结构域能够识别特异性糖组分及蛋白并与之结合, 识别的多糖分子中含有甘露糖和岩藻糖残基[43-45], 其中II型纤维连接蛋白结构域具有结合I、II、III和IV型胶原蛋白的特性[46]。

MR被认为是一个非典型的模式识别受体, 在巨噬细胞参与的免疫反应中, MR的作用包括介导病原菌的吞噬、抗原的递呈和转运、激活细胞内MR下游信号通路、诱导NO及多种细胞因子的产生[47]。石耳中分离的四种多糖组分由葡萄糖、半乳糖和甘露糖以不同摩尔比组成, 四种多糖均通过MR介导对巨噬细胞吞噬活性及NO产生以剂量依赖方式产生影响[48]。Wang等[33]从白灵菇中分离出的多糖含有甘露糖组分, 这在一定程度上说明MR在白灵菇多糖强烈刺激巨噬细胞细胞因子产生中起到了重要的作用。Li等[49]进行的黑灵芝多糖的巨噬细胞免疫反应

表2 巨噬细胞真菌多糖受体及其配体和信号转导通路

Table 2 Macrophage fungal polysaccharide receptor and its ligand and signaling pathway

真菌多糖受体 Fungal polysaccharide receptor	配体 Ligand	信号转导通路 Signaling pathway
TLRs	Polysaccharides, glycoproteins and lipoproteins	TLR4/MAPKs/NF-κB
CR3	Complement, β-glucan	CR3/MAPK/NF-κB
MR	Mannose, fucose residues, collagen	MR+TLR4/NF-κB
Dectin-1	β-1,3-glucan, β-1,6-glucan	Dectin-1+TLR2/NF-κB

实验证明, MR与巨噬细胞吞噬能力增强、TNF-α和IL-1β分泌增加有关, 但抗MR抗体处理后对TNF-α的浓度无影响, 这说明有另一受体参与到黑灵芝多糖触发的免疫反应中。进一步结果证明, MR和TLR4协同影响TLR4/NF-κB这一信号通路, 且NF-κB在该信号通路中具有核心作用。

2.4 树突状细胞相关C型凝集素-1(Dectin-1)

Dectin-1受体是一种II型跨膜结构, 属C型凝集素受体家族的一员, 具有内外源性配体双重识别功能。在单核巨噬细胞、中性粒细胞、树突状细胞等细胞中表达。Dectin-1的主要配体是β-葡聚糖, 可特异性识别β-1,3和β-1,6葡聚糖。与配体的结合主要由胞外C型凝集素样碳水化合物识别域(CTLD)介导, 但这种识别机制仍需深入研究[50]。Dectin-1与真菌细胞壁的β-葡聚糖结合后, 可以导致细胞骨架重排, 吞噬小体(phagosome)形成, ROS、细胞因子和趋化因子大量生成[51]。Dectin-1受体下游信号通路包括脾脏酪氨酸激酶(Syk)依赖通道和非脾脏酪氨酸激酶依赖通道[52]。

有研究证明, 灰树花多糖可以作为Dectin-1潜在的配体, 诱导巨噬细胞活化, 促进细胞因子分泌, 这一作用至少部分通过Dectin-1受体[53]。然而有研究证实, Dectin-1必须与其他受体(如Toll样受体等)协同作用才能完成这种识别过程。例如, Dectin-1和TLR2相互作用可增强MAPK通路的信号转导[54]。滑菇多糖(*Pholiota nameko* polysaccharides, PNPS)的三个组分中有两个组分(PNPS-1和PNPS-2)可以结合到巨噬细胞TLR2和Dectin-1上, 同时PNPS与受体的结合可以触发下游NF-κB信号通路[55]。另一种真菌多糖——酵母多糖作用巨噬细胞后, Dectin-1、TLR2 mRNA和蛋白质水平明显上调, TNF-α分泌浓度升高[56]。

对巨噬细胞真菌多糖受体、配体以及触发的下游信号通路的归纳总结见表2。

3 总结与展望

真菌多糖作为一种高效低毒的免疫调节剂, 能够靶向作用巨噬细胞表面的真菌多糖受体, 如Toll样受体、甘露糖受体、Dectin-1和补体受体3等, 并激活细胞内MAPK、NF-κB等下游信号通路, 促进NO和细胞因子(如TNF-α、IL-1β)的分泌, 调节免疫系统, 发挥免疫调节活性。然而, 真菌多糖结构极为复杂, 多糖与受体结合的具体机制仍不清楚。此外, 受体与多糖结合后触发下游信号转导通路如何影响免疫功能也需要深入的研究。我们需要不断地探究更有效的真菌多糖结构分析技术, 开拓新思路, 将真菌多糖作为免疫佐剂广泛地应用到临床治疗和保健品生产中。

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