多糖、肠道微生物与免疫之间的相互影响

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摘　要:多糖具有免疫活性,也可调节肠道微生物菌群,而肠道微生物对宿主的多糖代谢与免疫功能起到重要作用,同时机体免疫又对肠道微生物产生影响。本文综述了多糖、肠道微生物与免疫之间相互影响的相关研究进展,为探究多糖、肠道微生物、免疫三者之间的内在关系及作用机理提供了参考。

关键词:多糖,肠道微生物,免疫,相互影响

Interaction of polysaccharides, gut microbiota and immunity

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Abstract: Polysaccharides exhibite immune activity and regulate gut microbiota. Gut microbiota can play an important role in metabolism of polysaccharides and immune function of human hosts. At the same time, it is influenced by the immune. In this paper, the related progress in interaction of polysaccharides, gut microbiota and immunity was summarized, which provided guidelines to explore the intrinsic relationship and action mechanism among polysaccharides, gut microbiota and immunity.

Key words: polysaccharides; gut microbiota; immunity; interaction
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多糖存在于动植物体内和微生物中,由 10 个以上单糖通过糖苷键聚合而成[1]。研究表明多糖具有多种生物活性,如抗肿瘤、抗氧化、抗炎、免疫调节和免疫刺激[2-4]。其中,多糖在免疫中发挥重要作用,枸杞多糖激活巨噬细胞 RAW264.7 吞噬作用,促进 NO 产生[5]。同时,多糖作为益生元,可选择性地刺激肠道有益微生物的生长和代谢,改善肠道微生物平衡从而有利于人体健康。

肠道微生物被称为编码分解膳食纤维、氨基酸、药物和产生甲烷、维生素基因的“超级有机体”[6-8],其编码基因估计是人体基因数目的 150 倍[9]。大量实验证实,肠道微生物与宿主的代谢[10]、营养吸收、产生[11-13]以及免疫系统的发展、调节[14]密切相关。研究发现,肠道微生物中的糖苷酶对代谢不能被消化吸收多糖所必需[15]。此外,人出生时胃肠道是无菌的,免疫系统几乎没有发育,但很快随着种类繁多的细菌定植,免疫系统开始正常发育并逐步成熟[16]。因此,肠道微生物与多糖代谢,免疫密不可分。

免疫是机体免疫系统识别自身与异己物质,并通过免疫应答排除抗原性异物,以维持机体生理平衡。免疫系统由免疫器官、组织、细胞、免疫效应分子及有关基因等组成,具有抗御病原体的侵害、排除异物及癌细胞等致病因子、保护机体的作用。研究表明免疫系统在维持宿主-肠道微生物体内平衡起到重要作用,同时,肠道微生物也塑造机体免疫系统[17]。本文对多糖、肠道微生物与免疫之间的相互影响研究进展进行了综述。

1　多糖对免疫的影响

1.1　多糖对免疫器官的影响

多糖促进动物胸腺、脾脏等免疫器官生长发育。Li 等[18]研究发现灵芝多糖能够提高环磷酰胺(CTX)介导免疫抑制小鼠胸腺、脾脏指数,同时促进 T、B 细胞存活,增加 TNF-α、IL-2 水平。Ma 等[19]评价灰树花多糖 GFP-A 免疫活性,发现一定浓度 GFP-A 治疗后,CTX 介导免疫低下小鼠的胸腺、脾脏指数提高,而且,其脾细胞中的 TNF-α、IL-1β、IL-2 和 IL-6 mRNA 水平也提高。

1.2　多糖对巨噬细胞的影响

巨噬细胞是强大的吞噬细胞,几乎存在于身体所有组织,在先天和适应性免疫反应中发挥关键作

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用[20]。身体受到病理性或损伤刺激时,巨噬细胞分泌 NO、ROS、TNF-α、IL-1β、IL-6 等生物活性分子和细胞因子防御病原体入侵[21-22]。从青钱柳叶子提取的多糖 CP 经乙酰化修饰后得到的多糖 Ac-CP 显著促进巨噬细胞增殖,其作用明显强于未修饰的多糖 CP;但是,与 CP 组相比,Ac-CP 没有显著增强巨噬细胞产生 NO 活性;此外,在 Ac-CP 刺激下,巨噬细胞 RAW264.7 吞噬活性增强,细胞因子 TNF-α、IL-1β和 IL-6 水平升高[23]。ESPs-CP 是从海洋棕藻分离纯化的一种硫酸多糖,研究表明,ESPs-CP 增强巨噬细胞 RAW 264.7 TNF-α、TGF-β、IL-6、IL-1β 和 IL-10 mRNA 表达[24]。Liu 等[25]研究发现一种蘑菇多糖蛋白混合物激活鼠巨噬细胞 RAW264.7,显著增加 NO 产生,促进 IL-6、TNF-α 等细胞因子分泌。研究还发现桔梗多糖增殖鸡腹膜巨噬细胞,提高吞噬率,促进 NO 产生和 TNF-α、IL-1β 和 IL-6 分泌,以及刺激该细胞的 CD80、CD86 表达[26]。而且,尚庆辉等[27]报道了植物多糖通过增大巨噬细胞体积、促进巨噬细胞吞噬作用、调节巨噬细胞细胞因子分泌量和巨噬细胞酶活性发挥免疫作用。

1.3 多糖对免疫细胞的影响

1.3.1 多糖对自然杀伤细胞的影响 自然杀伤细胞是先天免疫系统中的关键细胞,能够直接杀灭肿瘤细胞和病原体感染的细胞[28-29]。Surayot 等[30]研究发现刺松藻多糖 SP-F2 显著增殖 NK 细胞,增加 NK 细胞对 HeLa 细胞的细胞毒性;另外,SP-F2 处理后,NK 细胞活化增强,可能是由于 NKp30 的表达增强,IFN-γ 的分泌,裂解蛋白、穿孔素和粒酶 B 的释放。来自植物和真菌的 5 种多糖通过增强 IFN-γ 和穿孔素分泌,增加 NKp30 表达,显著促进 NK 细胞细胞毒性[31]。

1.3.2 多糖对淋巴细胞的影响 另外,淋巴细胞是机体主要的免疫细胞,其中 T 淋巴细胞主要参与细胞免疫应答,B 淋巴细胞主要参与体液免疫应答。蔡琨等[32]采用环磷酰胺建立免疫低下小鼠模型,并连续灌胃仙茅多糖(COP)10 d,给药剂量分别是 400、200、100 mg/(kg·d)。结果表明,与正常小鼠相比,模型小鼠外周血 CD4 + T 亚群数量、CD4 + T/CD8 + T 比值下降显著,COP 处理后 CD4 + T 亚群数量、CD4 + T/CD8 + T 比值恢复,200 mg/(kg·d)效果最佳。钱叶等[33]研究发现,松乳菇多糖 LDG-A 剂量依赖性促进 T、B 细胞增殖,同时 LDG-A 减少 T、B 细胞在 G_0/G_1 期细胞百分比,促进细胞进入 G_2/M 期,促进 B 细胞分泌抗体 IgM、IgD 和 IgE。

1.3.3 多糖对树突状细胞的影响 树突状细胞(DC)作为 CD4 + T 细胞的专职抗原呈递细胞,它们在诱导和调节有效免疫应答抑制肿瘤细胞发挥重要作用,被认为是癌症免疫治疗靶点[34]。Zhong 等[35]研究低分子量牡蛎多糖对小鼠骨髓树突状细胞影响,结果表明,该多糖增加其表面 MHC-II、CD40 和 CD86 的表达,并诱导 TNF-α 和 IL-12 分泌。Minato 等[36]研究发现榆黄蘑多糖 PCPS 诱导 DC 细胞表面成熟标志物 CD80、CD86 和 HLA-DR 表达的上调,刺激 DC 细胞分泌促炎细胞因子 TNF、IL-1β、IL-6、IL-12 和抗炎细胞因子 L-10,并增加趋化因子 CCL2、CCL3、CCL8、CXCL9、CXCL10 和 LTA mRNA 水平。

1.4 多糖对补体系统的影响

补体系统是由超过 30 种蛋白质组成,在自我防御和炎症中发挥重要作用,并且包括经典、替代、和凝集素三种激活途径[37]。Zou 等[38]研究发现五种纯化的榄仁树多糖都呈现出补体结合活性,但多糖之间活性显示差异,可能是由于多糖单糖组成、糖苷键连接类型及相对分子量不同导致。另外,来自于接骨木果实和接骨木花的两种果胶多糖都呈现补体结合活性[39-40]。研究表明当归多糖、茯苓多糖、圆锥绣球多糖、酸枣仁多糖等均可激活补体系统[41]。

2 多糖与肠道微生物的相互影响

2.1 肠道微生物参与多糖代谢

由于人类基因组不能编码足够的碳水化合物活性酶,仅编码少量消化寡糖和多糖的酶,而宏基因组研究发现肠道菌群呈现碳水化合物活性酶的多样性,因此肠道菌群在代谢未消化多糖中起到关键作用[9,42]。拟杆菌门富含多条代谢碳水化合物的途径,而厚壁菌门编码相对更少降解多糖的酶[9]。Larsbrink 等[43]研究报道肠道菌群按照 PUL 模式代谢木聚糖。总之,肠道微生物将多糖降解为短链脂肪酸,主要是乙酸、丙酸和丁酸等,它们在维持上皮屏障功能,调节上皮增殖,调节免疫应答和预防结肠直肠癌症起着重要作用[44-46]。研究发现河蚬多糖 CSPF-N 不能完全被胃-肠道消化液降解,而能被肠道微生物降解成乙酸、丙酸和丁酸等[47];乙酸是合成胆固醇的重要底物,进入肝脏参与脂代谢,也作为肌肉、心脏、大脑的主要能源[48-49]。丙酸可作为宿主细胞能源,还能抑制胆固醇合成,调节血糖和胰岛素水平[50]。丁酸能被肠道上皮细胞吸收利用,还能调节上皮细胞和淋巴细胞生长及凋亡,调控肠道炎症反应和氧化应激[51]。另一方面,代谢产生大量酸导致 pH 降低,低 pH 抑制肠道部分病原体生长,也可以改变结肠细胞代谢吸收[52]。

2.2 多糖调节肠道微生物菌群

益生菌是定居于肠道内对宿主有益的微生物[53]。多糖促进人肠道内益生菌增殖,提高肠道微生物多样性[54-55]。张浩琪等[56]研究发现大蒜多糖显著增殖健康雌性昆明小鼠肠道内双歧杆菌,而肠杆菌数量显著下降,类杆菌数量变化不大。张圣方等[57]研究发现泰山蛹虫草多糖极显著增殖免疫环磷酰胺免疫抑制模型小鼠肠道双歧杆菌、乳酸杆菌,而大肠杆菌、肠球菌数量均下降。香菇多糖 L2 降低成年小鼠盲肠和结肠部位菌群的丰富度、多样性和均匀性,增加小鼠粪便菌群的丰富度,但降低粪便菌群的多样性[58]。两种笋多糖 WBP-1、WBP-2 显著促进青春双歧杆菌和两歧双歧杆菌增殖[59]。Fatma Bouaziz 等[60]从杏仁胶中提取多糖 AGP 和半纤维素 AGH,通过青春双歧杆菌,嗜酸乳杆菌体外发酵评估

其益生元特性,结果表明,AGP 和 AGH 都呈现良好益生元性质。同时,河蚬多糖 CSPF-N 改变肠道微生物结构,微生物结构主要由厚壁菌门、变形菌门、放线菌门和拟菌门组成[47]。

3 肠道微生物与免疫的相互影响

3.1 肠道微生物对免疫的影响

3.1.1 促进肠内外免疫功能的形成 肠道微生物菌群是免疫发育正常所需要,能够促进淋巴细胞发展和免疫功能形成,影响 T 细胞亚群组成[17]。研究表明无菌动物免疫系统发育不成熟,表现为淋巴滤泡不发育,分泌 IgA 能力下降,血浆、CD8 + 细胞数目减少等免疫缺陷[61]。无菌小鼠定植普通小鼠或人粪便菌群后,发展低下的免疫系统 3 周内可以恢复正常[62]。Grnlund 等[63]研究发现半岁以下健康新生儿肠道内脆弱类杆菌和双歧杆菌定植时间越早,外周血中 IgA 分泌细胞的含量就能更早被检测到,且随着肠内脆弱类杆菌和双歧杆菌数量增加,外周血中 IgA 分泌细胞数量也逐渐增加。吴娟娟等[64]建立"无菌鸡"模型,结果发现饲喂乳酸菌或盲肠内容物的仔鸡空肠长度、脾脏指数高于无菌饲粮组,另外,它们十二指肠、空肠和回肠隐窝深度降低、绒毛高度/隐窝深度也增大,而盲肠长度和体积更低。该研究表明,肠道菌群促进仔鸡肠道发育,盲肠体积变小;同时促进脾脏发育,提高免疫。

3.1.2 调节免疫系统免疫功能 人体肠道内有益菌中双歧杆菌数量最多,在维持肠道微生态平衡、刺激机体特异性和非特异性免疫发挥重要作用。双歧杆菌刺激免疫细胞分泌 IL-1、IL-6,促进 B 淋巴细胞分化成熟与 T 淋巴细胞增殖,增强 NK 细胞杀伤能力[65]。范金波等[66]对健康 SPF 级 BALB/c 小鼠灌胃双歧杆菌并测定各项免疫指标,结果表明双歧杆菌能增强小鼠 DTH 反应,提高巨噬细胞吞噬活性,自然杀伤细胞活性,血清溶血素水平及小鼠脾淋巴细胞增殖率。同时,一些双歧杆菌属的菌株呈现抗炎性质[67-69],增加肠道 IgA 分泌[70],诱导树突状细胞成熟[71]。

另外,其它正常菌群也能调节机体免疫功能,如嗜酸乳杆菌诱导人类外周血单核细胞分泌 TNF-α、IL-6 和 IL-10[72],促进小鼠、人树突细胞活化与成熟[73-74],诱导抗原刺激的 T 细胞凋亡[75]。徐基利等[76]研究也发现乳酸菌能提高肉仔鸡血清 IgG、IgA 含量及外周血 T 淋巴细胞增殖反应。

3.1.3 屏障作用 人体的非特异性免疫是机体免疫系统识别和排除各种异物的第一道屏障,越来越多研究表明肠道菌群在天然免疫中发挥重要作用[77]。与宿主相关微生物菌群干扰外来微生物的定居和建立,这种现象称为细菌干扰或定殖抗性[78]。病原菌入侵首先要粘附在肠粘膜表面,肠上皮细胞黏液层能够阻止病原菌的粘附,作为防御病原菌定植的一道屏障[79]。研究表明肠上皮细胞黏液层的发展依赖肠道菌群,与正常小鼠相比,无菌小鼠肠上皮细胞黏液层更薄。肠道菌群还与病原菌竞争营养物质产生定植抗性[80],例如,在无菌小鼠中,共生大肠杆菌与肠出血性大肠杆菌竞争脯氨酸,抑制其在盲肠定植[81]。肠道菌群也可通过竞争碳水化合物,对柠檬酸杆菌的感染,肠致病性大肠杆菌、肠出血性大肠杆菌感染的模型小鼠产生定植抗性[82]。然而,竞争营养只是肠道共生菌群对病原菌产生定植抗性的一种机制,某些病原菌能够逃脱这种机制[80]。某些致病性大肠杆菌利用共生大肠杆菌不能利用的糖[83]。另外,肠道菌群还分泌抗菌肽和毒素对病原菌起到抑制作用[78]。一些共生肠杆菌分泌的抗微生物肽特异性杀死病原菌[84-85],双歧杆菌分泌的细菌素表现出窄或宽的抑菌活性谱[86]。

3.1.4 免疫佐剂活性 甘萍等[87]研究发现来源于芽胞杆菌的表面活性素促进抗原的呈递、激活 MAPKs 信号转导通路和核转录因子 NF-κB、诱导 ROS 的产生和促进炎症小体的形成。López 等[88]研究发现暴露于双歧杆菌 LMG13195 膜囊泡的 DC 细胞显著促进功能性 $CD25^{high}FOXP3^{high}CD127^{-/low}$ Treg 细胞的分化,提高 IL-10 的水平。

3.2 免疫系统对肠道微生物的影响

研究表明免疫系统在塑造肠道微生物菌群的组成起到关键作用[17]。在缺乏 IgA 的模型小鼠中观察到小肠中分段丝状细菌异常扩张,而模型小鼠 IgA 恢复正常后,肠道微生物群体的组成也恢复正常[89]。Larsson 等[90]研究发现缺失 MYD88 的小鼠小肠含有更多分段丝状细菌,表明 MyD88 信号的缺失改变肠道微生物组成。罗兰等[91]用香菇多糖治疗肠道微生态失调模型小鼠结果表明,香菇多糖显著增殖模型小鼠肠道双歧杆菌、乳酸杆菌,而肠杆菌和肠球菌数量显著降低;脾脏指数和淋巴细胞转化率增加,而胸腺指数无变化;小鼠菌群失调得到调整可能由于其免疫的提高。另外,肠固有层分泌的 SIgA 对革兰阴性杆菌具有特殊亲和力,能包被细菌,抑制细菌与肠上皮细胞特异性结合,阻止细菌在肠上皮细胞粘附,从而避免细菌穿透肠上皮发生移位[92]。

4 结语

本文综述了多糖、肠道微生物与免疫之间的相互影响,多糖提高免疫,其调节机制包括:多糖激活巨噬细胞信号通路、激活 T/B 淋巴细胞信号通路[27];Wu 等[93]研究发现香菇多糖 PSCPL 通过介导 MyD88 依赖信号通路和 MAPK 信号通路抑制 LPS 刺激的 THP-1 细胞内 MyD88、TRAF-6、NF-κB 的表达,抑制 JNK 和 p38 的活化、磷酸化和细胞因子 TNF-α、IL-1α、IL-1β 和 IL-4 的产生。多糖也可调节肠道微生物菌群,而肠道微生物则参与多糖代谢,发酵宿主自身不能消化、分解的糖类。肠道微生物通过促进肠内外免疫功能的形成、调节免疫功能、屏障作用及免疫佐剂活性等途径提高机体免疫,而机体免疫功能又可塑造肠道微生物的组成。然而,多糖、肠道微生物、免疫三者之间的内在关联尚无文献报道。其一,多糖是否通过调节肠道微生物菌群,进而提高机体免疫功能。宗方方等[94]曾报道肠道菌群能通过调节免疫反应增强肿瘤治疗效果。其二,是否多糖及

多糖的代谢产物提高机体免疫功能，随后机体免疫功能又对肠道微生物产生积极影响。其三，上述两个问题是否同时存在？因此，三者内在联系有待进一步研究和明确。随着肠道微生物群落分析方法，如焦磷酸测序分析、基因芯片分析和宏基因组测序与生物信息分析等各种技术方法的出现和革新，可更清楚的研究肠道微生物群落组成及其功能。另外，研究表明人体中许多疾病与免疫密切相关，如类风湿性关节炎系统性红斑狼疮、脊柱关节炎，而肠道微生物也与这些疾病存在着千丝万缕的关系[95]。系统探究多糖、肠道微生物、免疫三者之间的内在关系及作用机理，而非只单纯研究两两之间的相互作用，将是该领域未来的着力方向，也有助于人们更有效预防和治疗免疫性疾病、肠道或肠道微生物相关性疾病。

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