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分子量影响多糖生物活性的研究进展

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摘要:多糖作为生物医药和食品加工与生产中广泛使用的高分子聚合物之一,具有抗肿瘤、免疫调节、降血糖、抗氧化、抑菌等生物活性。越来越多的学者从动物、微生物和植物中分离与纯化多糖并对其生物活性及应用进行研究。多糖的生物活性受单糖组成、分子量、糖苷键类型、分支度、空间构象等多种因素影响,如何实现活性多糖的设计、构建、筛选和高效生产一直是多糖研究的重点和难点。基于分子量与多糖生物活性的构效关系进行综述,介绍分子量对多糖抗氧化、抗肿瘤、抗炎、益生、免疫调节和抑菌等活性的影响,并对由分子量差异造成的多糖生物活性变化进行了讨论和展望,以期为从分子量角度改善多糖生物活性的研究及应用提供理论参考。

关键词:多糖;分子量;生物活性;构效关系
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Advances in research of molecular weight affecting the bioactivities of polysaccharides

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Abstract: Polysaccharide is one of the globally recognized micro-molecules used in biomedicine, food preparation and production, which has the bioactivities of anti-tumor, immunomodulatory, hypoglycemic, antioxidant and anti-bacteria. Recently, more and more researchers have studied the bioactivities and applications of polysaccharides derived from animals, microorganisms and plants. In general, bioactivities of polysaccharides are affected by the monosaccharide composition, molecular weight, glycosidic type, branching degree and spatial conformation in which. However, how to realize the design, construction, screening and efficient production of bioactive polysaccharides has always been the focus and difficulty of polysaccharide research. Therefore, based on the relationship between molecular weight and bioactivities of polysaccharide, the effects of molecular weight on antioxidant, anti-tumor, anti-inflammatory, probiotic, immunomodulatory and bacteriostatic activities of polysaccharides were introduced. Furthermore, this review discussed and prospected the variation of polysaccharide bioactivities induced by its molecular weight differences. In conclusion, we hope that this work could provide some theoretical references for the future research and application of bioactive polysaccharides from the perspective of molecular weight.

Key words: polysaccharide; molecular weight; bioactivity; structure-activity relationship

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多糖是一种通过 α-或 β-糖苷键将酮糖和醛糖进行连接而形成的高分子聚合物,分子量可从几千到上百万,具有无毒无害、结构各异、种类繁多、活性广泛等特性[1]。多糖可以从植物、动物及微生物中提取获得[2],具有免疫调节[3]、抗氧化[4]、抗炎[5]、抗肿瘤[6]、抗衰老[7]、抑菌[8]和降血糖[9]等多种生物活性。活性多糖已逐步开发并应用于医药、食品等领域[6,8-9]。同时,越来越多的研究证实,多糖的生物活性受其空间构象、糖苷键类型、单糖组成及分支程度等因素影响[10]。比如山药多糖 β-连接的甘露糖残基或者支链末端连接的 α-糖苷键可启动先天免疫,而主链中 β-(1→3)糖苷键可调节多糖发挥免疫活性,进而产生抗肿瘤、抗炎、免疫调节等功效[11]。王昭晶等[12]研究发现鼠尾藻多糖 STP-Ⅲ相比 STP-I 能更好抑制炎症相关因子表达而增强抗炎活性,使用透射电镜观察发现 STP-I 是网格状结构,而 STP-Ⅲ是线状且螺旋缠绕结构,表明伸展的线状缠绕链结构抗炎作用更好。Li 等[13]研究证实黄精多糖的单糖组成与其抗氧化活性密切相关:黄精多糖的 ABTS 自由基及羟自由基清除率与甘露糖摩尔比成反比、与阿拉伯糖摩尔比成正比,ABTS 自由基清除率与葡萄糖摩尔比成正比。阿拉伯半乳聚糖(AGW)经 Smith 降解法去除部分侧链糖基后得到 DAGW1 和 DAGW2,侧链度高的 DAGW1 促进小鼠巨噬细胞 RAW 264.7 分泌细胞因子(TNF-α、IL-6 以及 IL-1β)的能力要强于侧链度低的 DAGW2,表明多糖生物活性受其侧链基团分支度的影响[14]。

分子量同样可作为多糖的一个重要结构特征而影响其生物活性。2022 年关于国家重点研发计划“绿色生物制造”重点专项项目中提到:研究微生物多糖(前体)分子量可控合成的机制与方法,开发特定分子量分布的微生物多糖发酵生产与分离提取工艺。可见,研究分子量对多糖生物活性的影响对于活性多糖的开发及生产制备具有重要意义。研究证实,多糖分子量较高会使其具有较差的水溶性和较高的溶液黏度[15],不利于多糖在体内的吸收利用[16],同时也会降低多糖的生物活性,限制其在免疫、抗氧化、抗炎等方面的应用[17]。而分子量较低的多糖,分子内氢键作用较弱,会有更多的游离氨基和羟基,更利于发挥活性作用[18-20]。但也有研究表明分子量高的多糖生物活性往往较高[7,21-22],可能是因为多糖发挥生物活性时需要一定的空间结构,合适的高分子量才能形成有效的活性结构[23-24],如果分子量太低,多糖上所带的活性基团则太少而无法形成有效的活性空间结构,导致多糖失去生物活性[25-26]。因此,作者从分子量角度对多糖生物活性进行探讨,以期为多糖更好发挥活性作用、扩大应用范围及活性多糖的生产和制备提供指导和帮助。

1　分子量对多糖生物活性的影响

1.1　抗氧化活性

过量的氧自由基会损伤细胞,严重时可使机体内氧化失衡造成氧化损伤,导致多种慢性疾病发生[27]。与化学类抗氧化剂相比,多糖的毒副作用更小。王帅等[22]利用发菜多糖、地木耳多糖、葛仙米多糖、螺旋藻多糖-1、螺旋藻多糖-2、螺旋藻多糖-3、香菇多糖和茯苓多糖研究分子量对多糖抗氧化性的影响,发现小分子量香菇多糖具有较强抗氧化性,对 ABTS 自由基清除率达到 99.53%。Xu 等[28]采用超声对灵芝多糖降解后发现,随着灵芝多糖分子质量从 3.06×10^3 kDa 降至 13.6 kDa,小分子量灵芝多糖片段在降低小鼠体内丙二醛含量、增加小鼠血清中谷胱甘肽过氧化物酶和超氧化物歧化酶的活性方面比灵芝多糖效果更好。可能是由于分子量降低,多糖空间结构更加松散且更多活性基团暴露出来,进而赋予小分子量多糖更高的抗氧化活性[29]。但也有学者证实,分子量降低与多糖抗氧化性不成比例,如铁皮石斛多糖的分子量与其清除羟自由基和超氧阴离子的能力之间无对应关系[30]。Deng 等[31]在研究不同分子量魔芋葡甘露聚糖的抗氧化活性时也发现,中等分子量的魔芋葡甘露聚糖在提高 2 型糖尿病模型小鼠体内超氧化物歧化酶及降低丙二醛含量等方面比高分子量和低分子量魔芋葡甘露聚糖具有更好的活性。

1.2　抗肿瘤活性

2020 年全球约有 2 000 万新发癌症病例,其中死亡病例数近 1 000 万,预计 20 年后全球新发病例数将达 2 800 万[32]。为了提高肿瘤的治疗效果,减少患者生存痛苦,抗肿瘤多糖的筛选已成为研究热点[6,10]。虽然大量研究已经证实单糖组成、糖苷键类型和三螺旋结构影响多糖的抗肿瘤活性[33],但多糖的抗肿瘤效果与其分子量也密切相关。Yu 等[34]在研究不同分子量铁皮石斛多糖对 HeLa 细胞抗增殖活性的影响时发现,虽然

6 个不同分子量的铁皮石斛多糖组分对 HeLa 细胞的增殖活性均有一定抑制作用,但较大分子量组别的铁皮石斛多糖抑制 HeLa 细胞增殖的效果优于较小分子量组别。Li 等[35]研究不同分子量组分灰树花多糖对人肺癌细胞的抑制作用时发现,大分子量的灰树花多糖组分对人肺癌细胞的抑制率明显高于其他小分子量组分,原因可能是大分子量灰树花多糖组分中(1→3)α-*D*-Galp 的存在和较高的(1→3,4)α-*D*-Galp 含量,特殊糖苷键是其抗肿瘤活性高的关键。王佳奇等[36]利用不同分子量甘露聚糖对人结肠癌细胞的抑制率进行研究。随着甘露聚糖作用浓度增加,大分子量甘露聚糖对人结肠癌细胞的抑制率升高,而小分子量的抑制率呈下降趋势;中等分子量甘露聚糖在低浓度时能够明显抑制人类结肠癌细胞增殖,但随浓度升高却又能明显促进人结肠癌细胞增殖。可能是甘露聚糖相当于外来异物,所以机体细胞会诱发免疫反应,且分子量越大这种现象越明显;也可能是中等分子量甘露聚糖对人类结肠癌细胞具有双向免疫调节作用,在不同浓度时具有不同免疫刺激及诱发效果,并得到了其他学者的证实[37]。Zhang 等[38]也发现分子量能够影响铁皮石斛多糖对肿瘤细胞的抑制效果,中等分子量铁皮石斛多糖对肿瘤细胞抑制率最高,高分子量和低分子量铁皮石斛多糖对肿瘤细胞的抑制率较弱。Yu 等[39]发现除分子量之外,多糖的抗肿瘤活性还与肿瘤细胞类型相关。当不同分子量紫菜多糖对人胃癌细胞株 SGC7901 和人肺癌细胞株 95D 进行抑制时,低分子量紫菜多糖对人胃癌细胞株 SGC7901 抑制效果强于高分子量紫菜多糖,但对于人肺癌细胞株 95D 而言,两个不同分子量紫菜多糖的作用效果差异不大。

1.3 抗炎活性

炎症反应可以清除体内的感染,但炎症反应过于强烈会导致炎症细胞因子过盛从而使机体器官或组织受到严重损伤[40]。现代免疫学认为,天然活性物质比抗生素在提高机体免疫应答反应方面有更多的优点。多糖在炎症反应和预防各种炎症疾病中发挥着重要作用[41]。范信晖等[42]对黄芪多糖(APS)两个分子质量组别 APS-Ⅰ(>2 000 kDa)和 APS-Ⅱ(10 kDa)的抗炎活性进行研究,发现 APS-Ⅰ能显著抑制巨噬细胞 RAW 264.7 分泌 NO、TNF-α 和 IL-10,表明大分子量 APS-Ⅰ体外抗炎活性更优。对不同分子量硫酸多糖的体外抗炎活性研究发现,大分子量硫酸多糖组分的抗炎活性更好,具有开发为抑制炎症性疾病的药物或功能材料的潜力[43]。但 Zheng 等[44]研究发现,小分子量的氧化魔芋葡甘露聚糖对脂多糖诱导的 RAW 264.7 巨噬细胞具有较强的抗炎作用。张鑫等[45]对枸杞多糖的抗炎效果进行研究,通过灰度关联法发现枸杞多糖分子质量在 34.6 kDa 左右时抗炎活性最好。同时,廖海锋等[46]研究发现分子质量为 40~350 kDa 的枸杞多糖能够通过诱导树突细胞成熟而发挥更好的药理活性。

1.4 益生活性

益生元被酶水解后能够被肠道中的微生物群利用,可以选择性地刺激肠道益生菌生长[47]。多糖是一类大分子聚合物,可以通过调节肠道菌群和改善肠道微环境而促进机体健康[48]。肠道菌群对多糖的利用除受多糖的糖苷键和单糖组成类型影响之外[49],一般而言小分子量多糖的高溶解度和低黏度使其更容易被肠道菌群利用[18]。Yuan 等[50]对马尾藻多糖进行超声降解后发现,小分子量组别的马尾藻多糖比大分子量组别更容易被肠道菌群利用,促进肠道益生活性。Gao 等[51]采用钴射线对结冷胶进行降解后发现,低分子量结冷胶寡糖可以显著增加肠道中乙酸和丙酸的产量,进而利于肠道生态系统并发挥益生活性。Chen 等[52]发现使用低分子量竹笋多糖 U-CPS 和 E-CPS 作为碳源进行培养时可以增加短链脂肪酸含量,使乳酸、乙酸、丙酸和丁酸的产量更高,表明小分子量多糖可能有更高的概率被细菌细胞运输和代谢,从而产生更好的益生元效果。Hu 等[53]研究发现被超声降解后形成的低分子量车前草多糖组分在体外发酵过程中短链脂肪酸的产量显著增加,发酵培养体系中乳酸杆菌和拟杆菌的菌群丰度明显大于大分子量车前草多糖组分,可能是颗粒度的降低和空间结构的改变使得小分子量车前草多糖具有更强的益生元活性。Li 等[18]采用热水处理对硫酸化龙须菜多糖进行降解后发现,小分子量硫酸化龙须菜多糖组分的低黏度使其更容易被肠道菌群利用,提高益生菌和短链脂肪酸含量,降低致病菌和支链脂肪酸含量,从而发挥更好的益生活性。但是,也有学者认为多糖益生活性的提高与其分子量降低之间无必然联系。Deng 等[31]对不同分子量魔芋葡甘露聚糖的生物活性研究时发现,中等分子量魔芋葡甘露聚糖组分可以更好地提高 2 型糖尿病小鼠肠道菌群丰度和肠道中拟杆菌门/厚壁

菌门比例,降低肠道中有害菌种类和数量,进而调节肠道菌群稳态和健康。Hu 等[7]在研究岩藻多糖的生物活性时也发现,对肠道菌群的调控和益生活性可能是大分子量岩藻多糖具有较强抗氧化性和抗光老化活性的原因之一。

1.5　免疫调节活性

免疫指的是机体能够识别非己物质,通过免疫应答反应阻止抗原性外来物进入宿主,识别病原体并将其进行杀灭和清除[54]。多糖可以通过促进白细胞介素和干扰素生成,激活 T 淋巴细胞、B 淋巴细胞、补体和巨噬细胞等发挥免疫调节活性[41]。同时,良好的生物相容性和安全无毒等优点,预示着在未来市场上多糖可能会成为最好的免疫佐剂之一[55]。李苹等[56]采用透析分离方法获得了不同分子量醋柴胡多糖组分并对其免疫调节活性进行探究,发现分子质量≥100 kDa 的醋柴胡多糖组分能显著促进 RAW 264.7 巨噬细胞的吞噬活性,而分子质量<3.5 kDa 的醋柴胡多糖组分并未增强 RAW 264.7 巨噬细胞的吞噬活性,可能是分子量过低无法形成能够产生活性的聚合结构所致。Qian 等[57]采用酶法对马尾藻多糖 SFP 进行降解后获得了一种低分子量马尾藻多糖组分 ESFP,虽然 ESFP 和 SFP 在低质量浓度范围(10~250 μg/mL)内均能提高 RAW 264.7 巨噬细胞的吞噬活性,但 ESFP 的免疫调节活性显著高于 SFP,说明分子量降低使 ESFP 具有更好的免疫调节活性。Yao 等[58]采用碱法从薏仁种子中提取获得了分子质量分别为 94.2、82.3、63.1、60.4 kDa 的多糖组分,虽然 4 种多糖组分都可以促进 RAW 264.7 巨噬细胞分泌炎症因子,但是分子量最小的薏仁种子多糖组分能够显著提高 NO 产量和刺激 IL-6 产生,进而促进 T 淋巴细胞和 B 淋巴细胞增殖,免疫调节效果优于其他 3 个大分子量组分。并且很多学者研究也证实分子量的降低可以显著提高或增强多糖的免疫调节活性[59-61]。然而,Tao 等[62]研究发现采用梯度醇沉法获得的不同分子量半乳甘露聚糖,虽然各组别分子量的半乳甘露聚糖以浓度依赖型方式促进 RAW 264.7 细胞增殖和产生 NO,但是各分子量组别半乳甘露聚糖的免疫调节活性却并无显著差异。Toll 样受体 4(Toll-like receptors 4, TLR4)是巨噬细胞中多糖识别和激活的主要受体,TLR4 的激活导致细胞内信号级联,并最终诱导无数免疫细胞因子和趋化因子分泌,包括 TNF-α、IL-6、IL-1 等[63],多糖免疫活性的发挥还可能与细胞中 TLR4 含量和多糖空间结构相关。

1.6　抑菌活性

抗生素滥用所致药物残留和细菌耐药性等问题,已严重威胁到食品安全和人体健康[64]。多糖作为一种安全、无毒、无残留,且具有防病、抗病、提高机体免疫力和促生长作用的潜在绿抗替代品已逐渐受到业界关注[8,65]。Liu 等[66]研究证实,低分子量壳聚糖具有较强杀菌能力和优越的生物活性,对大肠杆菌和金黄色葡萄球菌的抑制率随分子量降低而增加。Qin 等[67]发现将不具有抑菌活性的燕麦 β-葡聚糖进行降解后,所得燕麦 β-葡聚糖寡糖对金黄色葡萄球菌和大肠杆菌均表现出很好的抑制作用,可能是由于分子量降低使葡聚糖寡糖更易进入细胞,干扰细菌代谢,进而导致细菌细胞的裂解,赋予了燕麦 β-葡聚糖寡糖抑菌活性[68]。Han 等[69]研究不同分子量构树果实多糖的抑菌效果时发现,小分子量的构树果实多糖组分对铜绿假单胞菌、大肠杆菌、金黄色葡萄球菌和枯草芽孢杆菌的抑制效果较好。Liu 等[70]发现褐藻中硫酸多糖分子质量小于 6 kDa 时对大肠杆菌和金黄色葡萄球菌的抑制作用较强,可能是小分子量多糖不仅可以破坏细胞膜流动性,还可以进入细胞通过激活细胞的自噬而发挥抑菌活性。而 Fleita 等[71]对不同分子量红藻多糖抑菌活性进行探究时发现,大分子量红藻多糖组分对金黄色葡萄球菌的抑制效果明显,但小分子量红藻多糖组分却没有抑菌活性,说明多糖在发挥抑菌活性时可能需要一定的聚合度和分子量。Brasselet 等[20]和 Li 等[26]认为具有 4~8 个葡萄糖胺单位的寡糖有更高浓度的正电荷,可以与细胞表面带负电荷的大分子残基发生反应,导致细菌胞内成分泄漏,使其能够更有效地穿透细胞壁,抑制细菌增殖。

1.7　其他活性

除上述活性之外,分子量还可能影响多糖的其他活性。如 Ma 等[72]和 Dou 等[25]发现,小分子量的蓝金银花多糖组分和黑莓果实多糖组分具有更好地抑制 α-葡萄糖苷酶活性,可能原因是通过改变 α-葡萄糖苷酶的刚性和环结构而发挥抑制作用。Zhou 等[73]证实通过酶法降解后,小分子量的浒苔多糖组分对酪氨酸酶和二酚酶具有更好的抑制活性。Lin 等[74]和 Wang 等[75]发现低分子量的枸杞叶多糖组分和浒苔多糖组分具有更好的抗凝血活性。Xu 等[28]对比不同分子量灵芝降解多糖的降血脂活性时发现,小分子量的

灵芝降解多糖降解组分具有更好的降血脂活性。Ma 等[76]通过对黑木耳多糖进行降解后发现,小分子量组分的黑木耳多糖具有更强的金属螯合作用。张铎等[77]在研究不同分子量八珍汤水溶多糖的活性时发现,低分子量和高分子量的八珍汤水溶多糖可使白血病细胞在合成后期和分裂期的细胞显著增加,合成前期细胞减少,而中等分子量八珍汤水溶多糖却无此活性。

2 展望

虽然多糖在医药、食品、化妆品等领域应用广泛,但单糖组成、分子量、糖苷键、分支度、空间构象等结构特征对其生物活性的影响却不尽相同,导致多糖的生物活性差异巨大。研究分子量如何影响多糖生物活性,以及分子量与其功能特性之间关联,可为以结构特征为标志设计、构建、筛选和生产功能多糖提供理论支持。但不同分子量造成多糖活性差异的具体机制还需进一步探究,深入而全面地了解和建立分子量与多糖生物活性之间的构效关系和分子机理,才有望通过分子量调控而实现功能多糖的开发与生产。

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