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褐藻寡糖与肠道菌群在肥胖中的研究进展

——褐藻寡糖和肥胖

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摘　要

近年来，肥胖已成为严重的全球性公共卫生问题。肠道菌群被认为是调节宿主健康的主要因素，更被认为是参与维持能量稳态和预防治疗肥胖的关键因素。在这里，我们将报告肥胖的流行现状和影响因素、肠道菌群的组成和疾病的联系、肠道菌群代谢产物与肥胖的联系以及益生元褐藻寡糖与肥胖的联系。益生元能够被肠道菌群所利用，增加有益菌减少有害菌改善肥胖及其相关代谢紊乱。但尚未有研究表明益生元褐藻寡糖是否能够调控色氨酸代谢通路改善肥胖相关代谢综合征，这为其提供了研究思路。我们希望这能为褐藻寡糖开发利用提供理论基础和灵感。

关键词

褐藻寡糖，肠道菌群，色氨酸代谢，肥胖

Research Progress on Alginate Oligosaccharide and Gut Microbiota in Obesity

—Alginate Oligosaccharide and Obesity

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Abstract

In recent years, obesity has become a serious global public health problem. Gut microbiota is con-

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sidered to be a major factor in regulating host health, and is also considered to be a key factor involved in maintaining energy homeostasis and preventing and treating obesity. Here, we report the prevalence status and influencing factors of obesity, the composition of gut microbiota and the association of disease, the relationship between the gut microbiome-derived metabolites and obesity, and the association of prebiotics, such as alginate oligosaccharide, with obesity. Prebiotics can be utilized by gut microbiota, increasing beneficial bacteria and reducing harmful bacteria to improve obesity and related metabolic disorders. However, no studies have shown whether alginate oligosaccharide can regulate tryptophan metabolic pathway to improve obesity-related metabolic syndrome, which provides research ideas. And we hope that this review will provide theoretical basis and inspiration for the development and utilization of algin oligosaccharides.

Keywords

Alginate Oligosaccharides, Gut Microbiota, Tryptophan Metabolic, Obesity

1. 引言

肥胖是指可能损害健康的不正常或过度的脂肪积累，具有复杂性和多因素的特点[1]。从 1975 年到 2014 年，全球男性肥胖患病率从 3.2%增加到了 10.8%，女性肥胖患病率从 6.4%增加到了 14.9% [2]。近年来，中国的肥胖患病率也在不断上升，近 34.8%的人超重，14.1%的人肥胖，这与全球肥胖患病率趋势相同[3]。WHO 预测到 2035 年，全球将有超过 40 亿人属于肥胖或超重，占全球人口的 51%，中国成年人肥胖率将达到 18% [4]。肥胖是遗传和环境因素共同作用的结果，其根本原因可归结为机体能量摄入、消耗和存储的失衡[5]。与 BMI 正常者相比，超重/肥胖者的并发症患病率更高，且 BMI 越高，并发症越多[3]，最常见的并发症有血脂异常、高血压、二型糖尿病、非酒精性脂肪肝、代谢综合征、心血管疾病、骨关节炎、抑郁症等[6]。肥胖已经成为能威胁到患者生活水平的重要公共卫生问题。肥胖的发病和发展的因素并不是任何单一因素引起的，多项研究表明了肥胖的影响因素(表 1)，包括遗传、表观遗传、缺乏运动、能量摄入过高、睡眠不足、药物、内分泌干扰物和肠道菌群。在众多的影响因素中，肠道菌群在机体能量代谢中具有重要功能，进而对肥胖的发生发展发挥了关键性作用。研究显示，个体膳食结构变化改变可导致其肠道菌群结构出现适应性变化，从而对三大宏量营养素的应答出现显著差异，进而造成肥胖的发生[7]。大量研究表明肥胖的发生与肠道菌群密切关联，肥胖人群和小鼠的肠道菌群发生了改变[8] [9] [10]。一项研究表明肥胖人群和小鼠的菌群多样性减少，拟杆菌门水平相对丰度降低，厚壁菌门相对丰度升高并增强了能量回收[11]。另一项研究表明，肥胖小鼠肠道中 *Ruminococcaceae*、*Paraprevotellaceae*、*Bacteroidaceae* 有害菌增加，减少了丁酸的产生以及损害了小鼠肠道屏障的完整性[12]。此外，Tadashi Takeuchi 等人报道 *Fusimonas intestini* 在肥胖和糖尿病患者和小鼠肠道中高度定植，产生长链脂肪酸，损伤肠屏障，促进饮食诱导的肥胖[13]。过去几十年，通过肠道菌群调节肥胖的研究迅速增加。研究发现肠道菌群可以通过影响能量平衡、调节脂肪储存以及抑制慢性炎症等多种方式影响肥胖[14]。通过益生元来干预肥胖已被认为是一种安全有效的策略[15]。在本文中，我们重点关注益生元通过调节肠道菌群，产生有益的代谢产物改善肥胖，以及提出一些用于干预肥胖的潜在机制，从而为肠道菌群与肥胖的预防和治疗提供指导。

Table 1. Influencing factors of obesity
表 1. 肥胖影响因素

影响因素	描述
遗传因素	单基因[16]、多基因[17] [18]、综合性肥胖[19]
表观遗传	DNA 甲基化[20]、组蛋白修饰[21]、miRNA 调控[22]
缺乏运动	体育活动减少[23]，能量消耗大幅度下降[24]
能量摄入过高	能量摄入过高引起肥胖[25]，降低能量摄入体重下降[26]
睡眠不足	睡眠调节葡萄糖代谢和内分泌功能[27]，睡眠不足与 BMI 呈正相关[28]
药物	激素水平、食欲增加和葡萄糖转化脂肪[29]，新陈代谢紊乱[30]
内分泌干扰物	干扰内分泌激素[31]，扰乱内分泌功能[32]
肠道菌群	肠道菌群失调[33]，增加能量回收[11]，影响脂肪组织代谢[34] [35]

2. 肠道菌群

肠道菌群在出生时就开始定植存在，在 1~3 年后趋于稳定，早期婴儿的肠道菌群结构与分娩前、分娩过程、分娩后环境密切相关[36]，菌群多样性并随着年龄的增长而增加，是人体不可分割的组成部分[37]。当肠道菌群失调后，大量格兰氏阴性菌会增殖产生内毒素(LPS)，破坏肠道屏障进而导致代谢紊乱引发各种肠道和肠外疾病[38] (表 2)。越来越多的证据表明肠道菌群可以通过影响营养获取、能量调节、调节脂肪储存以及抑制慢性炎症等多种方式影响肥胖[39]。肠道菌群现在被认为是有助于调节宿主健康的关键因素之一，在肥胖中发挥着重要的调节作用[14]。通过调节肠道菌群可能是预防和治疗肥胖的一种策略。此外，肠道菌群代谢产物与宿主细胞上的受体作用进而激活或者抑制信号通路来改善肥胖[40]。

Table 2. Intestinal flora disorders and intestinal parenteral diseases
表 2. 肠道菌群失调和肠道肠外疾病

疾病	菌群变化描述
肠道疾病	
溃疡性结肠炎[41]	*Clostridium symbiosum* 增多； *Verrucomicrobia, Leuconostocaceae, Ruminococcaceae, Lachnospiraceae* 减少；
克罗恩病[42]	*G. moniliformis, A. brassicicola, C. neoformans, Candida* spp.增多； *Synergistetes, Verrucomicrobia* 减少；
肠易激综合症[43]	*Enterococcaceae, Yersiniaceae, Streptococcus sp.*增多；
结直肠癌[44]	*Aspergillus rambellii, Cordyceps sp. RAO-2017, Erysiphe pulchra, Moniliophthora perniciosa, Sphaerulina musiva, Phytophthora capsici* 增多； *Aspergillus kawachii* 减少；
乳糜泻[45]	*L. bacterium, D. invisus, Parabacteroides sp.*增多； *B. vulgatus_str_3775_S_1080 branch, B.unformis_ATCC_8492* 减少；
肠外疾病	
肥胖[39] [46] [47] [48]	*Firmicutes* 增多； *Akkermansia muciniphila, Faecalibacterium prausnitzii, Bacteroides, Osillibacter, Alistipes* 减少；
二型糖尿病[49]	*Dallella* 增多； *Bifidobacteria, Akkermansia* 减少；

续表

非酒精性脂肪肝[50]	*Ruminococcus*, *F. prausnitzii*, *Coprococcus* 减少；
心血管疾病[51]	*Prevotella*, *Tyzzerella* 增多； *Alloprevotella*, *Catenibacterium* 减少；
高血压[52]	*Prevotella* 增多； *Faecalibacterium*, *Oscillibacter*, *Roseburia*, *Bifidobacterium*, *Coprococcus Butyrivibrio* 减少；
动脉粥样硬化[53]	*Enterobacteriaceae* and *Streptococcus* spp.增多；
帕金森[54]	*Akkermansia*, *Catabacter*, Lactobacillaceae, Akkermansiaceae 增多； *Roseburia*, *Faecalibacterium*, *LachnospiraceaeND3007*, *Lachnospiraceae* 减少；
阿尔茨海默症[55]	*Ruminococcaceae*, *Enterococcaceae*, *Lactobacillaceae* 增多； *Lanchnospiraceae*, *Bacteroidaceae*, *Veillonellaceae* 减少
自闭症谱系障碍[56]	*Lactobacillus*, *Bacteroides*, *Desulfovibrio*, and *Clostridium* 增多； *Bifidobacterium*, *Blautia*, *Dialister*, *Prevotella*, *Veillonella*, *Turicibacter* 减少；
肌萎缩侧索硬化[57]	*Lachnospira* 增多； *Oscillibacter*, *Anaerostipes*, *Lachnospiraceae* 减少；
焦虑抑郁[58]	*Coprococcus* and *Dialister* 减少；
肿瘤[59]	*Pseudoxanthomona*, *Saccharopolsypora*, *Streptomyces* 增多
皮肤病[60]	*Akkermansia*, *Ruminoccocus* 减少

3. 肠道菌群代谢产物与肥胖

肠道菌群代谢产物是肠道菌群产生的代谢物质，能够维持个体肠道和系统免疫稳态，在宿主健康和生理功能中发挥了重要作用。从目前研究来看，肠道菌群代谢产物以短链脂肪酸、胆汁酸、色氨酸作为主要的特定代谢物质。在这里，我们将介绍短链脂肪酸、胆汁酸、色氨酸与肥胖的关系。

3.1. 短链脂肪酸

短链脂肪酸(Short-chain fatty acids, SCFAs)是指 6 个碳原子以下的有机脂肪酸，是未消化碳水化合物(如膳食纤维和益生元)在结肠中发酵的主要产物，对能量代谢、肠道稳态和免疫调节具有巨大作用[61]。短链脂肪酸主要包括乙酸、丙酸、丁酸、异丁酸、戊酸、异戊酸、己酸，其中乙酸、丙酸、丁酸约占 SCFAs 的 90%。肠道菌群产生的短链脂肪酸可以直接作用于 GPR41、GPR43 和 GPR09A 受体，调控 PYY 和 GLP-1，诱导饱腹感和肠道转运，抑制胰岛素介导的脂肪积累[62]。乙酸、丙酸、丁酸都可以结合 GPR41 和 43 发挥抗肥胖作用[63]。然而，有文献报道乙酸虽然通过分泌 GLP-1 和 PYY 等肠道激素影响宿主食欲，但是会导致副交感神经系统的激活，增加肥胖风险[64]。丁酸不仅作用于 GPCR 配体，还可以从诱导线粒体、激活 AMPK 和 LSD1 来缓解肥胖和相关并发症[65]。一项随机对照实验表明，丙酸可以直接达到结肠，增加 PYY 和 GLP-1 的释放，减少能量摄入进而防止体重增加，减少超重成人腹内脂肪堆积[66]。短链脂肪酸是介导饮食、肠道菌群和宿主之间相互作用的信号分子，在宿主代谢、免疫系统、脂质代谢等方面具有重要作用[67]。

3.2. 胆汁酸

胆汁酸(bile acid, BA)是一种两性分子，是肝细胞中产生的胆固醇衍生代谢物，在调节脂质、葡萄糖和能量代谢方面具有重要作用，与肥胖相关的代谢性疾病与胆汁酸稳态失调有关[68]。胆汁酸一般可分为

初级胆汁酸和次级胆汁酸。当摄入食物后，胆汁酸会被释放到十二指肠并到达胃肠道被肠道微生物所代谢修饰。通过胆汁盐水解酶活性去除氨基酸残基、脱羟基、氧化脱氢或差向异构产生次级胆汁酸，例如去氧胆酸、石胆酸、熊去氧胆酸[69]。在结肠的肠细胞中，BA 将被重吸收，与法尼醇 X 受体(FXR)结合，刺激成纤维细胞生长因子 19 (FGF19)的产生并减少 BA 在肝脏的合成，通过 BA-FXR 通路抑制葡萄糖生长并促进糖原合成；此外，BA 通过激活 TGR5 促进肠细胞分泌 GLP-1 的产生提高葡萄糖耐量以及激活 cAMP 增加能量消耗，TGR5 该激素可以调节葡萄糖稳态、能量代谢以及 BA 的合成、结合和转运[70]。肠道菌群能将宿主衍生的初级胆汁酸转化为次级胆汁酸，在胆汁酸合成、修饰和信号传导中发挥巨大作用，同时当菌群酶促反应发生变化时，尤其是胆汁盐水解酶，胆汁酸的组成也会发生变化，从而促进脂肪的吸收并导致肥胖。研究表明与健康受试者相比，超重和肥胖受试者的初级胆汁酸比例明显降低，尤其是非 12-OH 胆汁酸，同时高脂饮食易胖组和抵抗肥胖动物实验表明，高脂肪饮食喂养的易肥胖组和抵抗肥胖组之间的微生物群组成没有显着差异，但在易胖组中存在大量的梭状芽胞杆菌(*Clostridium scindens* 和 *Clostridium hylemonae*)较抵抗肥胖组中具有显著差异。*Clostridium scindens* 和 *Clostridium hylemonae* *都是 XIVa* 梭状芽胞杆菌的成员，是 BA 代谢的重要物种，具有高生物转化能力，这些细菌会改变 BA 的代谢并促进肥胖，表明胆汁酸与肠道菌群失调相关会增加肥胖易感性[71]。因此，胆汁酸对维持代谢稳态和控制调节宿主代谢的细菌生长是必不可少的，这使胆汁酸及其受体不仅作为诊断生物标志物，也为代谢综合征治疗提供潜在的治疗靶点[72]。

3.3. 色氨酸

色氨酸是一种必需的芳香族氨基酸，人体无法自行合成，必须从食物中获取。被人体摄入后大部分在小肠中被消化吸收，还有一部分能到达结肠被肠道菌群所利用作为大量微生物和宿主代谢物的生物合成前体。色氨酸影响多种病理生理功能，包括新陈代谢、炎症反应、氧化应激、免疫反应、肠道稳态等[73]。

3.3.1. 色氨酸代谢通路

主要分为 3 条途径(图 1)：1) 通过 IDO1 作用的免疫和上皮细胞的犬尿氨酸通路；2) 通过 TpH1 作用的肠嗜铬细胞的 5-羟色胺途径；3) 通过肠道菌群作用的吲哚通路。

3.3.2. 犬尿氨酸通路与肥胖

犬尿氨酸通路是最主要的色氨酸代谢通路，约 90%的色氨酸通过犬尿氨酸通路降解为犬尿氨酸，犬尿烯酸，喹啉酸，2-吡啶甲酸，*烟酰胺腺嘌呤*二核苷酸[74]，IDO 主要在肝外表达，TDO 几乎都在肝内表达[75]。在代谢综合征患者中，IDO1 过度表达与血清 Kyn 水平升高有关，Kyn/Trp 比值作为 IDO1 活性标志物与肥胖、代谢综合征、BMI 和 TC 存在相关性[76]。在代谢综合症患者中，IDO1 活性与血清犬尿氨酸水平增加以及 Kyn/Trp 比值呈正相关，该比值与 BMI 和 TC 存在正相关性[77]。同时一项动物实验表明小鼠肠道 IDO 活性的增加会促进色氨酸分解为犬尿氨酸，改变肠道内色氨酸代谢平衡和菌群组成，从而促进肥胖和糖尿病，当敲除 IDO 后将有利于肠道菌群介导的代谢[78]。

3.3.3. 5-羟色胺通路与肥胖

约 3%的色氨酸经由 TpH 合成 5-羟色胺和褪黑激素，5-羟色胺通过 TpH2 在大脑中产生，但是超过 90%的 5-羟色胺由肠道产生，作为胃肠道信号分子，影响肠道蠕动，肠源性血清素也能诱导食欲和饱腹感，在空腹时会上升，刺激脂肪组织的分解和肝细胞的糖异生[79]。在一项队列研究表明，超重/肥胖的受试者 5-羟色胺水平低，BMI 与 5-羟色胺呈负相关[80]。

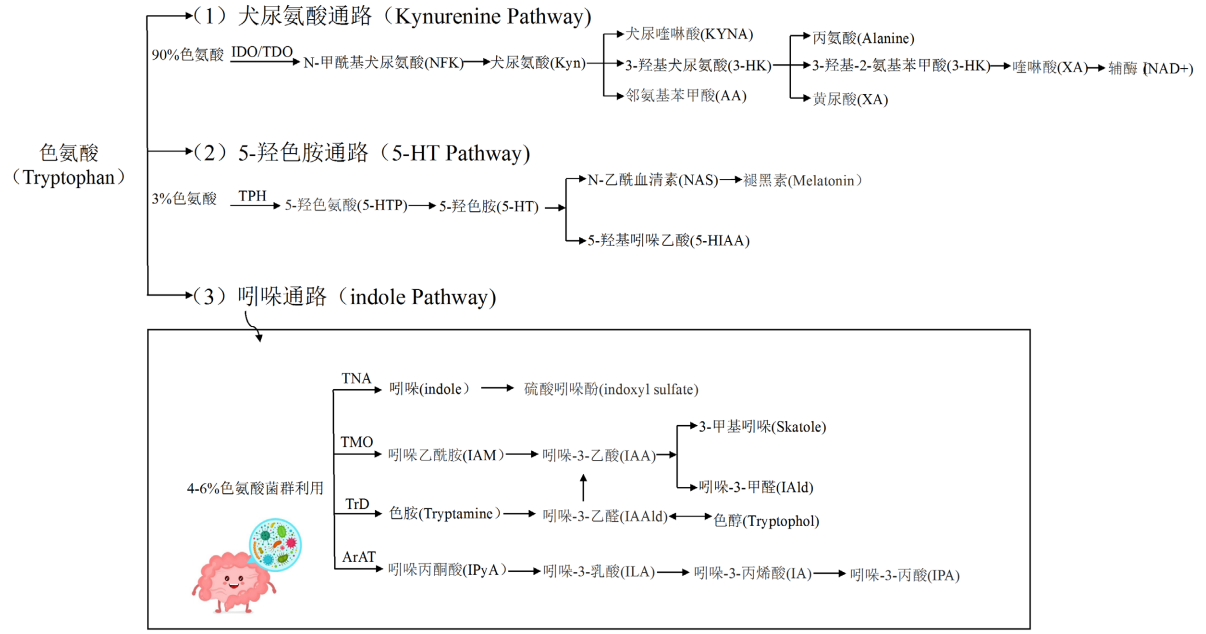

Figure 1. Tryptophan metabolic pathway
图 1. 色氨酸代谢通路

3.3.4. 吲哚通路与肥胖

4%~6%的色氨酸可以被肠道菌群直接利用代谢为吲哚及其衍生物，例如色胺、吲哚-3-乙酸、3-甲基吲哚、吲哚-3-甲醛、吲哚-3-乳酸和吲哚-3 丙酸。肠道菌群中的生孢梭菌和瘤胃球菌属将色氨酸转化为色胺，拟杆菌和梭菌将色氨酸转化为吲哚-3-乙酸和 3-甲级吲哚，乳杆菌将色氨酸转化为吲哚-3-醛，拟杆、梭菌和双歧菌将色氨酸转化为吲哚-3-乳酸，梭菌和链球菌将色氨酸转化为吲哚-3-丙酸[81]。

肠道菌群可以将未吸收的色氨酸转化为吲哚及其衍生物，肠道菌群产生的吲哚可以刺激肠内分泌细胞分泌 GLP-1，诱导胰岛素释放，延迟胃排空增加饱腹感，通过减少胃动力改善肥胖[82]。色胺在代谢综合症患者中具有较高水平，与葡萄糖耐量呈正相关，动物实验同样证明由瘤胃球菌(*Ruminococcus gnavus*)产生色胺会直接损害健康小鼠和猴子胰岛素信号肠道，导致代谢综合征[83]。吲哚-3-乙酸可以通过改善胰岛素抵抗和脂质代谢、氧化和炎症应激来减轻高脂饮食诱导的肝脏损伤[84]。3-甲基吲哚浓度的增加可以作为肠道疾病发展的标志物，在肠道疾病中 3-甲基吲哚浓度升高[85]。吲哚-3-醛可以激活 AhR-IL22 来恢复肠道黏膜完整性，缓解肝脏炎症和纤维化[86]。研究报告称综合症患者和高脂饮食诱导小鼠的吲哚乳酸水平与 BMI 呈强烈负相关，并且产吲哚乳酸的乳酸杆菌将通过 PXR 介导 IL-35^{+}B 细胞减缓肥胖的发展[87]。吲哚-3-乳酸主要有婴儿双歧杆菌所产生，吲哚-3-乳酸能增加 AhR 靶基因 CYP1A1 进而显著减弱由 TNF-α-和 LPS 诱导的肠屏障损伤，改善肠道上皮细胞炎症[88]。最新研究揭示了肠道菌群代谢产物吲哚-3-乳酸能够改善肠道炎症、肿瘤生长和肠道菌群失调[89]。吲哚-3-丙酸作为肠道衍生的色氨酸代谢产物，被报道在肥胖和 T2D 糖尿病患者水平低[90] [91]。吲哚-3-丙酸具有抗氧化、抗炎、抗高血糖、肠道、肝脏和神经保护作用[92]。一项人群研究报道超重和肥胖儿童的吲哚-3-丙酸水平明显低于正常体重儿童，且吲哚-3-乳酸水平与 BMI、腰围和高密度脂蛋白胆固醇呈反比[93]。同时动物实验表明肥胖与血清吲哚-3-丙酸水平呈负相关、降低小鼠结肠吲哚-3-丙酸的水平，然而对高脂饮食小鼠给予吲哚-3-丙酸治疗后，改善了脂肪炎症，下调了结肠炎症，防止了高脂饮食引起的肥胖和代谢紊乱的发展[94]。

4. 益生元定义

益生元概念于 1995 年由 Glenn Gibson 和 Marcel Roberfroid 首次提出被定义为“一种不易消化的食物成分，通过选择性地刺激结肠中的一种或少数几种细菌的生长或活动，对宿主产生有益影响”，并于 2016 年 12 月进行更新了益生元定义，“一种由宿主微生物选择性利用的底物，具有健康益处”[95]。益生元被菌群选择性利用发酵后产生益生元效应，包括防御病原体、调节免疫功能、增加矿物质吸收、改善肠道功能、影响代谢和调节食欲[96]。

益生元有很多种，包括果糖、半乳寡糖、淀粉和葡萄糖衍生的寡糖，其他寡糖，非碳水化合物寡糖，其中最为广泛的就是寡糖[97]。寡糖是指聚合度低、分子量低的碳水化合物，由 2~10 个糖苷键聚合而成，也称之为低聚糖。

5. 褐藻寡糖(AOS)

褐藻寡糖是海藻酸盐降解得到的具有不同比例的聚合程度(DP)线性寡聚物，由 β-D-甘露酸(M)和 α-L-谷氨酸(G)组成，并由 β-1,4-糖苷键连接，且相比于海藻酸盐，通过酸水解、氧化降解和酶降解产生的褐藻寡糖具有更低的分子量、粘度、溶解度和生物利用度[98]。不同比例 DP 的褐藻寡糖具有不同的生物活性，当褐藻寡糖的聚合程度降低的时候，一般不超过 4，具有一定的抗肥胖作用[98]。不同降解方法、G/M 比值、分子量使褐藻寡糖具有各种生物活性，通常来说，褐藻寡糖具有抗肿瘤、抗氧化、免疫调节、抗炎、神经保护、抗菌、低血脂、抗高血压和降血糖特性，以及抑制肥胖、促进细胞增殖和调节植物生长的能力[99]。研究表明，AOS 可以通过抑制高脂饮食诱导的肥胖斑马鱼中 STOML2 的过度表达来改善免疫代谢以及通过激活 AMPK 信号通路抑制脂肪生成，提高肥胖斑马鱼的能量的消耗具有抗脂肪生成活性[100]。李等人发现不饱和褐藻寡糖比酸水解饱和褐藻寡糖抗肥胖效果更加显著，能显著降低体重、血脂、脂肪质量、肝脏损伤，并且不饱和褐藻寡糖(UAOS)可以通过激活 AMPK 信号通路抑制脂肪生成和脂肪细胞分化而改善高脂饮食诱导的肥胖[101]。在另一项肥胖小鼠实验发现 UAOS 通过选择性地增加有益肠道菌(*Lactobacillus*、*Akkermansia* 等)的相对丰度，并减少了促炎菌(*Bacteroides*、*Parabacteroides* 等)的相对丰度以减轻 HFD 诱导的肥胖和相关代谢综合征，改善了与肥胖相关的代谢异常，包括高脂血症、胰岛素抵抗、葡萄糖耐量、炎症反应[102]。这些结果表明 AOS 可能是治疗肥胖症的候选益生元，且抗肥胖作用与肠道菌群调节密切。

6. 结论和观点

我们发现肥胖已经成为了全球公共卫生问题，并正处于迅速恶化发展阶段。虽然肥胖的病因是多因素的，是复杂的，但最近大量研究表明，肠道菌群及其代谢产物与肥胖密切相关。肠道菌群紊乱易导致肥胖和其相关疾病的发生发展。在益生元的干预下能一定程度改善菌群紊乱，这为我们提供了预防或治疗肥胖的机会。褐藻寡糖作为一种益生元，可以被利用降解，进而调节肠道菌群及其代谢产物短链脂肪酸，增加有益菌，减少有害菌。因此，补充褐藻寡糖可能是治疗肥胖及相关代谢疾病的方法。最近研究表明褐藻寡糖主要通过调节肠道菌群和激活 AMPK 信号通路发挥抗肥胖作用，然而通过肠道菌群调节的研究还在少数，缺乏褐藻寡糖与肠道菌群代谢产物色氨酸的相关研究，且研究尚未涉及人群临床实验。尽管存在这些问题，但褐藻寡糖具有巨大的研究意义和开发、应用价值。在未来的研究中，研究人员可以集中于褐藻寡糖与肠道菌群，尤其是褐藻寡糖是否能够调控色氨酸代谢通路改善肥胖相关代谢综合征，以提供更多的机制研究并应用到人群进行临床实验验证，使褐藻寡糖应用更具有可靠性和说服性。

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