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Sortilin蛋白在脂质代谢中的研究进展

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摘　要

血脂异常是导致各种心血管代谢疾病的重要危险因素，严重影响人类健康。Sortilin作为液泡分拣因子10结构域受体家族的一员，充当细胞的受体或共同受体，介导在细胞内靶向运输不同的蛋白质。它首次在人脑中发现，并广泛表达于神经元、肝细胞、脂肪细胞和巨噬细胞等。近年研究表明，sortilin与脂质代谢相关基因的表达、脂质的合成、转运、分解代谢等密切相关。Sortilin对脂质代谢的多重作用提示其有望作为心血管疾病等脂质代谢相关疾病的潜在治疗靶点。本文将对sortilin在脂质代谢中的作用作一综述。

关键词

Sortilin，脂质代谢，胰岛素抵抗

Research Progress of Sortilin Protein in Lipid Metabolism

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Abstract

Dyslipidemia has been considered a key factor associated with a series of cardiovascular and me-

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tabolic diseases, which seriously affects human health. Sortilin, a member of the vacuolar protein sorting 10 protein (Vps10p) domain receptor family, acts as receptor or co-receptor, mediating the targeted transport of different proteins within cells. It was first discovered in the human brain and is widely expressed in neurons, hepatocytes, adipocytes, and macrophages. Recent studies have shown that sortilin is closely related to the expression of lipid metabolism-related genes, lipid synthesis, transport, and catabolism. The multiple effects of sortilin on lipid metabolism suggest that it may be a potential therapeutic target for lipid metabolism-related diseases such as cardiovascular disease. This article will review the role of sortilin in lipid metabolism.

Keywords

Sortilin, Lipid Metabolism, Insulin Resistance

1. 引言

脂质在维持正常细胞生理结构及功能中发挥重要作用。血脂异常，包括血浆低密度脂蛋白胆固醇(Low-Density Lipoprotein Cholesterol, LDL-C)、极低密度脂蛋白胆固醇(Very-Low Density Lipoprotein Cholesterol, VLDL-C)和甘油三酯(Triglyceride, TG)水平升高，以及高密度脂蛋白胆固醇 High-Density Lipoprotein Cholesterol, HDL-C)水平降低。近几十年来，血脂异常已对人类健康构成严重威胁，并与肥胖、动脉粥样硬化、2 型糖尿病、脂肪肝等多种疾病密切相关[1]。SORT1 编码的 Sortilin 蛋白又称神经降压素受体-3，它最早在人脑组织中发现，在许多组织如肝脏、脂肪、心血管组织中也有表达[2]。近年研究发现，sortilin 蛋白在调节脂质代谢中起着重要作用。

2. Sortilin 蛋白的结构与功能

Sortilin 是一种由染色体 1p13 上的 SORT1 基因编码的 I 型跨膜多配体受体，属于液泡蛋白分拣 10 蛋白(vacuolar sorting protein 10 protein, Vps10p)结构域受体家族，分子量为 95 kDa。其主要在神经元、肝细胞、脂肪细胞和包括巨噬细胞在内的白细胞中表达[2]。Sortilin 的结构由 Vps10p 结构域、跨膜螺旋和细胞质尾部组成，这是内质体运输所必需的。Sortilin 前体在内质网中合成，并在跨高尔基体网络中切割加工成其成熟形式，其水平在细胞中最高。大部分的 sortilin 位于高尔基体，并作为溶酶体分拣受体发挥作用，而小部分的 sortilin 位于细胞膜上，通过受体介导的内吞作用控制跨膜蛋白的转运[2]。

越来越多的证据表明，sortilin 已经成为一种与脂质代谢密切相关的因子[3] [4]。Sortilin 广泛表达于与脂质代谢密切相关的细胞中，如巨噬细胞、肝细胞、脂肪细胞[5]。在基因层面上，SORT1 在人类中的广泛测序已鉴定出几种常见的单核苷酸多态性，长期的流行病学研究表明血浆脂质水平和 SORT1 基因之间有很强的关联[6]。Sortilin 参与脂质代谢的多种生物学过程，并与脂质紊乱显著相关。在细胞膜上，sortilin 主要参与了受体介导的内吞作用以及作为一种摄取受体，介导巨噬细胞对天然低密度脂蛋白的摄取[7]；在细胞内，sortilin 作为高尔基体、内体、溶酶体和细胞膜之间的转运蛋白，并介导不同配体的转运，如脂蛋白脂酶、载脂蛋白 E、载脂蛋白 A5 和载脂蛋白 B100 [8]。

3. Sortilin 的脂质代谢调控作用

3.1. Sortilin 对成脂分化的影响

脂肪组织中含有大量的脂肪来源的间充质干细胞(mesenchymal stem cells, MSCs)，它们经过有丝分裂克隆扩增,终末分化等阶段最终分化为成熟的脂肪细胞。成脂分化受到来自环境及细胞内外多个因子的整合调控并会发生基因表达和形态的变化，例如 CCAAT/增强子结合蛋白 β (CCAAT/enhancer binding proteins beta, C/EBPβ)是成脂分化早期的重要转录因子[9]，它可激活 CCAAT/增强子结合蛋白 α (CCAAT/enhancer binding proteins alpha, C/EBPα)和过氧化物酶体增殖物激活受体 γ (peroxisome proliferators-activated receptors, PPARγ) [10]。PPARγ 在脂肪细胞分化、脂肪酸吸收和脂肪生成中起重要作用。Breitling 等发现 SORT1 基因在人前体脂肪细胞分化的过程中表达增加[11]；另一项研究发现 sortilin 可通过与前体脂肪细胞因子(delta like non-canonical Notch ligand 1, DLK1)的结合抑制 DLK1 的降解，DLK1 的活性片段可进一步降低前脂肪细胞内 C/EBPβ 和 C/EBPα 的表达，显著抑制前脂肪细胞的成脂过程，提示 sortilin 具有抑制成脂分化的能力[12]。脂联素是一种与脂肪生成程度负相关的脂肪因子[13]，有研究发现，高脂肪高胆固醇饮食的 LDLR/SORT1 双基因敲除小鼠血浆脂联素水平更高，提示 sortilin 还可能通过调节脂联素影响成脂分化过程[14]。

3.2. Sortilin 对脂质合成的影响

在脂肪酸合成过程中，多种代谢酶作用至关重要，其中脂肪酸合成酶(fatty acid synthase, FAS)是脂肪酸合成中的关键酶；硬脂酰辅酶 A 去饱和酶 1 (Stearoyl-coenzyme A desatu-rase 1, SCD1)是催化饱和脂肪酸向单不饱和脂肪酸转化的关键限速酶，其催化产物单不饱和脂肪酸是甘油三酯、胆固醇酯、磷脂等形成的重要底物[15]。Rabinowich 等发现 SORT1 敲除小鼠的肝细胞中编码 FAS 和 SCD1 的基因显著下调，并显示出较低的肝细胞间 LDL-C 浓度，提示这可能是 sortilin 影响肝细胞中的脂肪合成及储存的机制之一[16]。

3.3. Sortilin 蛋白对脂质摄取、转运的影响

人体内胆固醇的来源主要包括肠道内吸收和肝脏及外周组织的从头合成。胆固醇经肠道吸收在机体胆固醇稳态的调节中起到了至关重要的作用。胆固醇转运体尼曼－匹克 C1 型样蛋白 1 (Niemann-Pick type C1-Like, NPC1L1)是肠道胆固醇吸收的关键转运蛋白，也是治疗高胆固醇血症药物依折麦布的作用靶点[17]。Hagita 等人发现在 LDLR 基因敲除的雌性小鼠中，敲除 sortilin 基因可抑制小鼠 NPC1L1 基因的表达，抑制了小鼠肠道组织对胆固醇的吸收，从而减轻了小鼠体重和白色脂肪组织的重量。他们还发现 Sort1 的缺乏抑制了体外肠道组织和人结肠 Caco-2 细胞对胆固醇的吸收[14]。

在肝细胞中，甘油三酯与载脂蛋白 B100 (Apolipoprotein B 100, apoB100)、胆固醇等结合，形成 VLDL 并释放入血，随后转变为 LDL。前蛋白转化酶枯草溶菌素 9 (Proprotein convertase subtilisin/kexin type 9, PCSK9)也可通过 LDLR 结合，触发其细胞内降解，导致 LDL 从循环中的清除率降低。研究发现 sortilin 可与肝细胞中的 PCSK9 结合并促进 PCSK9 的分泌，导致 LDLR 的降解和血浆中 LDL-C 水平的升高[18] [19] [20]。Kjolby 等人发现 Sort1 敲除小鼠血浆 LDL-C、apoB100 和 TG 分泌减少；利用腺病毒使肝脏过度表达 SORT1 会导致血浆胆固醇和 apoB100 质量增加。他们推测机制是 sortilin 在肝细胞高尔基体中与 apoB100 相互作用促进 VLDL 分泌，从而增加血浆中 LDL-C 的水平[21]。然而，Musunuru 等人发现 SORT1 的过度表达导致肝细胞对 LDL-C 摄取增强和血浆 LDL-C 浓度降低[22]。Bi 等人发现过表达 sortilin 会减少原代小鼠肝细胞和 HepG2 细胞的 apoB 分泌[23]。最近一项研究发现，在非应激条件下，sortilin 缺乏

对肝细胞 apoB 分泌的影响很小，但在脂质负荷或内质网应激下，sortilin 的缺乏会导致 apoB 分泌的增加[24]。综上，sortilin 对血脂水平和肝脏含载脂蛋白 B 的脂蛋白代谢的调节作用是矛盾的，这些结果的差异可能取决于不同的小鼠模型，病理生理状态和敲除 SORT1 的方法，未来需要更多研究探讨 sortilin 在肝细胞中脂质转运的真正作用。

在高脂血症中，巨噬细胞吞噬 LDL-C 并形成泡沫细胞，这些泡沫细胞向内皮下层转移，导致动脉粥样硬化的发生发展。Patel 等在 SORT1 敲除小鼠中，发现缺乏 SORT1 的巨噬细胞对 LDL-C 的摄取显著减少，进而抑制泡沫细胞的形成；而巨噬细胞中 sortilin 的过度表达则促进了 LDL-C 摄取和泡沫细胞形成[18] [25]，进而加速动脉粥样硬化。此外，巨噬细胞还能通过多种转运体介导的胆固醇流出过程清除细胞内过量的 LDL-C，从而抑制泡沫细胞的形成。巨噬细胞中的 sortilin 可促进胆固醇外排转运体的溶酶体降解，最终导致巨噬细胞产生脂质流出减少，加速泡沫细胞的形成，促进动脉粥样硬化[26] [27]。

3.4. Sortilin 对脂质分解的影响

胆固醇的分解代谢在肝脏内进行。胆固醇大部分可转变为胆汁酸，小部分经肠道内细菌作用转变为粪固醇随粪便排出体外。胆汁酸合成途径在清除体内胆固醇中起着关键作用，羧酸酯酶 1 (carboxylesterase 1, CES1)已被证明通过促进胆固醇进入胆汁酸合成途径来防止肝脏脂质堆积[28]。Li 等通过体内和体外实验发现，在高脂饮食条件下，sortilin 通过将 CES1 输送到溶酶体进行降解来降低 CES1 蛋白；抑制 SORT1-/-小鼠的肝脏 CES1 的表达能够显著增加血浆 VLDL-C 水平，促进肝胆固醇积聚，加重肝损伤。sortilin 通过减少 CES1 的表达来抑制胆固醇的分解代谢，从而促进肝脏胆固醇积累[29]。此外，胆固醇 7α-羟化酶(cholesterol 7α-hydroxylase, CYP7A1)也是胆汁酸合成途径的关键酶。Sortilin 还可能通过抑制肝 CYP7A1 催化的胆汁酸合成来促进肝脏胆固醇积累[30]。以上结果均提示 sortiin 可能通过影响胆汁酸合成途径，这与肝脏脂质累积和非酒精性脂肪肝发病相关。

3.5. Sortilin 与胰岛素抵抗

研究表明胰岛素抵抗引起肝脏 SORT1 表达降低，这提示 sortilin 可能在胰岛素信号通路以及胰岛素抵抗的脂代谢紊乱中发挥作用[31]。在胰岛素敏感的条件下，肝脏 sortilin 蛋白通过溶酶体途径减少和降解，从而降低了 apoB100 的产生，从而使肝脏 apoB100、VLDL 和血浆脂质的水平保持在正常范围内。但在胰岛素抵抗的情况下，肝 sortilin 蛋白通过蛋白酶体依赖性途径直接降解，从而干扰 sortiin 介导的肝脏 apoB100 合成和 VLDL 分泌到血浆。但胰岛素抵抗条件下血浆脂质不能被外周细胞长期吸收，这会盖过 sortilin 减少对血脂产生的影响，从而引起 D2M 的高脂血症[32]。

在脂肪细胞中，sortilin 与葡萄糖转运蛋白 4 (Glucose Transporter 4, GLUT4)共定位，是 GLUT4 储存囊中的主要蛋白质之一。Sortilin 负责在脂肪细胞和心肌细胞中形成胰岛素反应性 GLUT4 储存囊，刺激胰岛素调节的葡萄糖摄取。因此，sortilin 水平的降低可能会阻止 GLUT4 的运输和分泌，进而与胰岛素抵抗和 2 型糖尿病发病相关[33] [34]。另一项研究表明肥胖中的慢性低级别炎症可能通过调节控制 sortilin 而导致胰岛素抵抗[35]。

4. 总结与展望

综上所述，sortilin 对脂质代谢具有调控作用，sortilin 可影响成脂分化；影响肝细胞中的脂肪合成及储存；影响胆固醇在肠道的吸收，调节胆固醇在肝细胞、巨噬细胞的转运；影响肝脏胆汁酸合成和胆固醇排泄抑制肝脏胆固醇分解代谢，促进肝脏脂质积聚。研究发现通过调控 sortilin 可以降低肥胖、代谢紊乱和肝脏脂肪变性的发生几率[36]；sortilin 可以保护肝窦内皮细胞免受氧化修饰的 LDL-C 诱导的损伤[37]；

另有研究发现 microRNA-378a-3p 可通过调节 SORT1-apoB100 轴来控制循环甘油三酯和胆固醇的水平，提示其可作为血脂异常的治疗靶点[38]；以上均提示以 sortilin 为靶点在脂质代谢相关疾病的治疗中具有良好应用前景。然而，sortilin 作为一种分拣受体，对脂质复杂的运输行为可能导致了其在脂质代谢中的矛盾作用，未来需要进一步研究 sortilin 在各组织器官生理及病理条件下的作用及机制，完善机体脂质代谢相关理论体系，为脂代谢紊乱疾病的防治提供新思路。

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