· 综述 ·

CTRP 家族与糖尿病及其并发症

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【摘要】 补体 C1q/肿瘤坏死因子相关蛋白（CTRP）家族是近来新发现的脂肪因子，与脂联素具有高度同源性。CTRP 家族在糖、脂代谢、能量代谢、炎性反应调控、血管保护中发挥重要作用。近年来研究发现，CTRP 家族可以调控糖代谢、影响胰岛素抵抗等过程，参与糖尿病及其并发症的发生、发展，并有望为糖尿病及其并发症提供新的靶点。

【关键词】 CTRP 蛋白；糖尿病；糖尿病并发症
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【Abstract】 Complement-C1q/tumor necrosis factor-related protein (CTRP) family is a recently discovered adipokine, which is highly homologous with adiponectin. CTRP family plays an important role in the regulation of glycolipid metabolism, energy metabolism, inflammatory response and vascular protection. In recent years, the researchers found that CTRP family members can participate in the development of diabetes and its complications by regulating glucose metabolism, affecting insulin resistance, and is expected to provide new therapeutic targets for diabetes and its complications.

【Key words】 Complement-C1q/tumor necrosis factor-related protein; Diabetes mellitus; Diabetic complications
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脂肪组织不仅是机体能量的储存器官，而且是一个重要的内分泌器官，分泌和表达多种蛋白质，如脂联素、抵抗素、瘦素等[1]。新近研究表明，补体 C1q/肿瘤坏死因子相关蛋白（CTRP）属于脂肪细胞因子超家族，可以直接或间接的调节葡萄糖代谢，影响胰岛素敏感性，调控炎性反应，与糖尿病及其并发症密切相关。

1　CTRP 家族成员的结构与组织表达

CTRP 家族由一组高度保守，与脂联素结构相似的蛋白质组成[2]。其属于 C1q 家族的小分泌蛋白，共包括 15 个成员，分别为 CTRP 1～15，每个成员都有一个共同的结构，分别由氨基末端的信号肽、一个短的可变区域、一个胶原样结构域和一个羧基末端的球形结构域组成，其中羧基末端球形结构域是发挥生物学功能的重要结构。各个成员均可形成同源三聚体，多数成员可形成同源六聚体或高分子量的多聚体。CTRP 蛋白家族在组织表达中存在差异，其中，脂肪组织中表达 CTRP 家族种类最多，包括CTRP1～7、CTRP9、CTRP11～13。肺和睾丸主要表达CTRP7、CTRP8，胎盘主要表达CTRP1、CTRP3、CTRP6、CTRP10，心脏主要表达CTRP1、CTRP9，软骨细胞主要表达 CTRP3，同时发现 CTRP5 在人视网膜色素上皮细胞特异性表达。

2　CTRP 家族与糖尿病

2.1　CTRP 家族与糖代谢　CTRP 家族成员通过调控糖代谢，降低血糖。研究显示，重组 CTRP1 可激活分化的小鼠肌管中蛋白激酶 B（Akt）和 p44/42 丝裂原活化蛋白激酶（MAPK）信号通路，Akt 的激活增加了葡萄糖转运蛋白 4 向质膜的转运，从而增强肌肉组织对葡萄糖的吸收[3]。Peterson等[4]在培养大鼠 H4IIE 肝细胞中发现，重组 CTRP1 并没有改变 AMPK 信号途径、葡萄糖输出、糖异生基因表达，而是激活骨骼肌中AMPK信号途径，使乙酰辅酶 A 羧化酶磷酸化，增强脂肪酸氧化和能量消耗。以上研究

表明,肌肉组织可能是 CTRP 家族成员降糖的作用靶点,并且直接影响肌肉组织中的信号通路和糖代谢。

临床试验发现,与对照组相比,糖尿病前期者与 2 型糖尿病患者血浆 CTRP3 水平明显降低[5],表明 CTRP3可能与血糖有密切联系。相关动物实验也证实了这一点,Peterson 等[6] 通过重组蛋白CTRP3给药,发现野生型小鼠和肥胖 ob/ob 小鼠中血浆 CTRP3 水平增加 3 倍,血糖水平明显降低,并且未影响胰岛素、胰高血糖素和脂联素水平;其原因是 CTRP3激活肝脏中 Akt 信号通路,抑制肝脏糖异生酶的表达。表明CTRP3作为一种新的脂肪因子,在糖代谢中起重要作用。另外研究发现,过表达 CTRP9可以降低 ob/ob 小鼠血糖水平,同时,CTRP9 可以刺激分化的肌管中 AMPK、Akt 和p44/42 MAPK 磷酸化[7]。CTRP12 可通过激活磷脂酰肌醇 3 激酶(PI3K)-Akt信号通路,抑制肝细胞糖异生,促进脂肪细胞对葡萄糖的摄取,增强糖尿病小鼠脂肪组织和肝脏的胰岛素信号转导。以上均表明 CTRP 家族成员作为新的脂肪因子,可以通过多种机制调节糖代谢,将可能成为新的一种抗糖尿病因子[8]。

但 Bai 等[9] 最新临床相关试验显示,与对照组相比,2 型糖尿病患者血清 CTRP1 水平明显升高,差异具有统计学意义,而CTRP9与CTRP13无明显差异;行口服葡萄糖耐量试验 2 h 后,血清CTRP1水平显著升高,这些脂肪因子在糖尿病患者中没有降低反而升高,可能为机体保护机制的反馈调节使患者脂肪组织合成增多,亦有可能存在其他因素影响 CTRP家族水平,故CTRP与糖尿病的机制需要进一步研究。

2.2　CTRP 家族与胰岛素抵抗　Xin 等[10] 发现,CTRP1不仅增加脂肪细胞对葡萄糖的利用率,并且通过作用于胰岛素受体底物(IRS)-1 Ser^{1101} 的磷酸化,降低胰岛素抵抗。动物实验表明,CTRP1 过表达可以增加外周组织胰岛素敏感性,提示CTRP1在胰岛素抵抗中发挥重要作用[11]。相关临床试验发现,糖尿病患者循环CTRP1水平与胰岛素抵抗程度呈负相关[12]。

CTRP3 可以通过减轻炎性反应和改善胰岛素信号转导而改善胰岛素抵抗。研究人员将重组 CTRP3作用于胰岛素抵抗的3T3-L1脂肪细胞,结果白细胞介素-6 和肿瘤坏死因子-α的释放减少,抑制炎性反应,并且增加胰岛素敏感性;此外,CTRP3 还增加了 PI3K 和 Akt 及葡萄糖转运蛋白4 mRNA的表达,从而改善胰岛素信号转导,提高胰岛素敏感性[13]。这些研究表明 CTRP3 直接影响脂肪细胞内信号通路,抑制脂肪组织炎性反应,对抗胰岛素抵抗的发生。

另有实验表明,尽管在肥胖小鼠模型中CTRP12 mRNA水平受到抑制,但给予抗糖尿病药物罗格列酮后可上调该因子的表达,提示其在促进胰岛素敏感性方面可能起作用。给予腺病毒载体介导的 CTRP12可降低肥胖小鼠脂肪组织中巨噬细胞的积累和促炎基因的表达[14]。表明CTRP12可以通过抑制脂肪组织炎性反应,阻止胰岛素抵抗的发生,增加胰岛素敏感性,对糖尿病的防治可能起到关键性作用。

3　CTRP 家族与糖尿病并发症

3.1　CTRP 家族与糖尿病大血管并发症　以往的研究提示,CTRP9对大血管具有保护作用[15]。已证实 CTRP9 可减轻糖尿病小鼠主动脉内皮细胞活性氧簇的产生,抑制氧化应激,且增加内源性抗氧化酶的表达,提示CTRP9对高糖诱导的氧化应激具有保护作用[16]。线粒体生物合成已被发现有助于减轻氧化应激作用[17]。研究报道,在高糖处理的内皮细胞线粒体生物合成过程中,过氧化物酶体增殖物活化受体 γ 协同刺激因子-1α(PGC-1α)是一种重要的辅激活因子,PGC-1α在内皮细胞中的过度表达可上调线粒体膜电位和抑制细胞凋亡[18-19]。沉默信息调节因子 1(SIRT1)介导的PGC-1α去乙酰化是激活线粒体脂肪酸氧化基因所必需的[20]。Cheng等[16] 表明,CTRP9 可以通过上调PGC-1α和SIRT1表达,增加线粒体的合成,提示 CTRP9 可以减轻氧化应激,增加线粒体合成从而保护内皮细胞功能。

3.2　CTRP 家族与糖尿病微血管并发症　临床研究显示,在糖尿病视网膜病变非增殖期患者玻璃体中血管内皮细胞黏附因子-1(VCAM-1)水平升高,而 VCAM-1水平可能反映内皮细胞损伤[21-22]。Yan 等[23] 发现,CTRP3可以通过激活AMPK信号通路,抑制在高糖诱导下视网膜微血管内皮细胞VCAM-1的表达,ELISA法检测人血清中CTRP3含量,与对照组相比,糖尿病视网膜病变非增殖期与增殖期患者血清CTRP3水平逐渐降低,提示CTRP3对糖尿病视网膜病变的保护作用,其机制可能为CTRP3通过激活AMPK通路抑制VCAM堆积,保护视网膜微血管内皮细胞。糖尿病心肌病是糖尿病患者心力衰竭的主要诱因[24]。研究发现,在糖尿病大鼠心肌细胞中

CTRP3表达明显降低，敲除CTRP3基因后发现，心肌细胞氧化应激与炎性因子表达增加，心肌细胞存活率降低。通过链脲佐菌素诱导糖尿病大鼠心脏损伤和心功能减退模型，发现CTRP3可以改善糖尿病引起的心脏损伤与心功能不全[25]。结果表明，CTRP3具有治疗糖尿病心肌病变的潜力，机制为通过激活AMPK 通路，抑制氧化应激与炎性因子的表达，减少心肌细胞死亡，保护心功能。这也为治疗糖尿病心肌病提供了一种很有前景的方法。

综上所述，CTRP家族成员作为新发现的脂肪因子，与糖尿病以及糖尿病并发症存在密切关系。但现在的研究仍然十分局限，其生物作用需要更多临床试验支持。因此，深入了解 CTRP 家族将有助于加深对疾病的了解。

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