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· 综 述 ·

补体 C1q/ 肿瘤坏死因子相关蛋白在冠心病中的研究进展

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〔摘要〕 补体 C1q/ 肿瘤坏死因子相关蛋白 (CTRP) 是近年来炎症性和代谢性疾病, 如冠心病、2 型糖尿病、肥胖症等研究领域的热点分子。CTRP 可通过多条信号通路影响炎症激活、血管内皮损伤、脂肪代谢、血糖调控等。而冠心病与血管炎症相关, 且患者常伴发代谢性疾病。因此, 本文就 CTRP 在冠心病中作用的研究进展作一综述, 以期对冠心病的预防、诊断和治疗提供新靶点。

〔关键词〕 补体 C1q/ 肿瘤坏死因子相关蛋白; 冠心病; 炎症; 代谢性疾病

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Research progress of complement C1q/tumor necrosis factor-related proteins for coronary heart disease

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〔Abstract〕 Complement C1q/tumor necrosis factor-related proteins (CTRP) is a hot molecule in recent research fields on inflammatory and metabolic diseases such as coronary heart disease, type 2 diabetes, and obesity. CTRPs have impacts on inflammation activation, vascular endothelial injury, fat metabolism, and blood glucose regulation through multiple signaling pathways. Coronary heart disease is related to vascular inflammation, and mostly accompanied by metabolic diseases. This paper reviews the research progress of CTRPs in coronary heart disease, so to provide new targets for the prevention, diagnosis, and treatment of coronary heart disease.

〔Key Words〕 complement C1q/tumor necrosis factor-related protein; coronary heart disease; inflammation; metabolic disease

作为组成补体 C1 的重要成分之一, 补体 C1q 在触发激活经典免疫途径中起关键作用^[1]。其通过 C-末端的球状结构域结合多种细胞和血浆蛋白来发挥生物活性。许多非补体蛋白也具有与 C1q 相似的球状结构域, 称为 C1q 家族蛋白^[2]。该类蛋白与肿瘤坏死因子在晶体结构上相似, 同属脂肪组织源性细胞因子家族, 命名为补体 C1q/ 肿瘤坏死因子相关蛋白 (complement C1q/tumor necrosis factor-related proteins, CTRPs)^[3]。

目前在脊椎动物中共发现 15 个 CTRPs 家族

成员, 依次命名为 CTRP 1~15^[4]。近年来越来越多的基础研究证实 CTRPs 与心血管疾病以及 2 型糖尿病、胰岛素抵抗及肥胖等代谢性疾病的发生发展关系密切, 有望成为新的潜在诊断和治疗靶点^[5]。我国现有冠心病患者 1 100 万余人, 且患病率及死亡率仍呈上升趋势, 居城乡居民总死亡原因的首位^[6]。本文拟就 CTRPs 在冠心病及其高危因素疾病中的最新研究进展作一综述, 以期对临床诊治冠心病提供新思路。

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1 CTRPs与冠心病危险因素的关系

1.1 高血压病 血压增高会导致动脉硬化和血管壁变厚。高血压病患者的循环CTRP1水平高于健康人,而CTRP1通过刺激血管紧张素Ⅱ受体1-Rho/ROCK信号通路,诱导血管收缩提高血压,并防止脱水引起的低血压来参与维持血压稳态^[7]。CTRP1还可通过促进醛固酮释放,参与高血压的发生^[8]。另外,国内学者^[9]近期在大鼠中发现,CTRP6可通过激活血管紧张素Ⅱ的负调节因子过氧化物酶体增殖物激活受体- γ (PPAR γ)而减轻其诱导的高血压,这为高血压病的治疗提供了新思路。

1.2 肥胖和脂质能量代谢 肥胖或超重可加重心脏负荷,且该类人群常伴脂质代谢异常,是公认的冠心病易感因素^[10]。CTRPs与脂质能量代谢密切相关。CTRP1通过调节乙酰辅酶A羧化酶的磷酸化和失活来增强脂肪酸氧化,缺乏时会破坏能量平衡^[11]。CTRP3主要由脂肪组织表达,在调节新陈代谢方面不可缺少^[12]。肥胖型糖尿病患者血浆CTRP3浓度明显低于健康人,在调整一系列影响因素后,血浆CTRP3浓度仍与肥胖症显著相关^[13]。CTRP4转基因小鼠的食物摄入量增加,但可抵抗肥胖和高血糖,这可能与能降低肝脏脂肪水平和减少脂肪组织中炎症细胞浸润有关^[14]。向小鼠中枢注射CTRP4会下调下丘脑食欲素及相关神经肽基因的表达,使其食物摄入量减少^[15]。CTRP6的敲除使p38MAPK磷酸化增加,防止饮食引起的肥胖,并通过p38MAPK/Hh信号通路结合棕色脂肪标志物和线粒体代谢因子的上调,促进棕色脂肪生成,降低循环三酰甘油水平^[16]。而在小鼠中敲除CTRP9,则发现小鼠进食量增加,引起肝脂肪变性,体质量明显增加,其机制之一可能为CTRP9缺乏可导致下丘脑去氧化性神经肽表达上调^[17]。这些研究为临床上防治肥胖症及改善患者能量代谢提供了新的靶点。

最新研究^[18]发现,CTRP2缺乏上调了脂聚酶和蛋白激酶A表达,从而干扰脂质代谢,促进脂肪组织脂裂解,增加肝脏三酰甘油的分泌。CTRP3转基因小鼠能抵抗肝脏脂肪变性的发展降低血清肿瘤坏死因子- α (TNF- α)水平;持续予以小鼠

CTRP3可显著改善脂肪肝表型^[19]。国内有团队^[20]发现,CTRP6通过肌母细胞中的AdipoR1/Erk/PPAR γ 信号通路介导异位脂肪发生,进而调节脂肪细胞分化、脂肪酸氧化和三酰甘油积累,这为脂质代谢机制的研究提供了新方向。但上述研究更多阐明了CTRPs与三酰甘油代谢的关系,尚缺乏CTRPs介导胆固醇和低密度脂蛋白代谢的研究,待继续探索。

1.3 胰岛素抵抗 胰岛素抵抗是代谢综合征的重要特征,为多种代谢相关疾病的共同病理生理基础,能促进冠心病的发展。CTRP1可通过降低胰岛素受体底物1中的丝氨酸1101的磷酸化来改善胰岛素抵抗^[21]。有研究在高脂喂养诱导的肥胖小鼠模型中发现,CTRP2转基因小鼠胰岛素耐受性和急性脂质升高处理能力提高^[22]。CTRP3和CTRP9也可提高胰岛素敏感性,二甲双胍的降糖作用部分与其能上调CTRP3有关^[23]。CTRP13不仅能通过激活AMPK信号通路来促进培养的肌管、脂肪细胞和肝细胞的葡萄糖摄取,而且能通过下调葡萄糖-6-磷酸酶和磷酸烯醇式丙酮酸羧激酶表达来减少肝细胞的糖异生。胰岛素增敏药物罗格列酮也能上调脂肪细胞中CTRP13的表达,提示CTRP13可能在胰岛素增敏中起作用^[24]。

1.4 糖尿病 糖尿病是冠心病的独立危险因素,而血糖水平受多个CTRPs家族成员的影响。CTRP2可激活AMPK信号通路,刺激肌肉对葡萄糖的摄取,增加糖原累积、脂肪酸氧化,降低2型糖尿病患者的血糖和循环游离脂肪酸水平^[25]。CTRP5可通过p38MAPK和AMPK的磷酸化激活独立于胰岛素作用之外的葡萄糖摄取和脂肪酸氧化,并可改善心肌细胞通过GLUT4介导的葡萄糖摄取^[26]。CTRP6可通过抑制胰岛素刺激的Akt磷酸化调节糖代谢,过表达可使脂肪细胞摄取葡萄糖能力下降^[27]。CTRP10能导致心肌细胞内磷酸化果糖激酶和己糖激酶上调^[28]。因此,有望在CTRPs中找到治疗糖尿病的新靶点。

2 CTRPs与冠心病病理发展的关系

2.1 炎症 炎症假说是冠心病发病机制中较重要的理论之一。CTRPs可通过多条通路参与动脉

炎症发生(图1)。CTRP1可激活S1P/cAMP信号通路,具有抗炎、抗凋亡特性,是一种内源性心脏保护因子^[29]。但近期有研究^[30]发现,CTRP1亦可通过诱导白细胞介素-6和单核细胞趋化蛋白-1等表达促进动脉粥样硬化因子的上调。CTRP1这

种相反的作用可能与翻译后修饰不同有关,仍需进一步探索。CTRP3是一种有效的抗炎脂肪因子,可抑制Toll样受体及核因子 κ B信号通路,降低白细胞介素-6和TNF- α 的表达,有望用于治疗冠心病和2型糖尿病血管损害等炎症性疾病^[31]。

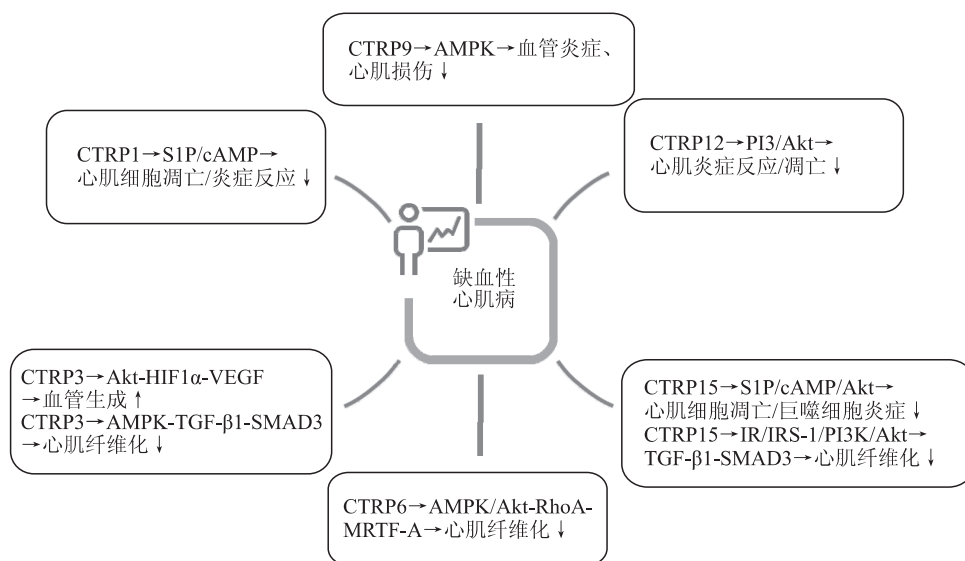


图1 CTRPs在缺血性心脏病中的作用和机制

2.2 血管内皮损伤 血管内皮损伤是动脉粥样硬化形成的重要因素。Shen等^[32]研究了冠状动脉药物洗脱支架植入后血清CTRP5水平与支架内再狭窄的关系,发现发生支架内再狭窄组患者血清中CTRP5水平高于非再狭窄组,推测CTRP5可刺激血管平滑肌内皮细胞增殖和迁移。Wang等^[33]进一步发现,CTRP5是一种促动脉粥样硬化细胞因子,通过上调12/15-脂氧合酶的表达,刺激内皮细胞摄取脂质和发生过氧化反应,促使动脉粥样硬化的发生发展。而CTRP9可改善动脉血管内皮功能障碍,抑制血管平滑肌细胞向巨噬细胞样细胞转分化,抑制病理性血管重塑,减轻内皮损伤,提高斑块稳定性,因此有望成为治疗心脑血管疾病的新靶点^[34]。相似地,CTRP12可通过抑制血管平滑肌细胞生长和减轻巨噬细胞炎症反应来防止病理性血管重塑^[35]。

3 CTRPs与冠心病风险预测的关系

冠心病的严重程度主要取决于病变累及冠脉的数量、狭窄程度和供血心肌范围。CTRP1能促进动脉粥样硬化和血管炎症,可能是筛查高危患

者心血管风险的潜在指标^[36]。急性冠脉综合征患者血清CTRP1水平较健康人升高,且CTRP1与冠心病的患病率和严重程度显著相关^[37]。另一项前瞻性研究^[38]也显示,循环中CTRP1水平升高与主要心血管不良反应风险增加显著相关。这些研究提示CTRP1是冠心病的有预测价值的生物标志物。最近一项研究^[39]表明,男性冠心病患者中,CTRP2高水平与疾病的严重程度独立相关。另一项研究^[40]显示,冠心病患者血清CTRP3水平明显高于非冠心病患者,且CTRP3水平与冠心病严重程度正相关。CTRP5也被发现在冠心病多支病变患者中的循环水平明显低于单支病变患者,并提示CTRP5是冠心病严重程度的独立预测因子^[41]。Petersen等^[42]比较了代谢紊乱人群CTRP7的水平差异,发现与健康消瘦组相比,肥胖人群CTRP7的血清水平显著增高,但冠心病组CTRP7水平明显低于非冠心病组,这可能是由于CTRP7的循环水平受不同饮食或代谢状态的影响。此外,两项病例对照研究^[43-44]显示,冠心病患者的循环CTRP12水平低于健康对照组,且与冠心病风险独立相关。然而,上述研究中存在临床研究与基础实验结果相

悖的现象,这可能与研究设计、人群选择、样本量大小及代偿机制等因素有关。CTRPs对冠心病发生的预测价值仍需进一步探讨。

4 CTRPs与冠心病预后的关系

随着冠心病病程进展,患者病情可能发展至缺血性心肌病、心肌梗死、心力衰竭、恶性心律失常等。目前,有多项研究探讨了CTRPs与心肌梗死后心衰的关系,以及其在心肌细胞保护方面的作用(表1)。其中,CTRP3可通过激活SMAD3、AMPK和Akt来减轻梗死后心肌纤维化,并抑制肌成纤维细胞的分化;其特异性上调能抑制氧化应激、炎症和细胞凋亡,并通过激活AMPK通路使心功能改善^[45]。然而,也有研究^[46]发现,CTRP3能促进压力超负荷诱导的小鼠心肌肥厚,而CTRP3缺乏则使心肌肥厚缓解。CTRP3这种相悖的研究

结论可能与疾病模型构建不同有关。CTRP6能通过激活蛋白激酶A(PKA)-Akt-PKB信号通路,使Akt磷酸化,有效地减少细胞凋亡,减轻心脏毒性,进而促进心脏修复;此外,CTRP6可通过AMPK和Akt激活RhoA-MRTF-A通路,进而抑制肌成纤维细胞分化,减轻心肌梗死后心肌纤维化^[47]。CTRP9通过调节能量代谢、保护内皮细胞、抑制病理性血管重塑、预防缺血性卒中、减少心肌细胞凋亡,通过钙网蛋白依赖的凋亡抑制改善心肌缺血/再灌注损伤,减小心肌梗死面积,在改善冠心病预后中发挥重要作用^[48]。CTRP15上调与缺血/再灌注损伤后心肌梗死范围缩小、细胞凋亡减少和炎性介质下调相关^[49],其可能通过激活Akt发挥作用。这些研究对于发掘心梗后心衰的治疗新靶点有一定意义。

表1 目前主要CTRPs家族成员相关研究成果

CTRP家族成员	主要表达部位	作用靶点和机制	参与疾病及效应
CTRP1	脂肪、心肌、胎盘、肝脏	激活AMPK信号通路 直接刺激肾上腺皮质,使其分泌醛固酮	心力衰竭 高血压病,升高血压
CTRP2	基质血管细胞	激活AMPK信号通路	增加糖原积累,促脂肪酸氧化
CTRP3	脂肪、肝脏、骨骼肌	激活AMPK、GLUT-4等信号通路 激活SMAD3、Akt	2型糖尿病,促胰岛素分泌 减轻心肌梗死后心肌纤维化
CTRP4	脑、脂肪组织、骨骼肌	刺激IL-6/STAT3和NF-κB信号通路	调节能量代谢、促炎症因子分泌
CTRP5	脂肪、视网膜、睫状体上皮	上调12/15-脂氧合酶	促动脉粥样硬化
CTRP6	脂肪组织	激活PPARγ 激活Akt/PKB信号通路	减轻高血压 减少心肌细胞凋亡
CTRP7	骨骼肌、脂肪组织等	作用于肝脏糖异生转录因子	调节炎症、细胞应激、糖代谢
CTRP8	肺、睾丸	—	—
CTRP9	脂肪细胞、基质血管成份细胞	激活AMPK信号通路 作用于内皮型一氧化氮合酶、参与内质网应激	改善缺血再灌注后心肌损伤 抑制血管炎症、改善内皮功能障碍
CTRP10	脂肪组织、间质血管细胞	上调心肌细胞磷酸化果糖激酶、己糖激酶	参与能量代谢
CTRP11	睾丸、胃、肾、骨骼肌、脂肪组织	抑制p42/44-MAPK信号转导	参与能量代谢、脂肪代谢
CTRP12	脂肪组织	作用于转化生长因子-β R2/SMAD2	抑制血管平滑肌增生
CTRP13	脂肪基质血管成份细胞	增加GTP环水解酶1表达	保护血管内皮功能
CTRP14	—	可能参与激活ERK1/2信号通路	促血管内皮细胞生成
CTRP15	骨骼肌	激活Akt信号通路	抑制细胞凋亡和巨噬细胞炎症

5 小结与展望

本文主要围绕CTRPs与冠心病危险因素、发生发展、诊断评估、预后转归等的关系,总结

近年来关于CTRPs的主要基础研究和临床研究成果。不同CTRPs家族成员在调节能量代谢、炎症通路、胰岛素信号等方面的作用不尽相同,甚至同一种蛋白的研究结论也有相悖的情况。目前对于

CTRP1、CTRP3、CTRP9等蛋白的研究较充分,而CTRP11~15在心血管疾病方面的研究相对较少,其潜在作用有待被发现。总之,动物模型及临床研究等均提示,CTRPs有望成为冠心病及相关风险疾病潜在的诊断和治疗靶点,并为其预防和预后提供依据,期望未来进行更深入的机制探讨和更大规模的临床研究。

利益冲突: 所有作者声明不存在利益冲突。

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