·综　述·

C1q/肿瘤坏死因子相关蛋白家族在冠状动脉疾病中作用机制研究进展

彭中兴[1,2],赵云峰[1*]

[1]南京医科大学康达学院第一附属医院(徐州医科大学附属连云港医院)心血管内科,江苏　连云港　222000;[2]南京医科大学康达学院,江苏　连云港　222000

[摘　要]　近年来,C1q/肿瘤坏死因子相关蛋白(C1q /tumor necrosis factor-related protein,CTRP)家族在动脉粥样硬化、缺血性心肌病、高血压等心血管疾病中作用广泛,吸引了越来越多的关注。CTRP家族成员(主要包括CTRP1、CTRP3、CTRP5、CTRP9、CTRP12和CTRP13等)通过调节影响免疫炎症反应、糖脂代谢、内皮功能等方式来影响冠状动脉疾病(coronary artery disease,CAD)的进展。

[关键词]　C1q/肿瘤坏死因子相关蛋白;冠状动脉疾病;作用机制

[中图分类号]　R543.2　　[文献标志码]　A　　[文章编号]　1007-4368(2021)10-1558-07

doi:10.7655/NYDXBNS20211026

Research progress on the role of C1q/tumor necroscs factor-related protein family in coronary artery disease

PENG Zhongxing[1,2],ZHAO Yunfeng[1*]

[1]Department of Cardiovascular Medicine,the First Affiliated Hospital of Kangda College,Nanjing Medical University(the Affiliated Lianyungang Hospital of Xuzhou Medical University),Lianyungang 222000;[2]Kangda College of Nanjing Medical University,Lianyungang 222000,China

[**Abstract**]　In recent years,C1q/tumor tumor necroscs factor-related protein(CTRP) plays an important role in the pathophysiology of various cardiovascular diseases such as atherosclerosis, ischemic cardiomyopathy and hypertension. CTRP family members including CTRP1, CTRP3, CTRP5, CTRP9, CTRP12 and CTRP13 can affect the development of coronary artery disease(CAD) by regulating immune inflammation,glucose and lipid metabolism,and endothelial function.

[**Key words**]　CTRP;CAD;mechanism

[J Nanjing Med Univ,2021,41(10):1558-1564]

脂联素是由脂肪组织分泌的一种脂肪因子,具有多效性,包括胰岛素增敏、调节葡萄糖及脂代谢、抗动脉粥样硬化、抗炎、抗肿瘤血管生成等,脂联素属于C1q蛋白超家族,含有补体C1q序列同源性的球状羧基结构域,C1q/肿瘤坏死因子相关蛋白(C1q /tumor necrosis factor-related protein,CTRP)家族是与脂联素结构相似的一组结构高度保守蛋白,包括15个成员(CTRP1~15),存在不同的聚合形式,包括三聚体、六聚体、高分子量多聚体、异源多聚体。研究表明CTRP家族在高血压、动脉粥样硬化及其他心血管疾病中发挥重要作用。本文从免疫、糖脂代谢、内皮细胞功能3个方面总结CTRP家族成员在冠状动脉疾病(coronary artery disease,CAD)中的作用。

1　调节免疫炎症

CAD是一个复杂长期的过程,不仅涉及动脉内胆固醇和钙的积累,炎症细胞和细胞因子导致的促

[基金项目]　国家自然科学基金(81970237,81800244);连云港市第一人民医院中西医结合科研项目(ZX09)

*通信作者(Corresponding author),E-mail:yfzhao7637@sohu.com

炎反应在动脉粥样硬化的发展、血栓形成以及最终的不良心血管事件中也占据了重要地位。

CTRP1调节炎症因子的水平，同时促炎细胞因子诱导CTRP1分泌增加。CTRP1通过激活p38丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)/核因子-κB(nuclear factor-kappa B，NF-κB)途径增加炎症因子如黏附分子、肿瘤坏死因子(tumor necrosis factor，TNF)-α、白介素(interleukin，IL)-6和IL-1β等的产生，炎症反应刺激白细胞黏附至内皮细胞，进一步促进巨噬细胞来源的泡沫细胞形成动脉粥样硬化斑块，从而产生促动脉粥样硬化作用和加速CAD的作用[1]。另一方面，CTRP1也可以通过激活心肌细胞中鞘氨醇-1-磷酸(sphingosine-1-phosphate，S1P)/环一磷酸腺苷(cyclic adenosine monophosphate，cAMP)信号通路减少凋亡和炎症反应，从而防止心肌缺血，对缺血性心脏病发挥有益作用[2]。血清CTRP1水平高与不良心血管事件显著相关。与非CAD组相比，CAD患者的CTRP1显著增加，CTRP1可能是CAD单支血管病变的标志物，可以作为诊断CAD患者血管病变严重程度的新型生物标志物[3]。

CTRP3是有效的抗炎脂肪因子，在心血管保护方面具有引人瞩目的作用。CTRP3有两种亚型，分别为CTRP3A和CTRP3B，两者在蛋白长度和糖基化上有区别。CTRP3可抑制单核细胞和巨噬细胞，发挥抗炎、抗凋亡的作用，从而延缓CAD发展，起到保护心脏的作用[4]。CTRP3通过促进PI3K/Akt/eNOS途径下调TNF-α和IL-6的表达，从而抑制氧化低密度脂蛋白(oxidized low-density lipoprotein，ox-LDL)引起的内皮炎症反应和内皮功能障碍，延缓动脉粥样硬化的进展[5]。人体内单核细胞目前已知有3种亚型，依据CD14、CD16抗原的表型分为经典型、非经典型及中间型，其中中间型单核细胞具有强的抗原提呈加工能力，活化后可促进炎症因子TNF-α和IL-6的产生，CTRP3可减少中间型单核细胞的产生，抑制脂多糖(lipopolysaccharide，LPS)诱导的IL-6的表达，增强急性心肌梗死(acute myocardial infarction，AMI)患者心脏修复过程，CTRP3可以干预炎症反应的过程，成为改善AMI患者预后的靶点[6]。

CTRP5在糖尿病和肥胖者体内水平高，来自上海交通大学附属瑞金医院的研究表明CTRP5可促进冠状动脉支架植入后支架内再狭窄[7]。CTRP5通过促进基质金属蛋白酶-2(matrix metalloproteinases 2，MMP-2)、细胞周期蛋白D1和TNF-α的表达，同时激活Notch1、转化生长因子(transforming growth factor，TGF)-β和hedgehog信号通路，从而促进血管平滑肌细胞的增殖、炎症和迁移。该研究CTRP5可通过转录因子6(signal transducer and activator of transcription6，STAT6)信号通路上调12/15-脂氧合酶(lipoxygenase，LOX)，而12/15-LOX是介导低密度脂蛋白(low density lipoprotein，LDL)转运和氧化的关键酶，抑制12/15-LOX能显著减弱ox-LDL在内皮下的沉积和动脉粥样硬化的进展，CTRP5是一种新型的促动脉粥样硬化细胞因子[8]。

CTRP9是脂联素最接近的旁系同源物，具有抗炎作用和抗动脉粥样硬化的功能，在CAD发展过程中具有心脏保护作用[9]。CTRP9通过激活一磷酸腺苷(adenosine monophosphate，AMP)活化的蛋白激酶抑制黏附分子如细胞间黏附分子(intercellular cell adhesion molecule-1，ICAM-1)、血管内皮细胞中的细胞黏附分子(vascular cell adhesion molecule-1，VCAM-1)的表达，减少促炎细胞因子如TNF-α和单核细胞趋化蛋白(monocyte chemotactic protein-1，MCP-1)的表达起到稳定动脉粥样硬化斑块的作用[10]，CTRP9可以抑制VSMC转变为巨噬细胞[11]，减少主动脉血管平滑肌(vascular smooth muscle cell，VSMC)的增生[12]，减轻内皮功能障碍，促进血管舒张，增加动脉粥样硬化斑块的稳定性[13]。CTRP9可以减少ox-LDL活化的巨噬细胞中含NLR家族Pyrin域蛋白3(the NLR family pyrin domain containing 3，NLRP3)蛋白的表达，并下调NLRP3炎性小体的活性[14]。抑制腺苷一磷酸蛋白激酶(AMP-activated protein kinase，AMPK)可以恢复NLRP3炎性小体的活性。在载脂蛋白E缺乏的小鼠中，CTRP9过表达可以抑制动脉粥样硬化的发展，这种作用可以通过抑制AMPK消除。CTRP9通过CTRP9-AMPK-NLRP3途径发挥抗动脉粥样硬化的作用。CTRP9还可以影响巨噬细胞的表型发挥改善心肌梗死(myocardial infarction，MI)预后的作用[15]。MI发生后外周巨噬细胞迁移至梗死区域分化为M1巨噬细胞，M1巨噬细胞产生促炎细胞因子，加剧心脏功能的恶化，而进入炎症消退阶段后心肌的巨噬细胞变成M2巨噬细胞，M2巨噬细胞具有抗炎特性，加速心脏的修复。M1到M2的表型转化可以显著改善MI的伤口愈合，改善心功能。CTRP9主要经由Toll样受体4(Toll-like receptors，TLR4)/髓样分化蛋白2(myeloid-differentiationprotein，MD2)/髓样分化因子88(myeloid differentiation factor，MyD88)和AMPK-NF-κB

途径调节M1/M2巨噬细胞的表型转化来改善MI后早期心脏功能。核因子E2相关因子2(nuclear factor E2 related factor 2,Nrf2)是人类不可缺少的一条抗氧化通路,是机体防御体系的重要部分。Nrf2与抗氧化反应元件结合后活化多种抗氧化酶,研究发现CTRP9通过活化Nrf2的表达减轻炎症反应,缓解大鼠MI的进展[16]。诱导型一氧化氮合酶(inducible nitric oxide synthase,iNOS)在正常情况下是不存在的,仅在经LPS和TNF-α刺激的情况下才会表达,其在CAD发生中的作用目前仍有争议。CTRP9可以通过蛋白酪氨酸激酶2/信号转导子与激活子3(Janus kinase signal transducers 2 and activator of transcription 3,JAK2-STAT3)途径剂量和时间依赖性地上调iNOS表达[17]。

CTRP12与炎症细胞因子有关,在动脉粥样硬化中起作用。CTRP12可以减少促炎细胞因子的表达从而减少巨噬细胞在肥胖大鼠脂肪组织内的积累,也可以抑制CAD患者体内IL-6和TNF-α等炎症细胞因子的水平[18]。因此,CTRP12过表达在CAD的发展中起抗炎作用。

CTRP13抑制巨噬细胞活化和血管壁浸润,减少斑块形成,从而抑制动脉粥样硬化的发展。此外,它通过减少脂质的摄入防止巨噬细胞的增殖和迁移,通过促进自噬的发生延缓局部和全身性的炎症反应,并加速CD36依赖的自噬吞噬体的降解,因此减少了病变中的巨噬细胞[19]。

2　糖脂代谢

葡萄糖和脂质代谢是增加CAD风险的两个主要生理过程,代谢异常会影响炎症程度和冠状斑块的形成,可以导致不良心血管事件的发生。

CTRP1参与肥胖相关的代谢,调节机体能量代谢和改善胰岛素的敏感性。CTRP1可以降低葡萄糖水平,通过降低胰岛素受体底物1的丝氨酸磷酸化改善胰岛素敏感性,从而增加成熟脂肪组织的糖摄取[20]。然而Yagmur等[21]却发现2型糖尿病(T2DM)患者的CTRP1水平较高,且与糖化血红蛋白(HbA1c)和体重指数相关,可能是由于T2DM导致的代谢紊乱限制了CTRP1的有益作用。葡萄糖转运蛋白(glucose transporter 4,GLUT4)在葡萄糖的摄取和代谢过程中发挥着重要作用,CTRP1通过PI3K/Akt信号通路增加肌细胞和脂肪细胞中GLUT4的转运[22]。CTRP1增加脂肪酸氧化和能源支出。抑制乙酰辅酶A羧化酶(acetyl coA carboxylase,ACC)可通过AMPK途径减轻肥胖[23]。

降低CTRP3浓度可能会导致肥胖并使正常体重的年轻人患糖尿病的风险增加。CTRP3浓度降低可能在肥胖引起的各种代谢异常的病理生理中起重要作用[24]。CTRP3参与肥胖相关的代谢,调节血糖和脂质代谢[25]。而且CTRP3明显抑制了参与肝糖异生的两种关键酶的表达,即葡萄糖-6-磷酸酶(glucose-6-phosphatase,G6Pase)和磷酸烯醇丙酮酸羧激酶(phosphoenolpyruvate carboxykinase,PEPCK),从而减少肝细胞糖异生[26],减缓CAD的发展。CTRP3通过p-p38 MAPK和p-ERK信号通路提高胰岛素敏感性,增强胰岛素介导的葡萄糖摄取[27]。

糖尿病性心肌病(diabetic cardiomyopathy,DCM)是糖尿病的常见并发症,可导致心力衰竭、心律不齐和猝死。Song等[28]研究表明在高糖诱导的AC16心肌细胞中miR-144表达水平升高,而CTRP3表达降低。CTRP3的过度表达可显著促进AC16心肌细胞的增殖并减少其凋亡,表明CTRP3/c-Jun氨基末端激酶(c-Jun N-terminal kinase,JNK)信号通路可调节高糖诱导的AC16心肌细胞增殖和凋亡,为治疗DCM提供了新途径。Wang等[29]用CTRP3通过激活Akt-mTOR信号通路阻断高糖诱导的人脐静脉内皮细胞(human umbilical vein endothelial cell,HUVEC)中炎症因子的积累和细胞凋亡。因此,CTRP3可能是预防糖尿病相关内皮功能障碍的潜在治疗药物。CTRP3可能参与糖尿病肾病的发生发展。研究表明,CTRP3通过使JAK2/STAT3信号通路失活而减弱了高糖诱导的肾小球系膜细胞增殖和细胞外基质产生[30]。因此,CTRP3可能是治疗糖尿病性肾病的潜在治疗靶标。除此之外,CTRP3可以抑制高糖诱导的视网膜色素上皮细胞的氧化应激和细胞凋亡[31],主要是通过Nrf2/HO-1途径介导ARPE-19细胞中的氧化应激和凋亡减弱。Moradi等[32]也发现T2DM和糖尿病肾病患者血清中CTRP3水平降低,提示CTRP3可能在糖尿病肾病中发挥作用。Chen等[33]发现肥胖儿童的血清CTRP3水平显著降低,且与胰岛素抵抗和胰腺β细胞功能指标呈负相关。

CTRP5在代谢综合征的人体内浓度明显低于正常成年人。血清中CTRP5高可能与胰岛素抵抗有关[34]。NADPH氧化酶(NOX)是一种重要的氧化剂,NOX家族包括7种亚型,分别是NOX1、NOX2、NOX3、NOX4、NOX5、DUOX1和DUOX2,其主要功能是产生活性氧(ROS),且NOX来源的ROS可以影响其他来源的ROS的产生,使ROS产生进一步增

加，形成氧化应激的一个恶性循环。NOX1是NOX的其中一种亚型，CTRP5通过促进NOX1信号转导而导致糖尿病血管内皮功能障碍[35]，阻断CTRP5的产生可以减轻糖尿病心血管并发症。

CTRP9调节脂质代谢并通过增强AMPK/mTOR自噬信号通路来增强胆固醇外流，增加了胆固醇转运受体如ATP结合盒转运体A1(ATP-binding cassette transporter A1，ABCA1)和ATP结合盒转运体G1(ABCG1)的表达，加速泡沫细胞中胆固醇的流出，从而防止THP-1巨噬细胞形成泡沫细胞，减少泡沫细胞的形成，减缓早期动脉粥样硬化的进展[36]。CTRP9可以激活Akt、AMPK和p42/44 MAPK通路，其浓度与内皮细胞的可溶性黏附分子(如ICAM-1和VCAM-1)呈正相关，CTRP9可以增加葡萄糖的摄取[37]。

CTRP12通过增强肝脏和脂肪组织中胰岛素信号转导来改善胰岛素的敏感性，此外还以不依赖胰岛素的方式直接激活PI3K/Akt信号通路抑制糖异生，并增加肝细胞摄取葡萄糖[38]。

CTRP13通过调节GTP环水解酶1(GTP cyclohydrolase 1，GCH1)/四氢生物蝶呤(tetrahydrobiopterin，BH4)轴依赖性eNOS的产生，在高糖环境中，CTRP13可避免高糖对蛋白激酶A(protein kinase A，PKA)活性的抑制作用，PKA活性增强，从而促进了过氧化物酶体增殖物α受体的磷酸化，从而激活GCH1转录，最终使内皮舒张功能激活，保留了糖尿病小鼠的内皮功能，表明CTRP13可以治疗糖尿病性血管病[39]。CTRP13对高糖诱导的钙/钙调蛋白依赖性蛋白激酶激酶β(Calcium/calmodulin-dependent protein kinase kinase beta，CAMKKβ)/AMPK途径引起的肝窦毛细血管化具有保护作用，CTRP13可能是治疗糖尿病性脂肪肝的潜在靶标[40]。

3 调节内皮细胞功能

冠状动脉内皮损伤是炎症细胞、炎症因子、血管内皮细胞、血管平滑肌细胞等共同介导的，是动脉粥样硬化形成的始动阶段。炎症细胞作用于内皮细胞后穿越内皮细胞向内膜下渗透，而当内皮细胞代偿性地发挥抗血栓、消炎、抗增殖作用的动态平衡被打破时会导致血管舒缩功能障碍和心肌梗死后的心室重塑[41]。

CTRP1是血管保护性脂肪因子，对血管损伤具有保护作用。CTRP1可减少血管损伤后新内膜动脉增生和细胞增殖，通过cAMP依赖途径抑制VSMC的生长[41]。

动脉粥样硬化斑块破裂和继发性血栓形成会导致血管疾病，如心肌梗死和不稳定型心绞痛。Chen等[5]研究表明，ox-LDL刺激小鼠后CTRP3表达增强，下调炎症因子CRP、TNF-α、IL-6、CD40和CD40L，CTRP3过表达可以提高细胞活性，减少乳酸氢化酶，显著减少细胞凋亡。同时，过表达的CTRP3导致血管紧张素Ⅱ(angiotensin，Ang Ⅱ)、ICAM-1和VCAM-1表达下降，并恢复了内皮素-1(endothelin，ET-1)和NO之间的平衡。进一步的机制研究发现CTRP3可以通过激活PI3K/Akt/eNOS途径来有效抑制ox-LDL诱导的小鼠主动脉内皮细胞的炎症反应和内皮功能障碍，有希望成为抗动脉粥样硬化的靶点。

最近研究表明CTRP3在心力衰竭的诊断上有帮助，Gao等[42]评估了射血分数降低的心力衰竭(HFrEF)患者中CTRP3和CTRP9的浓度以及是否与病死率相关，发现纽约心脏协会等级较高的患者CTRP3或CTRP9浓度明显较低，CTRP3和CTRP9水平与左室射血分数(LVEF)正相关，与N末端前体脑利钠肽(NT-proBNP)水平负相关，经过36个月的随访，发现低于25%分位水平的CTRP3或CTRP9水平是总死亡率和再住院率的预测指标。

关于CTRP3在心肌肥厚中的作用，Ma等[43]发现CTRP3通过活化PKA激活转化生长因子β激活激酶1(transforming growth factor β-activated kinase 1，TAK1)/JNK)信号通路导致心肌肥厚的发展。Zhang等[44]研究表明，CTRP3可以通过抑制p38MAPK/cAMP反应元件结合蛋白(cAMP response element-binding protein，CREB)途径起到抗心肌肥厚作用，CTRP3基因敲除的小鼠心肌肥厚加剧。主要考虑两项研究中心肌肥厚模型的建模方法差异导致，需要进一步研究探索CTRP3在心肌肥厚中的具体机制。Wu等[45]研究也表明CTRP3可减少缺血性心肌损伤，发挥心脏保护作用。

CTRP9具有较高的血管活性，在调节血管硬化中起重要作用[46]。它可以促进血管扩张，同时抑制新生内膜增生和VSMC增殖，减轻动脉粥样硬化，并对心脏产生保护作用。

4 结 论

CTRP家族通过调节免疫炎症、糖脂代谢和血管内皮功能在CAD的各个阶段发挥作用，CTRP1是促炎和促动脉粥样硬化的代表。CTRP5促进VSMC的生长、迁移和炎症。相反，CTRP3、CTRP9、

CTRP12和CTRP13具有抗炎和抗动脉粥样硬化作用。CTRP家庭成员通过调节糖脂代谢影响内皮细胞炎症和斑块血管形成。CTRP1、CTRP3和CTRP9抑制内膜增生和血管平滑肌细胞增殖,对缺血心肌有保护作用。CTRP1和CTRP5在CAD患者中升高。相反,CTRP3、CTRP9、CTRP12和CTRP13作为CAD的保护因子在CAD患者中降低。CTRP大家族的成员在多个系统都有广泛的功能,本文解读了CTRP家族在CAD发生及发展中各个阶段的作用。CTRP家族正不断发展壮大,对于CTRP家族成员的深入研究将为今后临床治疗代谢综合征、冠状动脉疾病提供新的思路。

[参考文献]

[1] MUENDLEIN A,LEIHERER A,SAELY C,et al. The novel adipokine CTRP1 is significantly associated with the incidence of major adverse cardiovascular events[J]. Atherosclerosis,2019,286:1-6

[2] YUASA D,OHASHI K,SHIBATA R,et al. C1q/TNF-related protein-1 functions to protect against acute ischemic injury in the heart[J]. FASEB J,2016,30(3):1065-1075

[3] ZHANG Y,LIU C,LIU J,et al. Implications of C1q/TNF-related protein superfamily in patients with coronary artery disease[J]. Sci Rep,2020,10(1):878

[4] LIN J,LIU Q,ZHANG H,et al. C1q/Tumor necrosis factor-related protein-3 protects macrophages against LPS-induced lipid accumulation,inflammation and phenotype transition via PPARgamma and TLR4-mediated pathways[J]. Oncotarget,2017,8(47):82541-82557

[5] CHEN L,QIN L,LIU X,et al. CTRP3 Alleviates ox-LDL-induced inflammatory response and endothelial dysfunction in mouse aortic endothelial cells by activating the PI3K/Akt/eNOS pathway[J]. Inflammation,2019,42(4):1350-1359

[6] 彭中兴,陈昊颖,李琳青,等. C1q肿瘤坏死因子相关蛋白3对AMI患者外周血中间型(CD14~(++)CD16~+)单核细胞分化的影响及其机制[J]. 东南大学学报(医学版),2019,38(2):242-248

[7] SHEN Y,LI C,ZHANG R Y,et al. Association of increased serum CTRP5 levels with in-stent restenosis after coronary drug-eluting stent implantation:CTRP5 promoting inflammation,migration and proliferation in vascular smooth muscle cells[J]. Int J Cardiol,2017,228:129-136

[8] LI C,CHEN J W,LIU Z H,et al. CTRP5 promotes transcytosis and oxidative modification of low-density lipoprotein and the development of atherosclerosis[J]. Atherosclerosis,2018,278:197-209

[9] APPARI M,BREITBART A,BRANDES F,et al. C1q-TNF-related protein-9 promotes cardiac hypertrophy and failure[J]. Circ Res,2017,120(1):66-77

[10] ZHANG P,HUANG C,LI J,et al. Globular CTRP9 inhibits oxLDL-induced inflammatory response in RAW 264.7 macrophages via AMPK activation[J]. Mol Cell Biochem,2016,417(1-2):67-74

[11] LIU Q,ZHANG H,LIN J,et al. C1q/TNF-related protein 9 inhibits the cholesterol-induced vascular smooth muscle cell phenotype switch and cell dysfunction by activating AMP-dependent kinase[J]. J Cell Mol Med,2017,21(11):2823-2836

[12] LI YX,RUN L,SHI T,et al. CTRP9 regulates hypoxia-mediated human pulmonary artery smooth muscle cell proliferation,apoptosis and migration via TGF-beta1/ERK1/2 signaling pathway[J]. Biochem Biophys Res Commun,2017,490(4):1319-1325

[13] SUN H,ZHU X,ZHOU Y,et al. C1q/TNF-related protein-9 ameliorates ox-LDL-induced endothelial dysfunction via PGC-1alpha/AMPK-mediated antioxidant enzyme induction[J]. Int J Mol Sci,2017,18(6):1097

[14] ZHANG H,GONG X,NI S,et al. C1q/TNF-related protein-9 attenuates atherosclerosis through AMPK-NLRP3 inflammasome singling pathway[J]. Int Immunopharmacol,2019,77:105934

[15] LIU M,YIN L,LI W,et al. C1q/TNF-related protein-9 promotes macrophage polarization and improves cardiac dysfunction after myocardial infarction[J]. J Cell Physiol,2019,234(10):18731-18747

[16] LIU T,XU B,LIU Z. CTRP9 alleviates inflammation to ameliorate myocardial infarction in rats by activating Nrf2[J]. Minerva Endocrinol,2020,45(3):268-270

[17] CHEN J Y,LEI S Y,LI T T,et al. CTRP9 induces iNOS expression through JAK2/STAT3 pathway in Raw 264.7 and peritoneal macrophages[J]. Biochem Biophys Res Commun,2020,523(1):98-104

[18] FADAEI R,MORADI N,KAZEMI T,et al. Decreased serum levels of CTRP12/adipolin in patients with coronary artery disease in relation to inflammatory cytokines and insulin resistance[J]. Cytokine,2019,113:326-331

[19] WANG C,XU W,LIANG M,et al. CTRP13 inhibits atherosclerosis via autophagy-lysosome-dependent degradation of CD36[J]. FASEB J,2019,33(2):2290-2300

[20] XIN Y,ZHANG D,FU Y,et al. C1qTNF-related protein 1 improve insulin resistance by reducing phosphorylation of serine 1101 in insulin receptor substrate 1[J]. Endocr J,2017,64(8):787-796

[21] YAGMUR E,BUERGERHAUSEN D,KOEK G H,et al.

Elevated CTRP1 plasma concentration is associated with sepsis and pre-existing type 2 diabetes mellitus in critically ill patients[J]. J Clin Med,2019,8(5):661

[22] YUASA T,UCHIYAMA K,OGURA Y,et al. The Rab GTPase-activating protein AS160 as a common regulator of insulin- and Galphaq-mediated intracellular GLUT4 vesicle distribution[J]. Endocr J,2009,56(3):345-359

[23] SHEN L, WANG S, LING Y, et al. Association of C1q/TNF-related protein-1(CTRP1) serum levels with coronary artery disease[J]. J Int Med Res, 2019, 47(6): 2571-2579

[24] ELSAID H H, ELGOHARY M N, ELSHABRAWY A M. Complement c1q tumor necrosis factor-related protein 3 a novel adipokine, protect against diabetes mellitus in young adult Egyptians[J]. Diabetes Metab Syndr, 2019, 13(1):434-438

[25] JAIN N B,YADAV A,SHANKAR N,et al. Correlation of C1q/TNF-related protein-3 with cardiac autonomic tone and metabolic parameters in obesity[J]. Int J Endocrinol Metab,2019,17(2):e74250

[26] PETERSON J M,WEI Z,WONG G W. C1q/TNF-related protein-3(CTRP3), a novel adipokine that regulates hepatic glucose output[J]. J Biol Chem, 2010, 285(51): 39691-39701

[27] KOPP A,BALA M,BUECHLER C,et al. C1q/TNF-related protein-3 represents a novel and endogenous lipopolysaccharide antagonist of the adipose tissue[J]. Endocrinology,2010,151(11):5267-5278

[28] SONG Y,MAI H,LIN Y,et al. MiR-144 affects proliferation and apoptosis of high glucose-induced AC16 cardiomyocytes by regulating CTRP3/JNK signaling[J]. Int J Clin Exp Pathol,2020,13(2):142-152

[29] WANG F, ZHAO L, SHAN Y, et al. CTRP3 protects against high glucose-induced cell injury in human umbilical vein endothelial cells[J]. Anal Cell Pathol(Amst), 2019,2019:7405602

[30] HU T Y,LI L M,PAN Y Z. CTRP3 inhibits high glucose-induced human glomerular mesangial cell dysfunction[J]. J Cell Biochem,2019,120(4):5729-5736

[31] ZHANG J,HE J. CTRP3 inhibits high glucose-induced oxidative stress and apoptosis in retinal pigment epithelial cells[J]. Artif Cells Nanomed Biotechnol,2019,47(1): 3758-3764

[32] MORADI N, FADAEI R, KHAMSEH M E, et al. Serum levels of CTRP3 in diabetic nephropathy and its relationship with insulin resistance and kidney function[J]. PLoS One,2019,14(4):e0215617

[33] CHEN T,WANG F,CHU Z,et al. Serum CTRP3 levels in obese children:a potential protective adipokine of obesity, insulin sensitivity and pancreatic beta cell function[J]. Diabetes Metab Syndr Obes,2019,12:1923-1930

[34] JIANG F,YANG M,ZHAO X,et al. C1q/TNF-related protein5(CTRP5) as a biomarker to predict metabolic syndrome and each of its components[J]. Int J Endocrinol, 2018,2018:7201473

[35] LIU J,MENG Z,GAN L,et al. C1q/TNF-related protein 5 contributes to diabetic vascular endothelium dysfunction through promoting Nox-1 signaling[J]. Redox Biol,2020, 34:101476

[36] ZHANG L,LIU Q,ZHANG H,et al. C1q/TNF-related protein 9 inhibits THP-1 macrophage foam cell formation by enhancing autophagy[J]. J Cardiovasc Pharmacol,2018, 72(4):167-175

[37] MORADI N,FADAEI R,EMANMGHOLIPOUR S,et al. Association of circulating CTRP9 with soluble adhesion molecules and inflammatory markers in patients with type 2 diabetes mellitus and coronary artery disease[J]. PLoS One,2018,13(1):e0192159

[38] WEI Z,PETERSON J M,LEI X,et al. C1q/TNF-related protein-12(CTRP12),a novel adipokine that improves insulin sensitivity and glycemic control in mouse models of obesity and diabetes[J]. J Biol Chem, 2012, 287(13): 10301-10315

[39] WANG C,CHAO Y,XU W,et al. CTRP13 preserves endothelial function by targeting GTP cyclohydrolase 1 in diabetes[J]. Diabetes,2020,69(1):99-111

[40] ZHANG Q,NIU X,TIAN L,et al. CTRP13 attenuates the expression of LN and CAV-1 induced by high glucose via CaMKKbeta/AMPK pathway in rLSECs[J]. Aging,2020, 12(12):11485-11499

[41] OBATA J E,HORIKOSHI T,NAKAMURA T,et al. Sustained endothelial dysfunction in the infarct-related coronary artery is associated with left ventricular adverse remodeling in survivors of ST-segment elevation myocardial infarction[J]. J Cardiol,2020,75(3):261-269

[42] GAO C,ZHAO S,LIAN K,et al. C1q/TNF-related protein 3(CTRP3) and 9(CTRP9) concentrations are decreased in patients with heart failure and are associated with increased morbidity and mortality[J]. BMC Cardiovasc Disord,2019,19(1):139

[43] MA Z G,YUAN Y P,ZHANG X,et al. C1q-tumour necrosis factor-related protein-3 exacerbates cardiac hypertrophy in mice[J]. Cardiovasc Res, 2019, 115(6): 1067-1077

[44] ZHANG B, ZHANG P, TAN Y, et al. C1q-TNF-related protein-3 attenuates pressure overload-induced cardiac hypertrophy by suppressing the p38/CREB pathway and p38-induced ER stress[J]. Cell Death Dis,2019,10(7):

520
[45] WU D, LEI H, WANG J Y, et al. CTRP3 attenuates post-infarct cardiac fibrosis by targeting Smad3 activation and inhibiting myofibroblast differentiation [J]. J Mol Med (Berl), 2015, 93(12): 1311-1325
[46] JUNG C H, LEE M J, KANG Y M, et al. Association of serum C1q/TNF-related protein-9 concentration with arterial stiffness in subjects with type 2 diabetes[J]. J Clin Endocrinol Metab, 2014, 99(12): E2477-E2484

[收稿日期] 2021-06-09

(上接第1557页)

[54] PICCOLI M T, GUPTA S K, VIERECK J, et al. Inhibition of the cardiac fibroblast-enriched lncRNA Meg3 prevents cardiac fibrosis and diastolic dysfunction [J]. Circ Res, 2017, 121(5): 575-583
[55] CHEN Y, ZHANG Z, ZHU D, et al. Long non-coding RNA MEG3 serves as a ceRNA for microRNA-145 to induce apoptosis of AC16 cardiomyocytes under high glucose condition[J]. Biosci Rep, 2019, 39(6): BSR20190444
[56] ZIMETBAUM P. Atrial fibrillation[J]. Ann Intern Med, 2017, 166(5): ITC33-ITC48
[57] LI Z, WANG X, WANG W, et al. Altered long non-coding RNA expression profile in rabbit atria with atrial fibrillation: $TCONS_{00075467}$ modulates atrial electrical remodeling by sponging miR-328 to regulate CACNA1C [J]. J Mol Cell Cardiol, 2017, 108: 73-85
[58] LI X, DAI Y, YAN S, et al. Down-regulation of lncRNA KCNQ1OT1 protects against myocardial ischemia/reperfusion injury following acute myocardial infarction[J]. Biochem Biophys Res Commun, 2017, 491(4): 1026-1033
[59] LI M, WANG Y F, YANG X C, et al. Circulating long non-coding RNA LIPCAR acts as a novel biomarker in patients with ST-segment elevation myocardial infarction [J]. Med Sci Monit, 2018, 24: 5064-5070
[60] SHEN C, KONG B, LIU Y, et al. YY_1-induced upregulation of lncRNA KCNQ1OT1 regulates angiotensin Ⅱ-induced atrial fibrillation by modulating miR-384b/CACNA1C axis[J]. Biochem Biophys Res Commun, 2018, 505(1): 134-140
[61] CAO F, LI Z, DING W M, et al. LncRNA PVT1 regulates atrial fibrosis via miR-128-3p-SP1-TGF-β1-Smad axis in atrial fibrillation[J]. Mol Med, 2019, 25(1): 7
[62] GUO J, JIA F, JIANG Y, et al. Potential role of MG53 in the regulation of transforming-growth-factor-β1-induced atrial fibrosis and vulnerability to atrial fibrillation [J]. Exp Cell Res, 2018, 362(2): 436-443
[63] BONOW R O, LEON M B, DOSHI D, et al. Management strategies and future challenges for aortic valve disease [J]. Lancet, 2016, 387(10025): 1312-1323
[64] YUTZEY K E, DEMER L L, BODY S C, et al. Calcific aortic valve disease: a consensus summary from the alliance of investigators on calcific aortic valve disease [J]. Arterioscler Thromb Vasc Biol, 2014, 34(11): 2387-2393
[65] YU C, LI L, XIE F, et al. LncRNA TUG1 sponges miR-204-5p to promote osteoblast differentiation through upregulating Runx2 in aortic valve calcification[J]. Cardiovasc Res, 2018, 114(1): 168-179
[66] XIAO X, ZHOU T, GUO S, et al. LncRNA MALAT1 sponges miR-204 to promote osteoblast differentiation of human aortic valve interstitial cells through up-regulating Smad4[J]. Int J Cardiol, 2017, 243: 404-412
[67] HE W, LI F, ZHANG S, et al. LncRNA AFAP1-AS1 promotes osteoblast differentiation of human aortic valve interstitial cells through regulating miR-155/SMAD5 axis [J]. Mol Cell Probes, 2020, 50: 101509

[收稿日期] 2021-01-04