doi: 10.3978/j.issn.2095-6959.2019.06.026
View this article at: http://dx.doi.org/10.3978/j.issn.2095-6959.2019.06.026

视黄醇结合蛋白4与心血管疾病的临床研究进展

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[摘 要] 视黄醇结合蛋白4(retinol binding protein 4，RBP4)是视黄醇在血液中运输的载体，以前被称为视黄醇结合蛋白。RBP4主要由肝细胞和脂肪组织分泌，是心肌代谢新的危险因子。RBP4参与胰岛素抵抗(insulin resistance，IR)发生，在诸如肥胖、2型糖尿病、代谢综合征、心血管疾病中血浆RBP4水平升高。因此深入探讨以RBP4作为心血管疾病代谢的重要预警因子的研究具有重要意义。

[关键词] 视黄醇结合蛋白4；心血管疾病；病理生理

Clinical research progress in retinol binding protein 4 and cardiovascular disease

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Abstract Retinol binding protein 4 (RBP4), previously called retinol binding protein (RBP), is considered a specific carrier of retinol in the blood. RBP4 is regarded as a novel cardiometabolic risk factor, which is secreted mainly by the hepatocytes and also by the adipose tissue. RBP4 has been shown to induce insulin resistance (IR), and plasma RBP4 levels are increased in type 2 diabetes mellitus, obesity, metabolic syndrome, and cardiovascular disease. Thus, further studies on the metabolic roles of RBP4 in cardiovascular diseases are crucial.

Keywords retinol binding protein 4; cardiovascular diseases; pathophysiology

维生素A又称视黄醇，是维持正常视觉功能、维护上皮组织细胞健康和促进免疫蛋白合成、维持骨骼正常生长发育、促进生长生殖、抑制肿瘤生长的重要营养元素。视黄醇结合蛋白4(retinol binding protein 4，RBP4)因其在视觉上的作用而成为眼科研究的药物靶点。RBP4与动脉粥样硬化[1-2]、胰岛素抵抗(insulin resistance，IR)[3]、心力衰竭[4]、缺血性脑卒中[5]、高血压、脂质代谢紊乱[6]等心血管疾病及其危险因素密切相关。然而，目前关于RBP4与心血管疾病的相关发病机制的研究甚少，因此深入探究RBP4在心血管疾病病理生理过程中的重要作用，从而对心血管疾病的防治提

收稿日期 (Date of reception)：2018–11–26

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基金项目 (Foundation item)：国家自然科学基金青年基金 (81401151)。This work was supported by the Youth Fund of National Natural Science Foundation of China (81401151).

供新的方向有着重要意义。此外，RBP4不但受年龄、性别的影响，多种非代谢因素也可以影响循环中的RBP4水平，如肝功能不全、慢性肾功能不全、恶性肿瘤、急慢性感染、血液系统疾病、免疫系统疾病等。本文主要就RBP4在心血管疾病中的临床应用、影响因素等作一综述。

1 RBP4 概述

1.1 理化性质

2005年Yang等[7]通过基因芯片技术鉴定出，在小鼠脂肪组织中敲除葡萄糖转运蛋白4(glucose transporter 4，GLUT4)后可引起RBP4明显升高的基因表达谱，并发现RBP4通过破坏肌肉组织中的胰岛素信号通路磷脂酰肌醇3-激酶(PI3K)从而引起IR，最终确定RBP4是一种可导致IR并引发2型糖尿病的新型脂肪细胞因子。RBP4的基因位于染色体10(10q23-q24)附近，mRNA全长914 bp，由单一肽链和小部分碳水化合物组成，含182个氨基酸残基，分子量为21 kD(1 D=1 u)。RBP4主要由肝细胞粗面内质网合成，但其mRNA可在各种肝外组织中表达，并分布于人体多种体液中。

1.2 生理功能

RBP4的主要作用是从肝中调集疏水性的视黄醇并通过血液循环运输到外周组织，完成维生素A从肝内到靶组织的转运。RBP4与视黄醇及前白蛋白以固定的比例形成独特的高分子化合物，既可降低RBP4在肾中的分解及在肾小球的滤过，又可使视黄醇的结构更加稳固、氧化率降低、毒性减少[8]。研究[9]证实：RBP4在高血压病、动脉粥样硬化、IR、2型糖尿病、代谢综合症、脂质代谢紊乱等多种心血管疾病及其危险因素的发病过程中发挥重要作用。

2 RBP4 与心血管疾病及其危险因素

2.1 RBP4 与冠心病

冠心病的发病率及病死率逐年升高，且呈年轻化趋势，已成为影响人们生活质量的重要心血管疾病。Lambadiari等[10]首次对RBP4与冠脉疾病进行研究，发现与对照组相比，冠脉疾病组RBP4浓度更高，并且和狭窄的冠脉血管数量密切相关。RBP4的浓度与冠脉病变密切相关，结合冠脉的病变程度，急性冠脉综合征组的RBP4浓度比稳定型冠心病组更高，RBP4的升高可以为复杂的冠脉血管病变提供更高的独立风险预测(约23%)[11]。RBP4的基因多态性和冠脉病变密切相关[12]。对大型女性人群在长达16年的临床研究[13]中发现，RBP4的浓度和冠心病的危险性密切相关。RBP4的水平在合并高胰岛素血症的冠脉疾病中比单纯冠脉疾病和对照组均显著增高，RBP4与IR及冠脉疾病相关的危险因素如BMI、三酰甘油、超敏C反应蛋白和脂联素等都密切相关[14]。RBP4是继传统的心血管危险因素后，新的心血管疾病死亡的预测因子，因此可以用于评价冠心病。

2.2 RBP4 与 IR 及糖尿病

高血糖是心血管疾病的重要危险因素之一，合并糖尿病的冠心病患者的血管病变会更重，行血运重建后的心血管事件的风险更高[15]。2型糖尿病的产生依赖于IR和胰岛素分泌不足。实验[16]证明：在动物脂肪组织GLUT4被敲除后，蛋白酶β亚基1的Y149位点磷酸化，促其易位进入3T3-L1脂肪细胞核，引起RBP4水平的高表达，最终促进2型糖尿病的产生。RBP4还可通过活化c-Jun氨基端激酶(JNK)、NF-κB抑制IKB激酶、胞外信号调节激酶及细胞因子信号转导抑制因子3等，作用于胰岛素受体/胰岛素受体底物(insulin receptor substrate，IRS)/PI3K/Ras/丝裂原活化蛋白激酶(MAPK)等信号通路中的各个环节，引起下游基因表达和信号转导的改变，最终诱发IR并加速2型糖尿病的产生[17-19]。

2.3 RBP4 与高血压

高血压病是引起心、脑、肾和血管等多个靶器官结构及功能障碍的慢性全身性疾病，主要是由于细小动脉硬化导致的血管重构。RBP4引起血压升高的机制可能为RBP4通过诱导IR引起血管内皮功能障碍，从而减弱了由一氧化氮介导的内皮依赖性血管舒张效应，进而内皮因子合成、释放、利用、失活，促进了血管收缩、细胞增殖，使其血栓形成的内皮因子产生更强的作用；低水平的RBP4可以保护由血管紧张素II引起的高血压及心肌肥厚。据推测，针对高水平的RBP4采取药物治疗将会增强血管舒张，改善血压和保护不良的心肌重构[20-21]。据报道[22-23]，在中国人的高血压前期阶段，RBP4与血压密切相关，尤其是和收缩压之间呈正相关，因此降压治疗对于预防心血管疾病非常重要。

2.4 RBP4 与脂质代谢紊乱

高脂血症是心血管疾病产生的重要危险因素

之一，而脂质代谢紊乱是形成高脂血症及促进动脉粥样硬化的重要因素。RBP4可以通过升高动脉粥样硬化损伤性因子低密度脂蛋白、总胆固醇、三酰甘油以及降低保护性因子高密度脂蛋白从而促进动脉粥样硬化的形成[24-25]。2型糖尿病患者高浓度的RBP4可通过其细胞表面受体视黄酸刺激因子6介导的Jak激酶(JAK)/信号转导及STAT级联反应影响脂质代谢[26-27]，降低极低密度脂蛋白，升高低密度脂蛋白、总胆固醇、三酰甘油[28-29]。RBP4还能通过上调蛋白二硫化物异构酶的表达来增强微粒体甘油三酸酯转运蛋白的活性，抑制低密度脂蛋白受体的表达和损伤胰岛素信号通路，从而引起apoB的分泌[30]。

2.5 RBP4与动脉粥样硬化

基线水平的RBP4也可以成为心血管不良事件发生的独立危险因子[2]。有学者[2]通过RBP4转基因小鼠模型(RBP4-Tg)，分析了RBP4的增多和缺失对巨噬细胞及泡沫细胞的形成过程和动脉粥样硬化的影响，发现RBP4定位在富含巨噬细胞及泡沫细胞的区域，提示RBP4对巨噬细胞及泡沫细胞的形成起重要影响，加入外源性重组RBP4或者令RBP4基因过表达，可促进巨噬细胞来源的泡沫细胞形成，这种巨噬细胞中的脂质紊乱，促进了动脉粥样硬化的发生。另有研究[31-32]指出：RBP4能利用JNK途径以及STAT1，增加促胆固醇吸收的清道夫受体CD36的表达，同时RBP4改变了酪氨酸激酶c-Src的膜分布，从而揭示了RBP4通过c-Src-JNK-STAT1-CD36依赖的信号通路，促进胆固醇的吸收，加速动脉粥样硬化形成的机制。

2.6 RBP4与炎症反应

慢性炎症反应是心血管疾病形成的基本病理生理过程[33]。研究[34-35]表明：细胞信号转导通路P38和JNK主要通过对炎性因子和细胞应激信号进行转导参与动脉粥样硬化的病理过程，RBP4可以促进P38和JNK的激活，而P38抑制剂可以减少RBP4刺激引起的血管细胞黏附分子、细胞内黏附分子、单核细胞化学引诱物蛋白质和IL-6的产生，JNK抑制剂可以减少RBP4刺激引起的内皮细胞选择素和单核细胞化学引诱物蛋白质的产生。Du等[36-37]研究发现：RBP4的升高也可以直接引起血管内皮炎症反应，相关机制可能为Toll样受体可以增加RBP4介导的促炎蛋白的表达和体外白细胞的产生，因此可能在心血管疾病和糖尿病的微血管并发症的发生发展中起决定性作用。

2.7 RBP4与血管内皮损伤

心血管疾病的发病机制和线粒体功能障碍及血管氧化损伤密切相关。在主动脉血管细胞内，线粒体融合与分裂的平衡控制线粒体的数量、长度和管型，一旦平衡被打破，将引起线粒体功能障碍[38]。RBP4引起线粒体功能障碍的相关机制可能为：RBP4可以抑制线粒体融合蛋白的表达，但同时也可以促进线粒体裂解蛋白的表达。RBP4还可通过减少线粒体的数量、完整性以及主动脉血管细胞内的膜电位引起线粒体功能障碍，从而调节细胞凋亡的内源性通路。RBP4疗法显著增加了细胞凋亡相关蛋白如细胞色素C，Bax等的表达。PI3K/AKT信号通路的激活抑制细胞凋亡及促进细胞生存，RBP4疗法也抑制了PI3K/AKT信号通路的磷酸化从而促进了细胞凋亡。RBP4引起血管内皮氧化损伤，从而促进动脉粥样硬化的进展。

2.8 RBP4与心力衰竭

心力衰竭是心脏结构和功能变化的终末期表现。研究[10]表明：RBP4可以影响心肌肥厚，可能引起心力衰竭。Chavarria等[39]研究表明：RBP4可能通过影响IR而引起心力衰竭，在植入左心室辅助装置之后，心力衰竭患者的RBP4水平和IR均明显改善。具体相关机制可能为IL-8依赖性地提高RBP4mRNA的表达，从而导致RBP4浓度升高及引起IR，最终诱发心力衰竭[40]。这些资料表明RBP4是左心室功能障碍的潜在生物标志物。然而，RBP4和心力衰竭最敏感的生物指标NT-proBNP之间却没有观察到有密切的相关性，而且受肾功能影响，在心肾综合症阶段重度心力衰竭时RBP4浓度才会升高，因此RBP4暂不可以作为评价心肌功能障碍的独立生物标志物[5]。

3 影响RBP4水平的因素

3.1 肝功能

RBP4主要由肝分泌，故RBP4水平受肝影响最大。据文献[41-43]报道：急慢性肝炎患者血清RBP4水平较正常人下降，归因于肝合成功能的减退，与肝组织纤维化或肝硬化程度密切相关。IR是非酒精性脂肪性肝病(non-alcoholic fatty liver disease，NAFLD)的特征性表现，RBP4可引起IR，故而认为RBP4在NAFLD发病机制中起一定的作用，NAFLD患者RBP4水平高于健康对照组，且与IR相关[44-45]。

3.2 肾功能

RBP4被肾小球滤过，随后被近端肾小管重吸收。此外，RBP4属于尿液样本中的低分子量蛋白，因此，血浆RBP4水平与血清肌酐和白蛋白尿程度呈正相关，与肾小球滤过率呈负相关，并且它们通常在肾功能不全时增加[46-47]。研究[48]指出：末期肾脏病患者血清RBP4浓度较正常对照组高出7倍，当接受肾移植术后，RBP4水平较前明显下降，所以血清RBP4浓度与肾功能密切相关。

3.3 药物

他汀类药物可引起RBP4水平减少，潜在机制可能为他汀类药物降低低密度脂蛋白，RBP4又与低密度脂蛋白代谢相关。贝特类药物可降低RBP4的水平，饮食和考来烯胺联合治疗后RBP4降低，但不能排除饮食引起RBP4的减少，而消胆胺本身对RBP4没有任何显著影响。热量限制可能诱导RBP4水平降低。胰岛素及降糖药物可能对RBP4有一定影响，但研究[49-50]报道差异较大。

3.4 运动

关于运动引起RBP4变化的相关研究[51]表明：运动减少了循环RBP4的水平，而有些却没有发现RBP4的任何变化，如强力活动与较低水平的循环RBP4相关，但中等强度活动、低强度活动或步行对RBP4没有任何重大影响。在阻力运动期间循环RBP4明显减少。

4 结语

RBP4是一种可诱导IR的新型脂肪细胞因子，参与2型糖尿病、动脉粥样硬化、高血压、冠心病、代谢综合征等心血管疾病及其危险因素的发生发展。多种非代谢因素可能影响RBP4的水平。深入探究RBP4在心血管疾病的病理生理过程中的作用，对心血管疾病的防治具有重要意义。

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本文引用： 陈景玲, 王姝. 视黄醇结合蛋白4与心血管疾病的临床研究进展[J]. 临床与病理杂志, 2019, 39(6): 1311-1316. doi: 10.3978/j.issn.2095-6959.2019.06.026

Cite this article as: CHEN Jingling, WANG Shu. Clinical research progress in retinol binding protein 4 and cardiovascular disease[J]. Journal of Clinical and Pathological Research, 2019, 39(6): 1311-1316. doi: 10.3978/j.issn.2095-6959.2019.06.026