Advances in Clinical Medicine 临床医学进展, 2022, 12(8), 7496-7504
Published Online August 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.1281082

Hans汉斯

II型糖尿病大血管病变防治新靶点的研究进展

王平义[1*]，孙若豪[1*]，张群辉[2]，赵万花[1]，李文华[1#]

[1]西藏民族大学医学院，陕西 咸阳
[2]青海大学医学院高原医学研究中心，青海 西宁

收稿日期：2022年7月11日；录用日期：2022年8月9日；发布日期：2022年8月16日

摘 要

背景：慢性病的发病率高、危险性大，是全球性公共健康首要问题。糖尿病宛如“慢性癌症”，是由饮食、环境、药物、遗传等因素导致的，体内胰岛素分泌相对或者绝对不足而出现的血糖代谢紊乱。常见以II型糖尿病为主，并发症可导致患者心肌梗塞、脑溢血、失明、肾功能衰竭和下肢截肢等严重后果，是影响人类健康和寿命的主要危险因素。目的：总结II型糖尿病大血管病变发病生物标志物的研究进展，以期为II型糖尿病大血管病变及其所引起的心脑血管疾病的防治提供新靶点。方法：以“macrovascular disease in type 2 diabetes mellitus，pathogenesis”为英文检索词，以“II型糖尿病并发大血管病变，发病机制”为中文检索词，应用计算机检索PubMed、Medline、中国知网和万方数据库发表的相关文献，最终纳入文献59篇进行归纳分析。结果与结论：II型糖尿病大血管病变是由多种因素共同作用导致的复杂疾病。近年来，大量实验室和临床研究表明，其发生发展主要与非编码RNA、外泌体、炎性小体、活化T细胞核因子、骨形态发生蛋白等生物标志物有关，上述生物标志物有望成为II型糖尿病大血管病变新靶点。

关键词

糖尿病，血管病变，生物标志物，新靶点

Research Progress of New Targets for Prevention and Treatment of Type II Diabetic Macrovascular Disease

Pingyi Wang[1*], Ruohao Sun[1*], Qunhui Zhang[2], Wanhua Zhao[1], Wenhua Li[1#]

[1]School of Medicine, Xizang Minzu University, Xianyang Shaanxi
[2]Research Center for High Altitude Medicine, Medical College of Qinghai University, Xining Qinghai

Received: Jul. 11th, 2022; accepted: Aug. 9th, 2022; published: Aug. 16th, 2022

[*]共同第一作者。
[#]通讯作者。

文章引用: 王平义, 孙若豪, 张群辉, 赵万花, 李文华. II 型糖尿病大血管病变防治新靶点的研究进展[J]. 临床医学进展, 2022, 12(8): 7496-7504. DOI: 10.12677/acm.2022.1281082

Abstract

Background: Chronic diseases are a major global public health problem due to their high incidence and high risk. Diabetes, like "chronic cancer", is caused by diet, environment, drugs, genetics and other factors, and the relative or absolute insufficiency of insulin secretion in the body leads to the disorder of blood glucose metabolism. Type II diabetes is the most common type. Its complications can lead to myocardial infarction, cerebral hemorrhage, blindness, renal failure and lower limb amputation and other serious consequences. It is a major risk factor affecting human health and life span. Objective: In order to provide new targets for the prevention and treatment of type II diabetic macroangiopaemia and its cardiovascular and cerebrovascular diseases, the research progress of type II diabetic macroangiopaemia biomarkers was summarized. Methods: Using the search terms of "macrovascular disease in type II diabetes mellitus, pathogenesis" in Chinese and English. Relevant literatures published by PubMed, Medline, CNKI and Wanfang database were searched by computer, and 59 literatures were finally included for induction and analysis. Results and Conclusion: Type II diabetic macrovascular disease is a complex disease caused by many factors. In recent years, a large number of laboratory and clinical studies have shown that its occurrence and development are mainly related to non-coding RNA, exosome, inflammasome, activated T nuclear factor, bone morphogenetic protein and other biomarkers, which are expected to become new targets of type II diabetic macrovascular disease.

Keywords

Diabetes, Vascular Disease, Biomarker, New Target

1. 引言

糖尿病并发大血管病变是指主动脉、冠状动脉、脑基底动脉、肾动脉及周围动脉等动脉粥样硬化。主要累及冠状血管、脑血管和周围血管，其所引起心脑血管疾病，是糖尿病患者致死及致残的主要原因[1]。目前，临床普遍认为 II 型糖尿病(type 2 diabetes mellitus, T2DM)合并大血管病变的病理基础为动脉硬化，且与脂代谢紊乱、增龄、氧化应激等多种因素相关[2]，但该病发病率仍持续增加，突显了探索其他介质和机制的必要性。近年来诸多研究表明[3] [4] [5] [6]，T2DM 大血管病变的发生主要与非编码 RNA、外泌体、炎性小体、活化 T 细胞核因子、骨形态发生蛋白等生物标志物有关。进一步了解潜在的分子机制有助于开发新的药物靶点和治疗方法，可以更有效地管理糖尿病并发大血管病变。回顾近年来关于 T2DM 大血管病变发病机制的最新研究进展，就参与 T2DM 大血管病变发病的标志物研究进展作一综述，以期为研究 T2DM 大血管病变的学者提供新靶点。

2. 资料和方法

2.1. 文献检索

要求应用计算机检索 PubMed、Medline 数据库、中国知网和万方数据库发表的相关文献。以“macrovascular disease in type 2 diabetes mellitus，pathogenesis”为英文检索词，PubMed 具体检索式为

(macrovascular disease in type 2 diabetes mellitus) AND (pathogenesis) OR (ncRNA) OR (exosome) OR (BMP) OR (NLRP3) OR (nuclear factor of activated t cell)；以“II 型糖尿病并发大血管病变，发病机制”为中文检索词。

2.2. 纳入标准

1) 研究类型为回顾性、前瞻性期刊论文、会议文献、学位论文、综述；2) 研究对象为 T2DM 大血管病变发病机制。

2.3. 排除标准

1) 设计不严谨或低质量的研究；2) 研究类型为讲座、评论；3) 无法获得全文；4) 重复发表的文献或阶段性报告。

2.4. 质量评估及数据的提取

经资料收集者互相评估纳入文献的有效性和适用性，通过阅读文题和摘要进行初步筛选；排除中英文文献重复性研究，以及内容不相关的文献，最后纳入 61 篇文献进行综述。

3. 发病机制

3.1. ncRNA

目前发现越来越多的 lncRNA 参与糖尿病引起的巨噬细胞、平滑肌细胞以及内皮细胞的病理学改变，从而导致血管炎症以及其他心血管病变，进而影响糖尿病血管病变的发生、发展[7]，表明其有很大的潜力作为疾病潜在生物标志物和治疗靶标。肺癌转移相关转录本 1 (metastasis associated lung adenocarcinoma transcript 1, MALAT1)在大血管中有表达。Gong 等[8]在高糖诱导的人脐静脉内皮细胞(human umbilical vein/vascular endothelium cell, HUVEC)发现 MALAT1 表达明显上调。同时，敲除 MALAT1 可以抑制 HUVEC 的凋亡和炎症的发生。另一项研究表明[9]，过表达的 MALAT1 以分子海绵形式与 miR-155-5p 结合，从而抑制其表达，同时上调核因子 I/A 的表达，进而抑制血管病变的进展。此外，许多研究支持了 lncRNA 调控糖尿病–动脉粥样硬化轴的观点，其中，INK4 基因座中反义非编码(long non-coding anti-sense RNA, ANRIL)是一种与动脉粥样硬化相关的 lncRNA，ANRIL 在动脉粥样硬化患者的内皮细胞、血管平滑肌细胞、炎性细胞和组织中均有表达，提示可能影响糖尿病大血管病变的发展[10]。Liu 等[11]研究发现 ANRIL 表达与白细胞介素-10 和单核细胞趋化蛋白 1 等细胞因子相关，而这些细胞因子上调是内皮功能障碍的标志物。ANRIL 通过 TGF-β R1/Smad 通路抑制 miR-let-7b 调节 HUVEC 功能，而内皮细胞作为糖尿病大血管病变进展过程中的基础细胞，其功能变化可影响糖尿病大血管病变的进展。lncRNA 可能作为早期糖尿病大血管病变的诊断标志物，还需要进一步研究来证实。MicroRNA (miRNA)可以通过调节几个关键的生物学途径和细胞功能来影响心血管系统。研究表明高糖引起的 miRNA 异常表达可导致心血管疾病相关的内皮细胞、血管平滑肌细胞、血小板及巨噬细胞功能障碍和脂质代谢异常，某些 miRNA 可作为糖尿病大血管病变的潜在生物标志物和治疗靶点[12]。Li 等[13]在研究中发现，IGF-1 是 miR-29 的潜在靶点，在糖尿病引起的血管病变中，由于 miR-29 的下调，促进了促血管生成过程，如细胞增殖和迁移，表明 IGF-1 可能直接参与 miR-29 介导的糖尿病心肌病血管生成的调控过程。miR-126 在内皮细胞凋亡体中丰富表达，可调控趋化因子 CXCL12 的产生及血管内皮生长因子的应答，对血管具有一定的保护作用[14]。miR-126 和 miR-132 作为内皮细胞特异性 miRNA，具有促进血管再生的作用。相关研究表明[15]，T2DM 小鼠心肌组织中 miR-126 和 miR-132 表达减少，可使血管内皮生长因子水平降低，促使糖尿病心脏病发生；此外，T2DM 心脏病前期患者循环血液中 miR-126 和 miR-132 异常表达，有成为早

期预测指标的潜能。T2DM 冠状动脉性疾病患者血清 miR-342 及 miR-450 差异性表达[16]。多种 miRNA 均有预测 T2DM 无症状患者急性心力衰竭发生的潜能，与糖尿病大血管病变的发生发展有密切的联系。研究表明，circRNA 010567 可通过调控 miR-141/TGF-β1 通路促进糖尿病心肌纤维化[17]。circRNA 0076631 在高糖培养的心肌细胞及糖尿病患者血清中高表达，通过 miR-214-3p/caspase-1 通路介导糖尿病性心肌细胞的炎症性坏死，促进糖尿病心血管病变的发生[18]。circRNA 000203 在糖尿病小鼠心脏和血管紧张素 II 诱导的小鼠心脏成纤维细胞中高表达，由此可作为糖尿病心脏纤维化的潜在诊断指标和治疗靶点[19]。此外，circRNA ANKRD36 在糖尿病炎症性心血管病变中异常表达，可将其视作监测指标[20]。血液中 circRNA 11783-2 与冠状动脉性疾病及 T2DM 具有一定相关性[21]。circRNA 参与糖尿病血管病变的发生发展，但其具体机制尚处于初步探究阶段。可见，ncRNA 在糖尿病血管病变时差异表达，同时参与调控其多种分子机制，对 ncRNA 的深入研究将为探索糖尿病血管病变非侵袭性诊断标志物提供新思路。

3.2. 外泌体

外泌体可以调节细胞粘附和迁移、炎症、血管损伤、血管钙化和血栓形成等[22]。糖尿病患者血液中的外泌体水平升高，并参与糖尿病相关的病理生理过程，包括血管并发症、炎症和凝血功能改变[23] [24] [25]。赵敏等[26]指出，外泌体可以作为疾病的标志物。Wang 等[27]确定，胰岛素抗性脂肪细胞衍生的外泌体通过诱导血管血管生成而加速动脉粥样硬化。研究发现糖尿病患者的循环中外泌体水平明显高于正常血糖控制的参与者。胰岛素抵抗驱动细胞外小泡分泌，糖尿病患者红细胞源性外泌体水平更高，高胰岛素抵抗和 β-细胞功能障碍个体的外泌体中胰岛素信号蛋白水平也发生了改变。此外，糖尿病患者的外泌体优先被循环白细胞内化。细胞因子在培养基和外泌体中的水平较高的单核细胞与糖尿病外泌体孵育。这些白细胞的芯片显示了与细胞生存、氧化应激和免疫功能相关的基因表达通路的改变。这可能有助于糖尿病中血浆外泌体的定量改变，并突出了它们作为 T2DM 诊断工具的潜力[28]。自噬与外泌体具有相同的分子机制[28]。相继有研究在核内体和吞噬体中检测到 ATG5-ATG12、ATG16L1 复合物和 LC3 [29] [30] [31]。这些自噬相关蛋白的功能是确保囊泡在溶酶体中被酸化和降解。糖尿病微环境中多个细胞的自噬途径被抑制，这可能增加糖尿病患者的外泌体[32] [33] [34]。Zhang 等人[35]将外泌体从糖尿病小鼠的血液中转移到非糖尿病小鼠，发现外泌体可以被运送到非糖尿病小鼠的主动脉内皮细胞，并损害内皮细胞功能。同时发现外泌体蛋白信号在这一过程中起主要作用，外泌体携带的某些调节蛋白可以通过影响其他正常细胞部分导致主动脉内皮损伤。Zhu 等[36]研究发现，尼古丁干预巨噬细胞的外泌体 miR-21-3p 可能通过增加血管平滑肌细胞的迁移和增殖，从而加速动脉粥样硬化的发展。Bouchareychas 等[37]研究发现，BMDM-IL-4-exo 通过 microRNA 转运靶向 NF-κB 和 TNF-α，进而缓解动脉粥样硬化和其他炎症性疾病的发生。Xu 等[38]研究发现，褪黑素干预的血管平滑肌产生的外泌体可以通过外泌体 miR-204/miR-211 旁分泌方式减弱血管钙化和衰老。Komaki [39]等证实，PlaMSC-exo 增强了体外和体内的血管生成，表明外泌体在 PlaMSC 的促血管生成活性中发挥作用，进而治疗缺血性疾病。由此可见，外泌体将为诊断和监测糖尿病血管病变提供新思路。

3.3. 炎性小体

最近的研究表明，NLRP3 炎症小体激活是糖尿病患者的病理机制之一[40] [41]。Chen 等[42]研究发现，NLRP3 炎症小体在早期糖尿病小鼠的冠状动脉内皮细胞中被激活。Ferreira 等[43]研究发现，NLRP3 炎性小体可介导 caspase-1 激活和促炎细胞因子 IL-1β/IL-18 的分泌，进而促进内皮中进一步的炎症过程和氧化应激[44]。内皮炎症可进一步发展为内皮功能障碍，并在随后的过程中相互促进导致血管病变。许多物质被证实可以通过激活 NLRP3 炎症小体来促进血管炎症，Sun 等[45]研究证实内脂素作为一种促炎

性脂肪因子，可以通过 NF-κB 通路促进炎症因子的产生，进而导致内皮炎症。Romacho 等[46]研究发现，NLRP3 炎症小体激活是内脂素诱导内皮炎症的潜在原因，这种炎症反应可导致内皮功能障碍，引发肥胖期间的动脉粥样硬化。NLRP3 炎症小体激活在外源性物质介导的内皮炎症也发挥着巨大的作用。Xia 等[47]研究发现，四氯苯醌(TCBQ)能促进内皮细胞 NLRP3 和 IL-1β 的分泌，进而导致内皮炎症。该研究还报道 TCBQ 诱导的 NLRP3 炎性小体激活可能与 K+外流、线粒体 ROS 产生和线粒体 DNA 损伤有关。TCBQ 通过破坏 NLRP3 炎症小体内外离子稳态，导致 GSDMD 和 MLKL 的外漏和细胞内容物释放，从而加重了 NLRP3 炎症小体的激活[48]。Chen 等研究证实，镉通过线粒体 ROS 介导的 NLRP3 激活诱导内皮细胞死亡和炎症反应，由此可知，NLRP3 激活与糖尿病相关的血管功能障碍和促炎表型有关，这些变化最终可导致心肌梗死的发生。

3.4. 活化 T 细胞核因子

随着研究的深入，活化 T 细胞核因子(NFATc1-c4)蛋白在免疫细胞外发挥的作用也日益明晰，对心血管系统的影响不容忽视。高血糖可以诱导 NFAT 激活，从而会诱导动脉壁中促动脉粥样硬化细胞因子骨桥蛋白(OPN)以及炎症介质的表达进而导致血管病变。Blanco 等[49]通过对 IGF-II/LDLR$^{-/-}$ApoB$^{100/100}$ 小鼠的研究发现，在主动脉血管平滑肌细胞中，NFAT 的抑制与抗动脉粥样硬化保护性 NOX4 和抗氧化酶过氧化氢酶的表达增加密切相关。Zetterqvist 等[50]研究发现，通过 NFAT 阻滞剂可以有效降低糖尿病小鼠的炎症因子在动脉壁中的表达，并降低血浆中的 IL-6，从而消除高血糖诱导的主动脉粥样硬化。Liu 等[51]发现高糖刺激下的 AGEs 通过激活 ERS 介导的 PERK/CaN/NFATc4 信号通路，加重心血管疾病。Liu 等[52]研究发现，巨噬细胞 NFATc3 上调 miR-204，降低 SR-A 和 CD36 水平，从而动脉粥样硬化，提示 NFATc3/miR-204 轴可能是动脉粥样硬化的潜在治疗靶点。Luo 等[53]发现指出 ETS2 在钙调神经磷酸酶/NFAT 通路驱动的心肌肥厚中起关键作用。Govatati 等[54]首次揭示了凝血酶诱导的人主动脉平滑肌细胞迁移和损伤诱导的新内膜生长需要 IL-33 的表达，而凝血酶诱导 IL-33 的表达需要 LMCD1 增强 NFATc1 和 E2F1 的组合激活。He [55]等发现蛋白 CIP 可以抑制 NFAT 通路，从而导致氧化应激通路关键成分 Nox4 的表达降低，从而减缓小鼠营养不良心肌病的发展。由此可见，高血糖诱发的 NFAT 激活在 T2DM 大血管病变的发生发展中起着重要作用。

3.5. 骨形态发生蛋白

近年来，随着研究的深入，发现骨形态发生蛋白(BMP)在 T2DM 动脉粥样硬化和血管钙化等血管疾病中发挥重要作用，功能远远超出了促进骨形成的范围。BMP 信号分子在血管钙化中的作用具有前后相关性、组织依赖性和细胞类型特异性[56]。BMP2、BMP4 在钙化的动脉粥样硬化斑块中有差异表达，BMP2、BMP4 和 BMP6，通过促炎症和促动脉粥样硬化作用促进氧化应激、内皮功能障碍和成骨分化，且与斑块形成增加有关[57]。Scimeca 等[58]在 52 名患者钙化颈动脉斑块的微阵列分析中，发现斑块中 BMP2 和 BMP4 的表达与不稳定斑块的存在之间有很强的相关性。在高血糖和糖尿病的条件下，血管 BMP 活性可以被激活，促进血管钙化，进而导致血管病变。Zhang 等[59]在对 124 名受试者的研究中发现，T2DM 合并冠心病患者中 BMP-2 含量升高，与冠状动脉粥样硬化病变的程度、复杂性及斑块钙化程度呈正相关。Sanchez 等[60]基于在钙化血管病变中内皮初级纤毛稀少的观察，发现从纤毛缺失小鼠获得的血管内皮细胞在体外对 BMP 诱导的成骨分化敏感，炎性细胞因子通过需要下调 BMPR2 的机制增强 BMP9 诱导的 EndMT，进而促使血管钙化[61]。综上所述，BMP 的含量升高是 T2DM 大血管病变导致的心肌梗死的发病因素之一。骨形态发生蛋白在血管钙化方面作用的进一步研究，将为 T2DM 并发大血管病变的发生机制的研究提供新思路。

4. 总结与展望

文章对参与 T2DM 大血管病变的生物标志物研究进展进行综述，以期为 T2DM 大血管病变的防治提供新思路。ncRNA 在糖尿病血管病变中发挥着重要作用，其中，lncRNA 可以通过提高 IL-10 和 MCP-1 来调控细胞凋亡和炎症的发生，miR-126、miR-132、miR-342 等 miRNA 和 ANKRD36、0076631 等 circRNA 在糖尿病血管病变时差异表达，有成为早期预测指标的潜能，circRNA 可通过调控 miR-141/TGF-β1 和 miR-124-3p/caspase-1 等信号通路导致糖尿病心血管疾病；外泌体递送的 microRNA 等生物学成分对糖尿病大血管病变的发生发展起着重要作用；NLRP3 炎性小体和 T 细胞核因子激活导致诸如 IL-1β、IL-6、IL-18 和 IL-33 等炎性因子释放，此外，T 细胞核因子还可以上调 miR-204，从而使 T2DM 患者的血管病变恶化；高糖环境下 BMP2、BMP4 和 BMP6 差异性表达，引起血管钙化，从而导致动脉粥样硬化等血管病变。对上述生物标志物的深入研究，将为探索糖尿病血管病变诊断标志物提供新靶点，为诊断和监测糖尿病血管病变提供新思路。

作者贡献

王平义与孙若豪对本文贡献相同，为本文共同第一作者。文章设计者为王平义、孙若豪和李文华。资料收集和文章写作者为孙若豪。文献分析者为王平义。李文华对文章修改提出指导意见。张群辉、赵万花作者审校。

基金项目

国家自然科学基金项目(81760332)，项目负责人：李文华；西藏自治区科技厅自然科学基金青年项目(XZ202001ZR0053G)，项目负责人：王平义；西藏科技厅厅校联合项目(XZ202101ZR0100G)，项目负责人：李文华；国家级大学生创新创业训练计划(202110695033)，项目负责人：孙若豪。

利益冲突

文章的全部作者声明，在课题研究和文章撰写过程中不存在利益冲突。

参考文献

[1] Madonna, R., Pieragostino, D., Balistreri, C.R., *et al*. (2018) Diabetic Macroangiopathy: Pathogenetic Insights and Novel Therapeutic Approaches with Focus on High Glucose-Mediated Vascular Damage. *Vascular Pharmacology*, **107**, 27-34. https://doi.org/10.1016/j.vph.2018.01.009

[2] Fang, Z., Hu, X., Chen, Z., *et al*. (2020) Radix Pseudostellariae of Danzhi Jiangtang Capsule Relieves Oxidative Stress of Vascular Endothelium in Diabetic Macroangiopathy. *Saudi Pharmaceutical Journal*, **28**, 683-691. https://doi.org/10.1016/j.jsps.2020.04.009

[3] Zhang, J.M., Yu, R.Q., Wu, F.Z., *et al*. (2021) BMP-2 Alleviates Heart Failure with Type 2 Diabetes Mellitus and Doxorubicin-Induced AC16 Cell Injury by Inhibiting NLRP3 Inflammasome-Mediated Pyroptosis. *Experimental and Therapeutic Medicine*, **22**, Article No. 897. https://doi.org/10.3892/etm.2021.10329

[4] Sargazi, S., Ravanbakhsh, M., Nia, M.H., *et al*. (2022) Association of Polymorphisms within HOX Transcript Antisense RNA (HOTAIR) with Type 2 Diabetes Mellitus and Laboratory Characteristics: A Preliminary Case-Control Study. *Disease Markers*, **2022**, Article ID: 4327342. https://doi.org/10.1155/2022/4327342

[5] Fluitt, M.B., Mohit, N., Gambhir, K.K., *et al*. (2022) To the Future: The Role of Exosome-Derived MicroRNAs as Markers, Mediators, and Therapies for Endothelial Dysfunction in Type 2 Diabetes Mellitus. *Journal of Diabetes Research*, **2022**, Article ID: 5126968. https://doi.org/10.1155/2022/5126968

[6] Liu, X., Zhang, Y., Liang, H., *et al*. (2020) MicroRNA-499-3p Inhibits Proliferation and Promotes Apoptosis of Retinal Cells in Diabetic Retinopathy through Activation of the TLR4 Signaling Pathway by Targeting IFNA2. *Gene*, **741**, Article ID: 144539. https://doi.org/10.1016/j.gene.2020.144539

[7] Rai, A.K., Lee, B., Gomez, R., *et al*. (2020) Current Status and Potential Therapeutic Strategies for Using Non-Coding

RNA to Treat Diabetic Cardiomyopathy. *Frontiers in Physiology*, **11**, Article ID: 612722. https://doi.org/10.3389/fphys.2020.612722

[8] Gong, Y.P., Zhang, Y.W., Su, X.Q., *et al*. (2020) Inhibition of Long Noncoding RNA MALAT1 Suppresses High Glucose-Induced Apoptosis and Inflammation in Human Umbilical Vein Endothelial Cells by Suppressing the NF-κB Signaling Pathway. *Biochemistry and Cell Biology*, **98**, 669-675. https://doi.org/10.1139/bcb-2019-0403

[9] Chen, L., Hu, L., Zhu, X., *et al*. (2020) MALAT1 Overexpression Attenuates AS by Inhibiting Ox-LDL-Stimulated Dendritic Cell Maturation Via MiR-155-5p/NFIA Axis. *Cell Cycle*, **19**, 2472-2485. https://doi.org/10.1080/15384101.2020.1807094

[10] Hu, Y. and Hu, J. (2019) Diagnostic Value of Circulating LncRNA ANRIL and Its Correlation with Coronary Artery Disease Parameters. *Brazilian Journal of Medical and Biological Research*, **52**, Article No. E8309. https://doi.org/10.1590/1414-431x20198309

[11] Liu, X., Li, S., Yang, Y., *et al*. (2021) The LncRNA ANRIL Regulates Endothelial Dysfunction by Targeting the Let-7b/TGF-BetaR1 Signalling Pathway. *Journal of Cellular Physiology*, **236**, 2058-2069. https://doi.org/10.1002/jcp.29993

[12] Barber, J.L., Zellars, K.N., Barringhaus, K.G., *et al*. (2019) The Effects of Regular Exercise on Circulating Cardiovascular-Related MicroRNAs. *Scientific Reports*, **9**, Article No. 7527. https://doi.org/10.1038/s41598-019-43978-x

[13] Li, Z., Jiang, R., Yue, Q., *et al*. (2017) MicroRNA-29 Regulates Myocardial Microvascular Endothelial Cells Proliferation and Migration in Association with IGF1 in Type 2 Diabetes. *Biochemical and Biophysical Research Communications*, **487**, 15-21. https://doi.org/10.1016/j.bbrc.2017.03.055

[14] 王磊，王红娜，祖晓麟. 血浆 miR-126 水平与冠状动脉慢血流现象的关系[J]. 中华医学杂志，2019，99(17): 1323-1327.

[15] Rawal, S., Munasinghe, P.E., Shindikar, A., *et al*. (2017) Down-Regulation of Proangiogenic MicroRNA-126 and MicroRNA-132 Are Early Modulators of Diabetic Cardiac Microangiopathy. *Cardiovascular Research*, **113**, 90-101. https://doi.org/10.1093/cvr/cvw235

[16] Seleem, M., Shabayek, M. and Ewida, H.A. (2019) MicroRNAs 342 and 450 Together with NOX-4 Activity and Their Association with Coronary Artery Disease in Diabetes. *Diabetes/Metabolism Research and Reviews*, **35**, Article No. E3130. https://doi.org/10.1002/dmrr.3130

[17] Zhou, B. and Yu, J.W. (2017) A Novel Identified Circular RNA, CircRNA_010567, Promotes Myocardial Fibrosis Via Suppressing MiR-141 by Targeting TGF-Beta1. *Biochemical and Biophysical Research Communications*, **487**, 769-775. https://doi.org/10.1016/j.bbrc.2017.04.044

[18] Yang, F., Li, A., Qin, Y., *et al*. (2019) A Novel Circular RNA Mediates Pyroptosis of Diabetic Cardiomyopathy by Functioning as a Competing Endogenous RNA. *Molecular Therapy - Nucleic Acids*, **17**, 636-643. https://doi.org/10.1016/j.omtn.2019.06.026

[19] Tang, C.M., Zhang, M., Huang, L., *et al*. (2017) CircRNA_000203 Enhances the Expression of Fibrosis-Associated Genes by Derepressing Targets of MiR-26b-5p, Col1a2 and CTGF, in Cardiac Fibroblasts. *Scientific Reports*, **7**, Article No. 40342. https://doi.org/10.1038/srep40342

[20] Xu, H., Guo, S., Li, W., *et al*. (2015) The Circular RNA Cdr1as, Via MiR-7 and Its Targets, Regulates Insulin Transcription and Secretion in Islet Cells. *Scientific Reports*, **5**, Article No. 12453. https://doi.org/10.1038/srep12453

[21] Li, C., Zhao, L., Jiang, W., *et al*. (2018) Correct Microarray Analysis Approaches in 'Hsa-CircRNA11783-2 in Peripheral Blood Is Correlated with Coronary Artery Disease and Type 2 Diabetes Mellitus'. *Diabetes and Vascular Disease Research*, **15**, 92-93. https://doi.org/10.1177/1479164117739435

[22] Kapustin, A.N. and Shanahan, C.M. (2016) Emerging Roles for Vascular Smooth Muscle Cell Exosomes in Calcification and Coagulation. *The Journal of Physiology*, **594**, 2905-2914. https://doi.org/10.1113/JP271340

[23] Akbar, N., Azzimato, V., Choudhury, R.P., *et al*. (2019) Extracellular Vesicles in Metabolic Disease. *Diabetologia*, **62**, 2179-2187. https://doi.org/10.1007/s00125-019-05014-5

[24] O'Neill, S., Bohl, M., Gregersen, S., *et al*. (2016) Blood-Based Biomarkers for Metabolic Syndrome. *Trends in Endocrinology and Metabolism*, **27**, 363-374. https://doi.org/10.1016/j.tem.2016.03.012

[25] 赵敏，冯柳祥，陈垚，等. 低氧环境下外泌体可作为疾病的标志物[J]. 中国组织工程研究，2021，25(7): 1104-1108.

[26] Wang, F., Chen, F.F., Shang, Y.Y., *et al*. (2018) Insulin Resistance Adipocyte-Derived Exosomes Aggravate Atherosclerosis by Increasing Vasa Vasorum Angiogenesis in Diabetic ApoE(−/−) Mice. *International Journal of Cardiology*, **265**, 181-187. https://doi.org/10.1016/j.ijcard.2018.04.028

[27] Freeman, D.W., Noren, H.N., Eitan, E., *et al*. (2018) Altered Extracellular Vesicle Concentration, Cargo, and Function in Diabetes. *Diabetes*, **67**, 2377-2388. https://doi.org/10.2337/db17-1308

[28] Salimi, L., Akbari, A., Jabbari, N., *et al*. (2020) Synergies in Exosomes and Autophagy Pathways for Cellular Homeostasis and Metastasis of Tumor Cells. *Cell & Bioscience*, **10**, Article No. 64. https://doi.org/10.1186/s13578-020-00426-y

[29] Guo, H., Chitiprolu, M., Roncevic, L., *et al*. (2017) Atg5 Disassociates the V1V0-ATPase to Promote Exosome Production and Tumor Metastasis Independent of Canonical Macroautophagy. *Developmental Cell*, **43**, 716-730.E7. https://doi.org/10.1016/j.devcel.2017.11.018

[30] Martinez, J., Malireddi, R.K., Lu, Q., *et al*. (2015) Molecular Characterization of LC3-Associated Phagocytosis Reveals Distinct Roles for Rubicon, NOX2 and Autophagy Proteins. *Nature Cell Biology*, **17**, 893-906. https://doi.org/10.1038/ncb3192

[31] Murrow, L., Malhotra, R. and Debnath, J. (2015) ATG12-ATG3 Interacts with Alix to Promote Basal Autophagic Flux and Late Endosome Function. *Nature Cell Biology*, **17**, 300-310. https://doi.org/10.1038/ncb3112

[32] Cheng, Z. (2019) The FoxO-Autophagy Axis in Health and Disease. *Trends in Endocrinology and Metabolism*, **30**, 658-671. https://doi.org/10.1016/j.tem.2019.07.009

[33] Lim, H., Lim, Y.M., Kim, K.H., *et al*. (2018) A Novel Autophagy Enhancer as a Therapeutic Agent against Metabolic Syndrome and Diabetes. *Nature Communications*, **9**, Article No. 1438. https://doi.org/10.1038/s41467-018-03939-w

[34] Kim, K.H. and Lee, M.S. (2014) Autophagy—A Key Player in Cellular and Body Metabolism. *Nature Reviews Endocrinology*, **10**, 322-337. https://doi.org/10.1038/nrendo.2014.35

[35] Zhang, H., Liu, J., Qu, D., *et al*. (2018) Serum Exosomes Mediate Delivery of Arginase 1 as a Novel Mechanism for Endothelial Dysfunction in Diabetes. *Proceedings of the National Academy of Sciences of the United States of America*, **115**, E6927-E6936. https://doi.org/10.1073/pnas.1721521115

[36] Zhu, J., Liu, B., Wang, Z., *et al*. (2019) Exosomes from Nicotine-Stimulated Macrophages Accelerate Atherosclerosis through MiR-21-3p/PTEN-Mediated VSMC Migration and Proliferation. *Theranostics*, **9**, 6901-6919. https://doi.org/10.7150/thno.37357

[37] Bouchareychas, L., Duong, P., Covarrubias, S., *et al*. (2020) Macrophage Exosomes Resolve Atherosclerosis by Regulating Hematopoiesis and Inflammation Via MicroRNA Cargo. *Cell Reports*, **32**, Article ID: 107881. https://doi.org/10.1016/j.celrep.2020.107881

[38] Xu, F., Zhong, J.Y., Lin, X., *et al*. (2020) Melatonin Alleviates Vascular Calcification and Ageing through Exosomal MiR-204/miR-211 Cluster in a Paracrine Manner. *Journal of Pineal Research*, **68**, Article No. E12631. https://doi.org/10.1111/jpi.12631

[39] Komaki, M., Numata, Y., Morioka, C., *et al*. (2017) Exosomes of Human Placenta-Derived Mesenchymal Stem Cells Stimulate Angiogenesis. *Stem Cell Research & Therapy*, **8**, Article No. 219. https://doi.org/10.1186/s13287-017-0660-9

[40] Zhang, J., Xia, L., Zhang, F., *et al*. (2017) A Novel Mechanism of Diabetic Vascular Endothelial Dysfunction: Hypoadiponectinemia-Induced NLRP3 Inflammasome Activation. *Biochimica et Biophysica Acta* (*BBA*) - *Molecular Basis of Disease*, **1863**, 1556-1567. https://doi.org/10.1016/j.bbadis.2017.02.012

[41] Shin, J.J., Lee, E.K., Park, T.J., *et al*. (2015) Damage-Associated Molecular Patterns and Their Pathological Relevance in Diabetes Mellitus. *Ageing Research Reviews*, **24**, 66-76. https://doi.org/10.1016/j.arr.2015.06.004

[42] Chen, Y., Wang, L., Pitzer, A.L., *et al*. (2016) Contribution of Redox-Dependent Activation of Endothelial Nlrp3 Inflammasomes to Hyperglycemia-Induced Endothelial Dysfunction. *Journal of Molecular Medicine*, **94**, 1335-1347. https://doi.org/10.1007/s00109-016-1481-5

[43] Ferreira, N.S., Bruder-Nascimento, T., Pereira, C.A., *et al*. (2019) NLRP3 Inflammasome and Mineralocorticoid Receptors Are Associated with Vascular Dysfunction in Type 2 Diabetes Mellitus. *Cells*, **8**, Article No. 1595. https://doi.org/10.3390/cells8121595

[44] Kelley, N., Jeltema, D., Duan, Y., *et al*. (2019) The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. *International Journal of Molecular Sciences*, **20**, Article No. 3328. https://doi.org/10.3390/ijms20133328

[45] Sun, L., Chen, S., Gao, H., *et al*. (2017) Visfatin Induces the Apoptosis of Endothelial Progenitor Cells Via the Induction of Pro-Inflammatory Mediators through the NF-KappaB Pathway. *International Journal of Molecular Medicine*, **40**, 637-646. https://doi.org/10.3892/ijmm.2017.3048

[46] Romacho, T., Valencia, I., Ramos-Gonzalez, M., *et al*. (2020) Visfatin/eNampt Induces Endothelial Dysfunction in Vivo: A Role for Toll-Like Receptor 4 and NLRP3 Inflammasome. *Scientific Reports*, **10**, Article No. 5386. https://doi.org/10.1038/s41598-020-62190-w

[47] Xia, X., Shi, Q., Song, X., *et al*. (2016) Tetrachlorobenzoquinone Stimulates NLRP3 Inflammasome-Mediated Post-Translational Activation and Secretion of IL-1beta in the HUVEC Endothelial Cell Line. *Chemical Research in Toxicology*, **29**, 421-429. https://doi.org/10.1021/acs.chemrestox.6b00021

[48] Xia, X., Lu, B., Dong, W., *et al*. (2018) Atypical Gasdermin D and Mixed Lineage Kinase Domain-Like Protein Leakage Aggravates Tetrachlorobenzoquinone-Induced Nod-Like Receptor Protein 3 Inflammasome Activation. *Chemical Research in Toxicology*, **31**, 1418-1425. https://doi.org/10.1021/acs.chemrestox.8b00306

[49] Blanco, F., Heinonen, S.E., Gurzeler, E., *et al*. (2018) in Vivo Inhibition of Nuclear Factor of Activated T-Cells Leads to Atherosclerotic Plaque Regression in IGF-II/LDLR−/− ApoB100/100 Mice. *Diabetes and Vascular Disease Research*, **15**, 302-313. https://doi.org/10.1177/1479164118759220

[50] Zetterqvist, A.V., Berglund, L.M., Blanco, F., *et al*. (2014) Inhibition of Nuclear Factor of Activated T-Cells (NFAT) Suppresses Accelerated Atherosclerosis in Diabetic Mice. *PLOS ONE*, **8**, Article ID: e65020. https://doi.org/10.1371/journal.pone.0065020

[51] Liu, Z., Zhu, H., Ma, Y., *et al*. (2021) AGEs Exacerbates Coronary Microvascular Dysfunction in NoCAD by Activating Endoplasmic Reticulum Stress-Mediated PERK Signaling Pathway. *Metabolism*, **117**, Article ID: 154710. https://doi.org/10.1016/j.metabol.2021.154710

[52] Liu, X., Guo, J.W., Lin, X.C., *et al*. (2021) Macrophage NFATc3 Prevents Foam Cell Formation and Atherosclerosis: Evidence and Mechanisms. *European Heart Journal*, **42**, 4847-4861. https://doi.org/10.1093/eurheartj/ehab660

[53] Luo, Y., Jiang, N., May, H.I., *et al*. (2021) Cooperative Binding of ETS2 and NFAT Links Erk1/2 and Calcineurin Signaling in the Pathogenesis of Cardiac Hypertrophy. *Circulation*, **144**, 34-51. https://doi.org/10.1161/CIRCULATIONAHA.120.052384

[54] Govatati, S., Pichavaram, P., Janjanam, J., *et al*. (2019) NFATc1-E2F1-LMCD1-Mediated IL-33 Expression by Thrombin Is Required for Injury-Induced Neointima Formation. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **39**, 1212-1226. https://doi.org/10.1161/ATVBAHA.119.312729

[55] He, X., Liu, J., Gu, F., *et al*. (2022) Cardiac CIP Protein Regulates Dystrophic Cardiomyopathy. *Molecular Therapy*, **30**, 898-914. https://doi.org/10.1016/j.ymthe.2021.08.022

[56] Perera, N., Ritchie, R.H., Tate, M. (2020) The Role of Bone Morphogenetic Proteins in Diabetic Complications. *ACS Pharmacology & Translational Science*, **3**, 11-20. https://doi.org/10.1021/acsptsci.9b00064

[57] Yung, L.M., Sanchez-Duffhues, G., Ten, D.P., *et al*. (2015) Bone Morphogenetic Protein 6 and Oxidized Low-Density Lipoprotein Synergistically Recruit Osteogenic Differentiation in Endothelial Cells. *Cardiovascular Research*, **108**, 278-287. https://doi.org/10.1093/cvr/cvv221

[58] Scimeca, M., Anemona, L., Granaglia, A., *et al*. (2019) Plaque Calcification Is Driven by Different Mechanisms of Mineralization Associated with Specific Cardiovascular Risk Factors. *Nutrition, Metabolism and Cardiovascular Diseases*, **29**, 1330-1336. https://doi.org/10.1016/j.numecd.2019.08.009

[59] Zhang, M., Sara, J.D., Wang, F.L., *et al*. (2015) Increased Plasma BMP-2 Levels Are Associated with Atherosclerosis Burden and Coronary Calcification in Type 2 Diabetic Patients. *Cardiovascular Diabetology*, **14**, Article No. 64. https://doi.org/10.1186/s12933-015-0214-3

[60] Sanchez-Duffhues, G., De Vinuesa, A.G., Lindeman, J.H., *et al*. (2015) SLUG Is Expressed in Endothelial Cells Lacking Primary Cilia to Promote Cellular Calcification. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **35**, 616-627. https://doi.org/10.1161/ATVBAHA.115.305268

[61] Sanchez-Duffhues, G., Garcia, D.V.A., Van De Pol, V., *et al*. (2019) Inflammation Induces Endothelial-To-Mesenchymal Transition and Promotes Vascular Calcification through Downregulation of BMPR2. *The Journal of Pathology*, **247**, 333-346. https://doi.org/10.1002/path.5193