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综 述

外泌体在糖尿病及其并发症的发生、发展和诊治中的作用

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摘 要：外泌体是一种纳米级大小，由细胞主动吞吐而分泌的具有膜结构的细胞外囊泡样小体，可以携带和转移很多生物分子，如DNA片段、环状RNA (circRNA)、mRNA、微小RNA (miRNA)、功能蛋白、转录因子等，从而成为细胞间信息传递的载体。近年来外泌体与糖尿病的关系受到广泛关注，它们在胰岛素敏感性、葡萄糖稳态、血管内皮功能等方面发挥重要作用。本文综述外泌体参与糖尿病及其并发症的病理生理过程，并探讨了外泌体作为糖尿病治疗的靶点及其在糖尿病的诊断与治疗中的作用和前景。

关键词：外泌体；糖尿病；糖尿病并发症
中图分类号：R335；R587.1；R587.2

Exosomes and their roles in diabetes mellitus and its complications: from pathogenic, diagnostic and therapeutical perspectives

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Abstract: Exosome is a kind of nanoscale-size extracellular vesicles secreted by the means of cell active stimulation with outer membrane structure of vacuoles corpuscle. It can carry and transfer a lot of biological molecules, such as DNA fragments, circular RNA (circRNA), messenger RNA (mRNA), microRNA (miRNA), functional proteins, transcription factors, etc., so as to achieve the goal of information transmission between cells. The relationship between exosomes and diabetes has received extensive attention in recent years. The exosomes play an important role in insulin sensitivity, glucose homeostasis and vascular endothelial function. This paper reviews the role of exosomes in the occurrence and development of diabetes and its complications, and discusses the role and prospect of exosomes as a target for diabetes treatment and its role in the diagnosis and treatment of diabetes.

Key words: exosomes; diabetes; diabetic complications

分泌至细胞外的外泌体 (exosomes) 是细胞外囊泡中的“明星”分子，它们可以携带并转移多种生物学信号，并且通过自分泌、旁分泌等方式作用于远距离的细胞，从而达到细胞间信息传递的目的。目前，已有最新研究将外泌体引入糖尿病领域，为该领域的研究打开了新的局面 [1]。本文综述了外泌体在糖尿病及其并发症的发生和发展中的作用，并探讨了外泌体作为糖尿病治疗的靶点及其在糖尿病的诊断与治疗中的作用和前景。

1 外泌体的生物学特点及其功能

外泌体是一种纳米级大小，由细胞主动吞吐而分泌的具有膜结构的细胞外囊泡样小体。外泌体直径为 30~150 nm，密度为 1.10~1.19 g/mL [2, 3]，人体

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中大约有 10^{14} 个，近乎于平均每个细胞产生 1 000~101 000 个。外泌体作为一种膜囊泡，主要由细胞内多泡体与细胞膜融合并释放到细胞外基质中。外泌体在电镜下表现为脂质双分子层包裹的扁平球体，呈特征性的杯托状外形 [4]。几乎所有的真核细胞都可以产生外泌体，包括一些微生物都可以产生外泌体 [5–7]。外泌体可稳定存在于细胞外液中，包括细胞培养上清液、血浆、血清、唾液、尿液、羊水、腹水、乳汁、脑脊液、鼻灌洗液、关节腔液、精液、前列腺液、胆汁以及其它生物体液。分泌外泌体的细胞可以包括 T 细胞、B 细胞、血小板、树突细胞、肥大细胞等。事实上，细胞外囊泡除了外泌体之外，还有微泡 (microvesicles, MVs) 和凋亡小体 (apoptotic bodies)。它们的直径比外泌体大，且机制也与外泌体有所区别 [8]。关于外泌体直径大小，实际上不同的细胞类型也会决定外泌体的大小，例如脂肪细胞分泌的外泌体直径就比较大，约在 150~200 nm [9]。因此，外泌体直径并不能绝对限定在 < 150 nm 这个范围之中。另外，也只有外泌体能够由细胞不断释放，其他细胞外囊泡只能由活化或凋亡的细胞所释放 [10]，这也是外泌体的与众不同之处。

外泌体的形成始于细胞外物质或细胞膜蛋白的内吞作用，形成小囊泡，小囊泡进而会互相融合形成早期内吞小体 (early endosomes, EE)，接着 EE 经细胞内运输逐渐成熟酸化成晚期内吞体 (late endosomes, LE)，此时内吞体膜通过返褶内向出芽凹陷，将细胞内经过分拣的 DNA 片段、环状 RNA (circRNA)、mRNA、微小 RNA (microRNA, miRNA)、蛋白质、转录因子等包裹起来形成多个管腔内囊泡 (intraluminal vesicles, ILVs)，即外泌体的前体 [10]。LE 会包含多个管腔囊泡，被称为多泡体 (multivesicular body, MVB)，这些多泡体具有蛋白运输与分拣功能。接着有部分 MVB 与细胞质膜融合，并向外释放外泌体到细胞外基质，其他 MVB 则与溶酶体融合，内含物被降解参与再循环 [10]。释放到细胞外基质的外泌体会再次通过内吞作用或以识别膜表面特定受体模式进入受体细胞，将其携带的“货物”释放入受体细胞的胞质，发挥信号转导作用。外泌体内含物的成分与受体细胞的种类决定了外泌体的功能 (外泌体在细胞间的传递过程见图 1)。

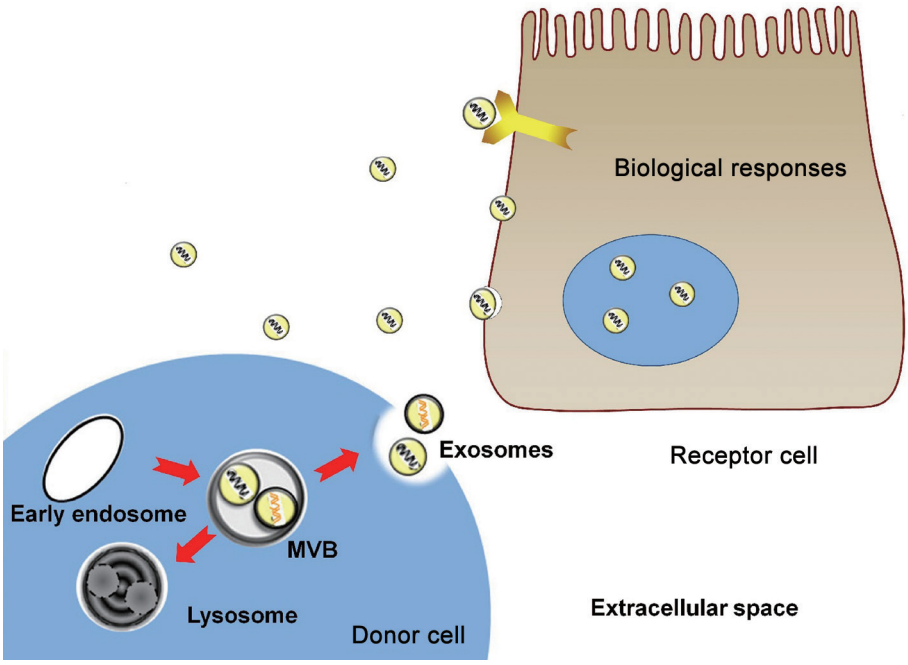

图 1. 外泌体在细胞间传递的过程

Fig. 1. Exosomes-mediated intercellular transmission. After early endosomes (EE) gradually mature into multivesicular bodies (MVBs) by intracellular transportation, some MVBs may fuse with cytoplasmic membrane and release their contents as exosomes to extracellular matrix, and other MVBs may fuse with lysosome, and the contents are degraded and involved in recycling. Then these exosomes enter the receptor cells by endocytosis or recognition of specific receptor patterns on the membrane surface, and release the “cargo” into the cytoplasm of the receptor cells to play a role in signal transduction.

外泌体可以携带转移很多生物分子，如 DNA 片段、circRNA、mRNA、miRNA、功能蛋白、转录因子等，从而达到细胞间信息传递的目的；而其本身的膜结构还能表达多种抗原、抗体分子，从而参与细胞间的信息交流与物质交换，在多种生理、病理过程中都起到重要作用：比如细胞通讯、细胞迁移、分化、促血管新生、免疫应答、抗原提呈、肿瘤侵袭等，还可作为纳米载体装载基因或药物到达靶器官等 [11]。

2 外泌体对糖尿病研究的重要意义

外泌体在胰岛素敏感性、葡萄糖稳态、血管内皮功能等方面发挥重要作用 [12]。糖尿病是一种常见的代谢紊乱，其特征是胰岛 β 细胞分泌胰岛素的功能紊乱，不同程度的胰岛素抵抗合并胰岛素相对缺乏。胰腺、肝脏、肌肉或脂肪等器官均牵涉其中，而这些器官之间的交流是维持葡萄糖稳态的关键环节 [11]。当患者发生代谢紊乱时其循环血里的外泌体数量增加 [13]，胰岛素抵抗越严重，胰岛 β 细胞功能越紊乱，外泌体内胰岛素信号蛋白改变就越多，这些外泌体优先被白细胞内化，改变白细胞功能 [14]，外泌体内还含有会引起血管功能障碍的成分 [13]。

糖尿病与外泌体的关系已受到广泛关注。研究表明，外泌体参与了糖尿病及其相关并发症的发生与发展，它不仅可以作为糖尿病早期诊断和分期的生物学标记，还可作为糖尿病治疗的靶点 [11]，更重要的是可以监测糖尿病患者对治疗的反应 [15]，为实施糖尿病的个体化治疗提供依据 [11]。

2.1 外泌体与胰岛素及其受体的关系

胰岛 β 细胞是胰岛素的唯一来源，胰岛素是胰岛 β 细胞受内源性或外源性刺激而分泌的一种蛋白类激素，参与调节糖代谢，控制血糖平衡 [16]。分泌胰岛素的 β 细胞和胰岛素敏感组织将含有蛋白质和 miRNA 的外泌体释放到细胞外，并可转移到其他代谢器官或免疫内皮细胞。外泌体以自分泌和旁分泌的方式起作用，有利于维持葡萄糖体内平衡或造成胰岛素抵抗 [17]。外周血中的外泌体数量或脂肪细胞来源的外泌体数量与稳态模型评价胰岛素抵抗指数 (homeostasis model assessment insulin resistance index, HOMA-IR) 呈正相关 [14, 18]，并且这些外周血或脂肪细胞来源的外泌体所携带的特异性生物信息也与胰岛素敏感性相关 [14, 19]。外泌体调节胰岛素敏感性至少通过 2 条途径：一种是通过调节炎症途径；另一种是通过对胰岛素反应器官的直接相互作用途径，这种方式能够直接或间接影响胰岛素信号通路。

胰岛素与细胞膜上的胰岛素受体 (insulin receptor, IR) 结合激活酪氨酸激酶，从而启动细胞内胰岛素信号通路。钙蛋白酶 -2 (calpain 2) 是一种钙依赖的蛋白酶，它不包含信号肽，但却是调节分泌途径所必需的酶，它的作用并不是降解蛋白，而是分裂蛋白。在高糖条件下，细胞分泌的外泌体内含有 calpain 2，这让 calpain 2 得以借助于外泌体而被释放到细胞外的空间；在细胞外，calpain 2 可以在 IRβ 胞外结构域中的特殊位点直接催化 IR 使其分裂，成为可溶性胰岛素受体 (soluble insulin receptor, sIR)；下一步就是由 γ- 分泌酶负责启动 IR 在细胞膜内的分裂。IR 在细胞外部分与细胞膜内部分的连续分裂，最终导致胰岛素受体底物 -1 (insulin receptor substrate 1, IRS-1) 的酪氨酸磷酸化和蛋白激酶 B (Akt) 磷酸化受到抑制，进而导致胰岛素信号通路受损，引发胰岛素抵抗。这也就是 2 型糖尿病 (type 2 diabetes mellitus, T2DM) 患者血浆 sIR 水平与胰岛素敏感性呈负相关的原因。二甲双胍可能正是因为可以抑制外泌体释放 calpain 2，干扰 IR 分裂 (通过敲除 calpain 2 和 γ- 分泌酶的途径) 进而恢复 IRS-1 和 Akt 的作用，重新建立胰岛素信号，从而缓解胰岛素抵抗，增强胰岛素敏感性。因此通过对外泌体的研究实际上发现了一种胰岛素抵抗的新机制 [20]。

2.2 外泌体与低度慢性炎症及胰岛素抵抗的产生

1 型糖尿病 (type 1 diabetes mellitus, T1DM) 和 T2DM 二者具有不同的发病机制：T1DM 是由于产生胰岛素的细胞逐渐丢失，导致胰岛素产量低或不分泌；而 T2DM 通常被认为是由于机体对胰岛素产生了胰岛素抵抗。尽管 T1DM 和 T2DM 的发病机制迥异，但其致病因素、病程、病理生理、疾病进展和并发症是有联系的：二者都是由遗传易感性和环境因素共同作用引起的，只是易感基因不同；T2DM 可以以酮症酸中毒起病，而 T1DM 中部分患者隐匿起病、尤其是胰岛自身抗体阳性的成人患者；部分 T2DM 患者在病程中可并发继发性的自身免疫过程，而 T1DM 可逐渐出现肥胖和胰岛素抵抗；二者都涉及免疫系统和代谢系统之间的相互作用 [21]。值得注意的是，慢性炎症是两种糖尿病的共同表现 [22, 23]。最近，外泌体被认为是连接炎症和糖尿病的中间体 [24]：来自自身免疫易感动物的胰岛间充质干细胞 (mesenchymal stem cell, MSC) 释放高促炎症

性外泌体，有助于 T1DM 发生 [25]；肥胖中低级别炎症性外泌体可能刺激促炎症性外泌体的释放，加速 T2DM [26, 27]，最终可导致全身胰岛素抵抗 [18]。因此肥胖是导致胰岛素抵抗的主要致病因素，当胰岛 β 细胞不能分泌足够的胰岛素以补偿胰岛素敏感性降低时，可导致 T2DM 的发生 [28]。

2.3 外泌体与脂肪组织相关的胰岛素抵抗

脂肪组织是一种动态的内分泌器官 [29]，分泌多种脂肪因子 [30]、酶、生长因子和调节糖脂代谢的激素来调节全身能量的稳态 [31]。胰岛素抵抗部分程度上与脂肪细胞分泌的物质有关。在糖尿病前期的胰岛素抵抗肥胖人群中发现其脂肪细胞可以产生外泌体，这些外泌体被称为脂质体 (adiposomes, ADEs) [32]。ADEs 内含有糖基磷脂酰肌醇锚定蛋白的脂筏微区，可供磷酸二酯酶和 5’- 核苷酸酶 CD73 水解细胞内的 cAMP，以此来阻断 cAMP 所传导的生化作用。ADEs 由较大的供体脂肪细胞分泌，随后由较小的脂肪细胞吞噬，同时伴有脂肪酸酯化甘油三酯的过程加快和甘油三酯释放的过程变慢 [32]。脂肪组织所产生的血管生成因子被装载到 ADEs 中，参与血管生成；ADEs 还参与诱导细胞迁移和人脐静脉内皮细胞管腔的形成。由脂肪组织内皮细胞释放的外泌体富含血浆成分，可以借助这种方式将血浆里物质转移到脂肪细胞中，向脂肪细胞传递全身营养状况变化的生物学信息，这充分说明通过外泌体交流以维持代谢平衡的重要意义 [33]。已发现 CD14 表达阴性的 ADEs 与 T2DM 风险呈负相关 [34]。

ADEs 内含有大约 7 000 个 mRNA 和 140 个 miRNA，大部分是脂肪细胞特异性和显性基因的转录本，其丰度主要与供体细胞有关，ADEs 以旁分泌或内分泌的方式传递 RNA [35]。糖尿病前期胰岛素抵抗肥胖人群的 ADEs 所含的 miRNA 表达谱相对于健康人群发生了显著改变，能通过传递差异表达的 miRNA 进一步调控受体 β 细胞 [36]，甚至还能调节远端器官 (例如肝脏) 的细胞内基因表达 [37]。在肝脏中，成纤维细胞生长因子 21 (fibroblast growth factor 21, FGF21) 的作用是减少 miRNA，如果组织中成熟 miRNA 水平显著下降，循环外泌体中成熟 miRNA 水平也会显著下降 [38]，葡萄糖耐量下降；把白色和褐色脂肪组织都移植到组织后能够通过降低 FGF21 从而部分恢复循环 miRNA 的水平，改善葡萄糖耐量 [38]。用于加工 miRNA 的 Dicer 酶在脂肪组织中表达随着年龄增长而表达下调 [38]。一旦敲除脂肪特异性 Dicer 酶会使小鼠对氧化应激反应超敏。因此，如果脂肪组织中 miRNA 调节失衡会直接导致老年人糖尿病等代谢疾病的发病率增加。重要的是，这些影响可能不仅仅是因为脂肪细胞本身出现问题，还代表它们与其他器官的沟通出现了缺陷 [38, 39]。骨骼肌细胞能够摄取 ADEs，ADEs 分泌的 miR-27a 能够抑制靶基因过氧化物酶体增殖物活化受体 γ (peroxisomal proliferator-activated receptor-γ, PPARγ)，引起骨骼肌葡萄糖摄取受损 [40]。

除了 miRNA 之外，肥胖者的腹腔大网膜脂肪干细胞来源的外泌体所包含的长链非编码 RNA (long non-coding RNA, lncRNA) 浓度显著升高 [41]，而在节食或减肥手术后 lncRNA 水平显著下降 [42]。

ADEs 还富含脂联素，而脂联素是只能由脂肪细胞分泌的脂肪因子，且它们与脂质代谢和胰岛素抵抗有关 [43–45]。富含脂联素的外泌体可以影响远距离细胞的代谢。脂肪酸结合蛋白 (aP2) 在脂肪酶激活时能通过非经典途径调控不同组织细胞内脂质运输，外泌体内 aP2 水平在脂肪分解作用刺激下显著升高。肥胖时，脂肪组织对胰岛素介导抑制脂肪分解产生抵抗，从而增加 aP2 的分泌，导致肝脏葡萄糖输出增加并出现糖尿病 [46]。还有 Sonic Hedgehog (Shh) 也是一类由外泌体包裹的蛋白，在 T2DM 患者循环外泌体中 Shh 表达升高，能够刺激巨噬细胞分泌炎性因子，通过 Ptch/PI3K 信号通路介导 M1 巨噬细胞极化，进而导致脂肪细胞胰岛素抵抗 [47]。外泌体内还含有一些脂肪细胞特定蛋白，如肿瘤坏死因子 α (tumor necrosis factor α, TNF-α)、巨噬细胞集落刺激因子 (macrophage colony stimulating factor, MCSF) 和视黄醇结合蛋白 4 (retinol binding protein 4, RBP-4)[18] 等。妊娠糖尿病患者的 ADEs 会选择性地富集一组特定的蛋白，这些蛋白与胎盘细胞中葡萄糖代谢的变化有关 [48]。

有趣的是，将人脂肪组织离体培养后，又将继代培养的脂肪组织切段移入到新的培养基中，这些人脂肪组织外植体会释放外泌体，该过程依赖于脂肪因子的含量，这些外泌体可以抑制胰岛素诱导的肝细胞 AKT 磷酸化 [49]。从维持在低氧条件下的人脂肪组织细胞培养基中分离出来的外泌体通过降低葡萄糖摄取和胰岛素介导的 AKT 磷酸化来直接影响其他脂肪细胞的功能 [50]。

脂肪组织间充质干细胞 (adipose tissue mesenchymal stem cells, AT-MSCs) 释放的外泌体治疗肥胖

小鼠，通过传递活化信号转导与转录激活因子 -3 (signal transducer and activator of transcription 3, STAT3)，引导 M2 型替代激活的巨噬细胞，改善胰岛素敏感性，减轻肥胖，改善肝脏脂肪变性 [51]。同样是 MSCs，由脂肪细胞、肌细胞和肝细胞组成的老年小鼠骨髓间充质干细胞 (marrow mesenchymal stem cells, M-MSCs) 释放的外泌体可以在体内和体外产生胰岛素抵抗，miR-29b-3p 的数量在 M-MSCs 释放的外泌体中明显增加，下调 miR-29b-3p 可以显著改善胰岛素抵抗 [52]。总之，外泌体能够作为一种新的治疗肥胖人群胰岛素抵抗的靶点 [53]。

2.4 外泌体内miRNA与糖尿病

在外泌体所含的不同内容物中，miRNA 是一类非常丰富的非编码 RNA (其长度约为 19~22 个核苷酸)，由发夹结构的约 70~90 个碱基大小的单链 RNA 前体经过 Dicer 酶加工后生成的。它们通过与 mRNA 靶向结合，诱导其降解或抑制其翻译 [54]。研究表明，miRNA 在外泌体里的浓度始终高于其在体液里的浓度，且其拷贝数足以对受体细胞产生生物学效应 [55, 56]。由外泌体分泌的 miRNA 可以转移到邻近的细胞，将母细胞暴露于糖尿病常见的病理生理环境下，可以调节 miRNA 的释放，并影响受体细胞的存活，这种全新的细胞间通讯的机制调控了胰岛 β 细胞的活性 [57]。

研究表明，胰腺分泌的外泌体中含有 miR-375，它能调控胰岛素分泌以及胰岛的形成。miR-375 是少数几个从血清或血浆中分离出来的组织特异性已被证实的 miRNA 之一 [58, 59]。缺乏 miR-375 会出现高糖血症，伴有胰岛 α 细胞分泌增多、糖异生增多和肝糖元输出增多 [60]；当过表达 miR-375 时，胰岛素分泌会被抑制。深入研究发现肌侵蛋白 (myotrophin, MTPN) 是 miR-375 的作用靶点 [61]。脂肪组织中分离出来的巨噬细胞释放出的外泌体会导致葡萄糖耐受不良和胰岛素抵抗，这些外泌体通过增加 miR-155 靶向作用于在脂肪细胞中高表达的 PPARγ 来降低其他组织 (例如肝脏) 的胰岛素敏感性 [62]。

外周血单核细胞 (peripheral blood mononuclear cell, PBMC) 来源的细胞群可以促进血管生成，调节血管生成的 miRNA 是关键调控因子，$CD34^+$ PBMC 亚群的 miR-126 在血管内皮细胞中高表达，如果阻断该外泌体释放，会导致血管生成功能受损。糖尿病患者 $CD34^+$ PBMC 中 miR-126 的表达改变造成血管生成前效应受损 [63]。有人总结了诸多与糖尿病进程相关的外泌体内 miRNA：与葡萄糖耐受不良相关的 miR-27a-3p、miR-27b-3p、miR-192 [64]；与疾病进展相关的 miR-122 [64]；反映血糖控制情况及用药后反应的 let-7a、let-7f [15] 等。这些外泌体 miRNA 在糖脂代谢调控中发挥了关键作用 [64]。

然而由于 miRNA 可能参与多种生理和病理学过程，因此很难确认某个 miRNA 为某种特定生物学标志，这也限制了 miRNA 在临床中的使用。不过通过在未来不断扩大样本量与实验室或临床数据汇总以后，找到具有特异性的 miRNA 生物学标志指日可待 [11]。

2.5 外泌体与T1DM

通过检测 T1DM 和外泌体传递效应后发现 T1DM 的血清中含有更多的外泌体，其所包裹的 miRNA 参与心脏发育调节 [65]；并且这些外泌体可以遗传给胎鼠，直接导致先天性心脏缺陷发生率增加。

外泌体含有强大的免疫刺激物质，胰岛素瘤释放的外泌体能够刺激非肥胖糖尿病 (non-obese diabetic, NOD) 小鼠的自身免疫反应，从 NOD 小鼠朗格汉斯胰岛 (islet of Langerhans of NOD mice) 中分离出细胞进行体外培养，培养的胰岛细胞释放出的纤维母细胞样的快速复制样细胞表达了 MSC 标记物，包括 CD105 和干细胞抗原 -1。这些胰岛 MSC 样细胞释放高度免疫刺激的外泌体，可以激活 NOD 小鼠自身免疫 B 细胞和 T 细胞。说明外泌体是 NOD 小鼠自身抗原载体，具有强大的免疫活性，可能是 NOD 糖尿病小鼠自身免疫的触发器 [25]。

miR-21-5p 在用促炎细胞因子处理 T 细胞或胰岛细胞释放的外泌体中富集，在 T1DM 患者和 NOD 小鼠血清中均有升高 [66]，进而触发受体细胞凋亡通路，说明这一过程可以在 T1DM 的发展进程中发挥作用 [67]，外泌体 miR-21-5p 可能成为一种 T1DM 生物标志物 [66]。

糖尿病前期患者血清外泌体水平外源性干扰素 γ 的产生与疾病进展呈正相关，$CD105^+$ 细胞局限于正常胰岛细胞的外周区域，但随着淋巴细胞浸润，$CD105^+$ 细胞进入胰岛中心区域 (主要是 β 细胞区)，外泌体的免疫促进了致糖尿病性转移性 T 细胞扩增，加速效应 T 细胞介导的胰岛细胞破坏 [25]。从罹患 T1DM 多年的患者中分离得到的外泌体中发现，有的 miRNA 表达上调，如 miR-25-3p；有的 miRNA 表达下调，如 miR-16-5p、miR-302d-3p、miR-378a、miR-570-3p、miR-574-5p 等 [68]。上述这些研究结果

都为寻找 T1DM 的治疗新靶点提供了思路。

胰岛细胞移植是治疗自身免疫性 T1DM 的有效方法，移植胰岛特异性释放到血液循环中的外泌体对区分胰岛 β 细胞损伤二次复发性自身免疫和免疫排斥具有潜在诊断价值，表明外泌体可用于胰岛移植诊断的生物学标志 [69]。

从 MSCs 中分离出的外泌体具有免疫调节作用，可以通过增加调节性 T 细胞及其抗炎产物 IL-4 和 IL-10 的数量来改善胰岛功能，因此可被用于治疗 T1DM [70]。但是对此也有学者提出不同看法 [71]：从 M-MSCs 中提取的外泌体具有促进骨再生作用，而在 T1DM 患者中这种功能受损，表明对于 T1DM 患者来说，自体骨髓干细胞移植促进骨再生可能是不合适的。

2.6 外泌体与T2DM

胰淀粉样多肽储存于胰岛 β 细胞的胰岛素分泌颗粒中，与胰岛素共同被分泌，其血清浓度约为胰岛素的 1/10；在很多 T2DM 患者的胰腺中，胰淀粉样多肽含量增加 [72]。正常人的胰腺外泌体能够通过肽清除降低胰岛淀粉样多肽的形成，但是 T2DM 患者胰腺外泌体和血清外泌体则没有相似作用，且 C 肽比例和脂质组成与正常人不同 [73]。

外泌体携带有 T2DM 致病的重要生物信息。外泌体和其所携带的 miRNA 从脂肪组织经过血液，渗透到骨骼肌及肝脏中，这种组织间迁移时所诱导的反应可能直接导致了 T2DM 与代谢有关的紊乱的细胞间通讯 [62]。T2DM 患者血浆中 miR-15a 升高，它在胰岛 β 细胞胰岛素生成中起重要作用，与病情严重程度相关。实际上，血液中的 miR-15a 升高是源于胰岛 β 细胞分泌的外泌体，miR-15a 升高后靶向作用于 Akt3 引起氧化应激，进而导致细胞凋亡 [74]。miR-126 下降 [75] 或 miR-192 和 miR-193b 增加等 [76] 都是 T2DM 前期存在的信号，从而可以早期识别有风险的受试者。上述这些都说明了胰岛细胞分泌的外泌体中所含有的 miRNA 以旁分泌的方式调节 β 细胞功能，且这种情况在正常人和 T2DM 患者之间是有显著差异的 [77]。

另外，T2DM 患者循环外泌体含有的 lncRNA-p3134 的水平高于非 T2DM 患者，且与空腹血糖和 HOMA-β 水平相关，进一步研究发现 lncRNA-p3134 能通过促进 β 细胞中关键调控因子 (Pdx-1、MafA、GLUT2、Tcf712) 的表达，正向调控血糖刺激胰岛素分泌 (glucose-stimulated insulin secretion, GSIS) 功能，说明调控胰岛 β 细胞 lncRNA-p3134 能够维持血糖内稳态 [78]。

T2DM 被认为是一种慢性低度炎症性疾病 [79]，涉及到免疫细胞和内皮细胞 [80]。低度炎症过程的特征是内皮细胞活化 [81, 82]。这种细胞活化导致内皮细胞和单核细胞分泌细胞因子，表达黏附分子，如 I 型细胞内黏附分子 (intracellular adhesion molecule type I, ICAM-1)[83, 84]，进而将免疫细胞黏附和转移到血管壁上。T2DM 患者的血液循环中 ICAM-1 水平升高 [85]，这是内皮细胞活化的标志 [86]。内皮细胞和单核细胞可以释放出外泌体 [87, 88]，这些外泌体调节内皮细胞和单核细胞的功能，并且参与内皮细胞与免疫细胞之间的互相作用 [89]，这对高糖环境下内皮细胞和单核细胞的活化至关重要。在高糖环境下，内皮细胞释放的外泌体的动力学受到了明显影响 [90]，并且外泌体与 T2DM 或糖尿病相关的心血管并发症中的炎性细胞激活有密切关系 [91]。

人间充质干细胞分泌的外泌体 (human umbilical cord MSC-derived exosome, hucMSC-ex) 可以通过逆转外周血胰岛素抵抗和抑制 β 细胞凋亡来缓解 T2DM。hucMSC-ex 修复了 IRS-1 磷酸化 (酪氨酸位点) 和 T2DM 中 Akt 的表达，促进肌肉葡萄糖转运蛋白 -4 (glucose transporter 4, GLUT4) 的表达和膜转运，增加肝糖原的储存来维持血糖稳态 [92]，说明 hucMSC-ex 可能成为 T2DM 的一种治疗手段。

在另一方面，有研究显示，如果长期食用乳制品，乳制品中的外泌体 miR-29b- 支链氨基酸 (branched-chain amino acids, BCCA) 造成胰岛素过度合成以及 BCAA mTOR 依赖性胰岛素抵抗，这说明乳制品中的外泌体是 T2DM 的潜在启动子；而由 miR-29b 介导的抑制富含半胱氨酸的酸性分泌蛋白 (secreted protein acidic and rich in cysteine, SPARC) 和由 miR-148a 介导的抑制 V-Maf 肌腱膜纤维肉瘤癌基因同源物 B (V-Maf musculoaponeurotic fibrosarcoma oncogene homolog B, MAFB) 都可以通过增加内质网应激和 β 细胞凋亡而损害胰岛素分泌 [93]。

2.7 外泌体与妊娠糖尿病(gestational diabetes mellitus, GDM)

GDM 约占妊娠期的 9%，是糖尿病的另一种表现 [94]。虽然 GDM 通常在分娩后恢复正常，但妊娠期间代谢需求增加导致糖代谢的暂时缺陷。随着肥胖的发生率增多，GDM 的发病率也逐渐增加，并会影响到后代的健康，因为胚胎长期受到紊乱的代

谢环境的影响会发生表观遗传的改变[95]。包括胎盘释放的胎盘激素 (placental hormone, PH) 在内的一些因素与胰岛素抵抗和 GDM 的发生有关。然而，在整个妊娠期内，血 pH 水平与母体胰岛素敏感性并没有很好的相关性，这表明可能其中存在其他未被识别的机制[96]。

胎盘从妊娠 6 周起就向母体循环释放外泌体，此过程受到氧分压和血糖浓度等因素调节，与胎盘质量和灌注有关。胎盘外泌体对正常胎盘发育和母体免疫耐受具有重要作用。不同的妊娠周期和妊娠状态都会影响血浆外泌体的浓度。随着妊娠孕周的延长，血浆外泌体浓度逐渐升高，且母体血浆中分离的外泌体在体外具有生物活性，并通过内吞作用与靶细胞结合，与妊娠合并糖尿病和子痫前期有关[96]。GDM 与骨骼肌胰岛素抵抗、循环胎盘外泌体水平增加有关[97]。这些患者胎盘外泌体包裹了一些特定的与骨骼肌胰岛素敏感性相关的 miRNA，且它们在胎盘、循环外泌体和骨骼肌中表达一致。GDM 的胎盘外泌体可使具有正常胰岛素敏感性的原代骨骼肌细胞迁移和葡萄糖摄取率下降，说明胎盘外泌体可能在正常妊娠和 GDM 胰岛素敏感性的变化中发挥作用。而 GDM 患者的循环外泌体水平高于正常人，GDM 与高血糖引起的胎儿胎盘内皮功能障碍有关，GDM 衍生的外泌体能从内皮细胞中释放更多的促炎因子[98]，它们参与了 GDM 内皮功能障碍的疾病进展[84]。

3 外泌体参与糖尿病靶器官损害的机制

糖尿病易并发大中血管 (动脉粥样硬化) 及微血管病变 (视网膜病变、肾病和神经病变)，可累及全身重要靶器官损害，最终导致靶器官功能衰竭[99]。而对外泌体的研究也渗透到关于糖尿病并发症的各个环节之中。

3.1 外泌体与糖尿病心血管并发症

胰岛素对于心脏收缩性、生长和代谢至关重要，因此受损的胰岛素信号在糖尿病心血管并发症中起到关键作用[100]。而糖尿病性心血管并发症是糖尿病患者致残和死亡的主要原因。这些并发症与胰岛素抵抗和血脂紊乱密切相关。由于不同类型的心脏细胞都会分泌各自的心源性外泌体，因此学术界开始推测外泌体可能参与包括糖尿病性心肌病变 (diabetic cardiomyopathy, DCM) 在内的心血管疾病的病理生理机制[101]。将来外泌体在某种程度上也许能被用来治疗糖尿病心肌损害[102]。

在糖尿病初期，高血糖可导致内皮和微血管功能障碍[103, 104]。有人认为心肌血管生成失调是糖尿病心血管疾病的关键原因[105–107]，心脏内皮细胞在心肌细胞功能和结构中起着关键作用[108, 109]。外泌体内含有糖尿病动脉粥样硬化的致病因子[110]。糖尿病 db/db 小鼠的血清外泌体被正常小鼠主动脉内皮细胞摄取以后发生了严重的内皮功能损害，这种损害是由血清外泌体将精氨酸酶 -1 (arginase 1) 传递给内皮细胞造成的[111]。心肌微血管内皮细胞 (cardiac microvascular endothelial cells, CMECs) 释放的富含哺乳动物 STE20 酶 -1 (mammalian sterile 20-like kinase 1, MST1) 的外泌体在抑制自噬方面具有多效性，可以促进细胞凋亡，抑制细胞葡萄糖代谢[112]。血管内皮细胞分泌的外泌体所包裹的 miRNA (如 miR-214、miR-143/145) 在血管生成和抗动脉粥样硬化中同样具有重要作用[113, 114]。

心肌细胞来源的外泌体被称为心小体 (cardiosomes)[115]，含有不同数量的核酸、蛋白质和脂质，这些都可以转移到邻近的心脏内皮细胞并调节其功能[116–119]。心小体包裹了 miR-455、miR-29b、miR-323-5p 和 miR-466，这些 miRNA 可以结合到金属蛋白酶 -9 (matrix metalloprotease 9, MMP9) 并下调其表达，减少心肌纤维化，抑制心肌细胞的解耦联，从而促进心肌再生[120]。心小体还可以调节内皮细胞的葡萄糖转运[102]。在被脂质预处理的心小体中 miR-1 和 miR-133a 含量较高，而这些 miRNA 均与糖尿病心肌损害呈正相关[121]。心小体所富含的 HSP70 在心肌细胞中激活了由 ERK1/2 和 HSP27 诱导的心脏保护信号通路；当出现 T2DM 时，虽然心小体 HSP70 表达仍然增加，但却失去对心脏的保护作用[122]。采用糖尿病心小体干预缺氧复氧下的心肌细胞，加剧细胞死亡[122]。说明糖尿病心肌血管损害可能是由心肌细胞分泌的抗血管生成的外泌体引起的[116]。

另外，血管滋养管 (vasa vasrum, VV) 血管生成增加可以促进 T2DM 动脉粥样硬化斑块破裂，ADEs 参与促进斑块加重和斑块破损，一部分通过诱导 VV 血管生成，另一部分通过上文所提到的外泌体内的 Shh 蛋白来加重糖尿病性动脉粥样硬化[123]。

因此，对于糖尿病性心血管病变来说，外泌体不仅能够作为潜在的生物标志物，而且具有治疗作用，能够作为靶点或药物来逆转受损的胰岛素信号。

3.2 外泌体与糖尿病肾病

糖尿病肾病是糖尿病的严重并发症，是终末期肾病的常见原因。高糖条件下肾小球系膜细胞释放的外泌体体外诱导足细胞损伤，导致糖尿病肾病[124]。

有人认为，外泌体的蛋白标志物比全尿分析更能准确地反映糖尿病肾病患者的潜在病情变化，并且其内含物被外泌体膜性结构包裹避免被蛋白酶降解，从而使检测结果更真实[125]。糖尿病肾病患者尿液外泌体中含有 352 种蛋白质，其中肾上皮细胞分泌的尿外泌体 WT1 蛋白可以作为一种预测早期糖尿病肾损害的非侵入性生物学标志[126]；α1 微球蛋白 /bikunin 前体 (α-1-microglobulin/bikunin precursor, AMBP)、组蛋白赖氨酸甲基转移酶 (histone-lysine N-methyltransferase, MLL3)、电压依赖性阴离子通道蛋白 -1 (voltage-dependent anion-selective channel protein, VDAC1) 是可用来预测糖尿病肾病早期异常的生物学指标[127]；亮氨酸氨基肽酶 (leucine amino-peptidase, LAP) 及二肽基肽酶 4 (dipeptidyl peptidase 4, DPP4) 水平则是与糖尿病肾病严重程度密切相关的生物学指标[128]。

在尿液中能够稳定存在的外泌体及其所含的 miRNA 是糖尿病肾病发展的标志，在发病机制中发挥重要作用[129]。由肾小球系膜细胞 (glomerular mesangial cells, GMSs) 释放的外泌体中的 miR-130a、miR-145 及外泌体数量与葡萄糖浓度呈正相关[58]。T2DM 肾病患者尿液中外泌体 miRNA 与 T2DM 患者相比，miR-320c 表达尤其异常[130]，它可能通过介导凝血酶敏感蛋白 -1 (thrombospondin-1, TSP-1) 影响 TGF-β 信号通路，该指标有望作为 T2DM 肾病的新候选标志物，用于 T2DM 肾病的疾病评估[129]。

目前已知自噬对糖尿病肾病具有防御作用[131]，而 MSCs 来源的外泌体可以诱发自噬，显著改善肾功能，修复肾组织，是一种治疗糖尿病肾病的新方法[132]。尿源性干细胞 (urine-derived stem cells, USCs) 分泌的外泌体能够在高糖环境中对足细胞起保护作用，抑制足细胞凋亡，促进血管再生和细胞存活，减少糖尿病肾病大鼠蛋白尿的排出，这说明外泌体具备与其母细胞相同的保护能力[133]。脂肪源性干细胞 (adipose-derived stem cells, ADSCs) 来源的外泌体 (ADSCs-Exo) 能够通过提高 miR-486 的表达，下调 Smad1 的表达来抑制 mTOR 的激活，导致自噬增加，减少足细胞凋亡，减轻自发性糖尿病，改善糖尿病肾病的症状[134]。可见，外泌体具有广阔的预防糖尿病肾损伤的临床应用前景[135]。

3.3 外泌体与糖尿病视网膜病变(diabetic retinopathy, DR)

DR 是糖尿病的微血管并发症，是成年人视力下降的主要原因[136]。糖尿病周围血管病变合并眼部并发症占 DR 严重病例的 41%。

研究表明，血浆外泌体中的细胞因子 (RANTES 和 Ang-2) 参与调节 DR 的病程和预后[137]。胰岛 β 细胞分泌的外泌体中含有 miR-15a，它可以诱导人 Müller 细胞过表达 miR-15a，进而靶向 Akt3 导致氧化应激，引起细胞凋亡，致使视网膜损伤[74]。糖尿病脂肪组织中分离的 MSCs 释放的外泌体内 miR-222 表达水平与视网膜修复作用呈负相关[138]。含有 IgG 的血浆外泌体激活经典补体通路也参与了 DR 的进程[136]。

3.4 外泌体与糖尿病神经病变

研究表明，M-MSCs 分泌的外泌体能够修复受损神经元和星形胶质细胞，逆转其功能障碍，说明外泌体能够成为一种糖尿病神经损害的理想治疗手段[139]。丰富环境 (an enriched environment, EE) 刺激内源性 M-MSCs 分泌的外泌体内 miR-146a 上调，对糖尿病大鼠大脑中受损的星形胶质细胞具有抗炎作用，可预防糖尿病所引起的认知功能损害[140]。

3.5 外泌体与糖尿病骨骼肌、骨代谢病变

骨骼肌外泌体在高脂饮食引起的胰岛素抵抗状态下通过类似旁分泌传递方式来调节骨骼肌的内稳态[141]，它们能被胰腺吸收；外泌体内的 miR-16 参与高脂饮食诱发的 MIN6B1 细胞和胰岛的增殖变化并调控 Ptch1 基因，从而参与胰腺的发育[26]。骨髓来源的外泌体 miRNA 在数量、种类和表达水平方面存在差异，针对胰岛素分泌和胰岛素信号通路的外泌体 miRNA 谱在 T2DM 条件下发生变化，其中 Wnt 信号通路的改变是骨代谢的关键[142]。

4 总结与展望

由于不同类型糖尿病临床表现的复杂性，有时依靠目前的实验室手段无法及时鉴别出来。因此亟需寻找到某种既能实时反映病理生理学特点或疾病进展的标志物，同时这种标志物又是简便廉价、操作易得的[143]。也许未来外泌体是能够符合这种对糖尿病全新生物学标志需求的物质[11]，人们通过对外泌体内脂质、蛋白质、核酸等内容物进行分析，从而能够监测生理和病理学变化 (总结见表 1、图 2)。

同时，外泌体作为药物的天然内源性载体具有独特优势：它免疫相容性好，免疫原性低，能巧妙地避开单核巨噬细胞的快速清除[144]，延长外泌体在外周循环中的滞留时间，在血液中表现出极大的稳定性，从而提高疗效[145]；它分布广泛，甚至能够穿过完整的血脑屏障[146]；它的直径大小恰好可以利用增强渗透滞留效应(enhanced permeability and retention effect, EPR)选择性地向某些特定组织外渗；

表1. 外泌体作为糖尿病及其并发症作用靶点

Table 1. Exosomes as a novel target for diabetes mellitus and its complications

Source of exosomes	Bioactive factors	Disease model	Application	References
HepG2	Calpain 2	High-glucose conditions	Treatment	[20]
Mouse adipocyte	Caveolin 1	Obesity	Treatment	[33]
Human/mouse adipocyte	miR-125b/lin-4	Obesity	Diagnosis	[38]
Mouse adipocyte	miR-27a	Obesity	Treatment	[40]
Human adipose-derived stem cells	GAS5	Obesity	Diagnosis	[41]
Human adipose-derived stem cells	lincRNA-VLDLR	Obesity	Diagnosis	[41]
Human adipose-derived stem cells	MALAT1	Obesity	Diagnosis	[41]
Mouse serum	Adiponectin	Obesity	Diagnosis	[44]
Mouse adipocyte	ap2	Obesity	Treatment	[46]
3T3-L1	Shh	High-glucose conditions	Treatment	[47]
M-MSCs	miR-29b-3p	Senescence	Treatment	[52]
Mouse pancreas	miR-375	Normal	Diagnosis/treatment	[58–61]
Macrophage	miR-155	Obesity	Diagnosis/treatment	[62]
PBMC	miR-126	T2DM	Diagnosis	[63]
Mouse plasma	miR-27a-3p	Obesity	Diagnosis	[64]
Mouse plasma	miR-27b-3p	Obesity	Diagnosis	[64]
Mouse plasma	miR-192	Obesity	Diagnosis	[64]
Mouse plasma	miR-122	Obesity	Diagnosis	[64]
Human/Mouse pancreatic β cells	miR-21-5p	T1DM	Diagnosis	[66, 67]
Human plasma	miR-25-3p	T1DM	Treatment	[68]
Human plasma	miR-16-5p	T1DM	Treatment	[68]
Human plasma	miR-302d-3p	T1DM	Treatment	[68]
Human plasma	miR-378a	T1DM	Treatment	[68]
Human plasma	miR-570-3p	T1DM	Treatment	[68]
Human plasma	miR-574-3p	T1DM	Treatment	[68]
Human pancreatic β cells	miR-15a	T2DM	Diagnosis	[74]
Human plasma	miR-126	Prediabetes	Diagnosis	[75]
Human/Mouse plasma	miR-192/193	Prediabetes	Diagnosis	[76]
Human pancreatic β cells	lncRNA-p3134	T2DM	Diagnosis	[78]
Human endothelial cells	PAPP-A	GDM	Diagnosis	[98]
Human endothelial cells	CAMK2β	GDM	Diagnosis	[98]
Mouse serum	Arginase 1	db/db	Diagnosis	[111]
Mouse cardiac microvascular endothelial cells	MST1	T1DM (STZ+mouse)	Treatment	[112]
Human/Mouse endothelial cells	miR-143/145	Lipid loaded	Treatment	[113]
HMEC-1	miR-214	Senescence	Treatment	[114]
Mouse cardiomyocyte	mir-455	db/db	Treatment	[120]
Mouse cardiomyocyte	mir-296	db/db	Treatment	[120]
Mouse cardiomyocyte	mir-323-5p	db/db	Treatment	[120]
Mouse cardiomyocyte	mir-466	db/db	Treatment	[120]
HL-1	miR-1	Lipid-loaded	Diagnosis	[121]
HL-1	miR-133a	Lipid-loaded	Diagnosis	[121]

表1. 续表

Source of exosomes	Bioactive factors	Disease model	Application	References
Rat cardiomyocyte	HSP70	Gotokakizaki	Treatment	[122]
Human urine	WT1	T1DM	Diagnosis	[126]
Human urine	AMBP	DN	Diagnosis	[128]
Human urine	MLL3	DN	Diagnosis	[127]
Human urine	VDAC1	DN	Diagnosis	[127]
Human urine	LAP	T2DM	Diagnosis	[128]
Human urine	DPP4	T2DM	Diagnosis	[128]
Human urine	miR-145	DN	Diagnosis	[86]
Human urine	miR-130a	DN	Diagnosis	[58]
Human urine	miR-320c	DN	Diagnosis	[130]
Adipose-derived stem cells	miR-486	DN	Diagnosis	[134]
Human plasma	RANTES	DR	Diagnosis	[137]
Human plasma	Ang-2	DR	Diagnosis	[137]
Rabbit adipose MSCs	miR-222	T1DM (STZ+rabbit)	Treatment	[138]
M-MSCs	miR-146a	T1DM (STZ+rat)	Treatment	[140]
Mouse skeletal muscle	miR-16	HPD	Treatment	[26]

M-MSCs: marrow mesenchymal stem cells; MSCs: mesenchymal stem cells; PBMC: peripheral blood mononuclear cell; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; GDM: gestational diabetes mellitus; DN: diabetic nephropathy; DR: diabetic retinopathy; HPD: high palmitate diet.

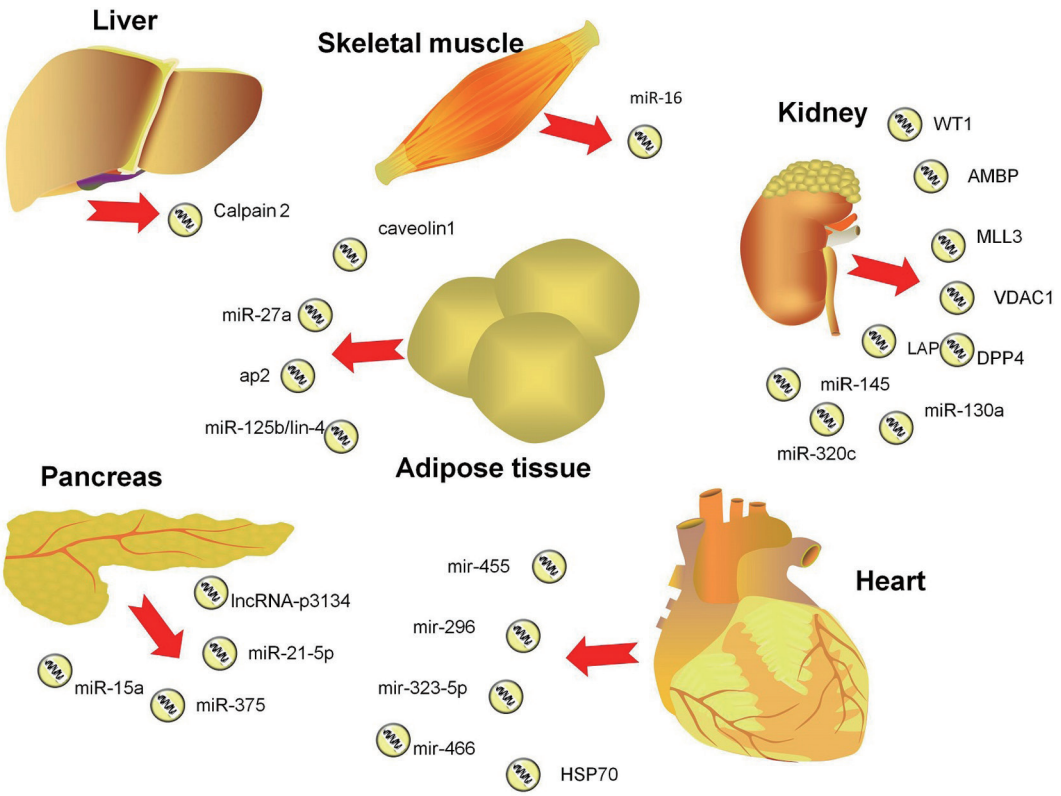

图 2. 外泌体作为糖尿病各主要靶器官重要媒介总结图

Fig. 2. Exosomes as mediators of related organs in diabetes. (1) Exosomes secreted by pancreatic tissues carry miR-15a, miR-375, miR-21-5p, and lncRNA-p3134; (2) Exosomes secreted by liver tissues carry Calpain 2; (3) Exosomes secreted by skeletal muscle tissues carry miR-16; (4) Exosomes secreted by adipose tissues carry caveolin1, miR-27a, ap2, and miR-125b/lin-4; (5) Exosomes secreted by heart tissues carry mir-455, mir-296, mir-323-5p, mir-466, and HSP70; (6) Exosomes secreted by kidney tissues carry WT1, AMBP, MLL3, VDAC1, DPP4, LAP, miR-145, miR-320c, and miR-130a.

外泌体还可以将药物递送到特异性组织或器官。因此，外泌体可以克服目前封装以 miRNA 为主的核酸药物所面临的困难，将使今后核酸药物广泛投入临床成为可能。目前已知的能作为靶点的外泌体内 miRNA 有：与改善胰岛素抵抗相关的 miR-27a [40]、miR-155 [62]、miR-143/145 [113]、miR-16 [26] 等；与 T1DM 相关的 miR-222 [138]、miR-146a [26]、miR-25-3p [68]、miR-16-5p [68] 等；与 T2DM 相关的 mir-455、mir-296、mir-323-5p、mir-466 等 [120]。外泌体研究对未来糖尿病药物的开发尤其是靶向治疗具有很好的启示作用 (总结见表 1、图 2)。

综上所述，人们对外泌体的产生、调节分泌或摄取机制的深刻理解为糖尿病病理生理机制研究提供了更深层次的认识，也为未来开发更多的糖尿病及其并发症的诊断及治疗手段提供了参考。

* * *

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