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Hans汉斯

Mfn2在动静脉内瘘血管内膜增生中作用机制的研究进展

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摘　要

终末期肾脏病(End-Stage Renal Disease, ESRD)患者大多数选择血液透析治疗。动静脉内瘘(Arteriovenous Fistula, AVF)是血液透析患者最常用的血管通路，但血管内膜增生导致的AVF功能障碍是临床面临的重大挑战。线粒体融合蛋白2 (Mfn2)为线粒体外膜上的跨膜蛋白，不仅可以调控线粒体本身的融合和分裂，还参与氧化应激反应、细胞增殖、细胞死亡、线粒体内质网连接、内质网应激及线粒体自噬等病理生理过程。研究表明，Mfn2可以通过多种机制抑制血管平滑肌细胞(Vascular Smooth Muscle Cells, VSMCs)增殖。文章通过对Mfn2结构、功能及其在血管内膜增生中的潜在作用机制进行研究，旨在为Mfn2与动静脉内瘘成熟不良及远期狭窄的基础研究及临床应用提供科学参考。

关键词

线粒体融合蛋白2，动静脉内瘘，新生血管内膜增生，血管平滑肌细胞

Research Progress on the Mechanism of Mfn2 in Vascular Intimal Hyperplasia of Arteriovenous Fistula

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Abstract

The majority of end-stage kidney disease patients choose hemodialysis therapy. The arteriovenous

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fistula (AVF) is a frequently utilized vascular access method for hemodialysis, but it encounters difficulties related to dysfunction caused by intimal hyperplasia. Mfn2, a transmembrane protein on the outer mitochondrial membrane, plays a crucial role in mitochondrial dynamics and is involved in various physiological and pathological processes such as oxidative stress response, cell proliferation, cell death, mitochondria-endoplasmic reticulum interactions, endoplasmic reticulum stress, and mitophagy. Studies have shown that Mfn2 can impede vascular smooth muscle cell (VSMC) proliferation through diverse mechanisms. This investigation aims to explore the role of Mfn2 in addressing poor maturation and long-term stenosis of arteriovenous fistulas by examining its structure, function, and potential mechanisms in intimal hyperplasia, offering insights for both basic research and clinical applications.

Keywords

Mitofusin 2, Arteriovenous Fistula, Neointimal Hyperplasia, Vascular Smooth Muscle Cells

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1. 引言

对于进入肾脏替代治疗的慢性肾脏病患者，目前有血液透析、腹膜透析和肾脏移植三种治疗方式，但超过 70%的 ESRD 患者选择血液透析[1]。动静脉内瘘是终末期肾病患者选择血液透析的首选血管通路。动静脉通路相关并发症的主要病理改变是动静脉通路内的内膜增生，最终导致狭窄、成熟失败(6 个月内为 33%~62%)、较差的通畅性(2 年内为 60%~63%)或透析效果不佳[2]。AVF 失功主要是由于 AVF 血管外向扩张障碍和血管内膜过度增生、狭窄两方面原因所致，其中，新生内膜增生(NIH)是血管对血流动力学改变的一种病理性适应反应，是 AVF 失功的关键，涉及血管平滑肌细胞增殖迁移表型转换、内皮细胞功能障碍、炎症反应、细胞外基质沉积、免疫微循环改变等多种病理过程[3] [4]。

线粒体作为细胞能量代谢和信号转导的中心，其不断融合、裂变和运动状态，可以响应不断变化的细胞状态或代谢需求，在血管重塑中发挥关键作用[5]。Mfn2 作为增殖抑制基因，其在自发性高血压大鼠动脉、球囊损伤的 SD 大鼠动脉的 VSMCs 中表达显著降低[6]。而过表达 Mfn2 可抑制血清诱导的 VSMCs 增殖，并抑制大鼠颈动脉球囊损伤诱导的新生内膜 VSMCs 增殖和再狭窄[7]。迄今为止，虽然药物涂层球囊、切割球囊、支架植入等治疗内瘘狭窄的手段逐渐运用至临床，但目前对 Mfn2 在 AVF 建立前或术后狭窄干预方面的研究匮乏，临床上也很少有有效措施能够防治 NIH。因此，本文旨在综述 Mfn2 在 AVF 内膜增生中的潜在作用机制，为临床防治 AVF 功能障碍提供新思路。

2. Mfn2 的结构与表达

2.1. Mfn2 的结构

Mfn2 是一种定位在线粒体外膜(OMM)的高度保守的跨膜 GTP 酶，但其在线粒体外膜和肌浆网/内质网膜中均有表达[8]，与 Mfn1 共同参与线粒体外膜融合。其核心结构域包括线粒体外膜跨膜结构域、GTPase 结构域、七肽重复结构域 1 (HR1)以及七肽重复结构域 2 (HR2)，介导外膜融合[9]。跨膜结构域是 Mfn2 嵌入线粒体外膜的关键，也是介导线粒体融合运动的结构基础[10]。GTPase 结构域位于 Mfn2 的 N 端，具有 GTP 结合与水解活性，该结构域为 Mfn2 的寡聚化和膜融合过程提供能量[11]。HR1 结构域紧

邻 GTP 酶结构域，主要参与 Mfn2 分子在同一线粒体上的反式寡聚化。而 HR2 结构域位于 C 端，参与不同线粒体上的 Mfn2 分子间结构域的相互缠绕，将两层外膜紧密拉近[12]。因此，HR1 和 HR2 是 Mfn2 实现膜融合的关键。

2.2. Mfn2 的表达

Mfn2 是从大鼠血管平滑肌细胞中通过差异筛选克隆出的一个与细胞增殖相关的新基因，可通过多种信号传导途径调控 VSMCs 增殖与凋亡[13]。Mfn2 在多种组织中均有表达，尤其在线粒体密度较高的组织中，如骨骼肌和心脏组织[14]。Mfn2 上有多个翻译后修饰位点(例如磷酸化和泛素化位点)，使其能够根据各种细胞信号(包括能量和应激信号)对其稳定性及 GTP 酶活性进行精确调控[8] [15]。Mfn2 除了参与调控线粒体融合过程和间接调控线粒体裂变外，还参与受损线粒体的修复、高效的线粒体能量代谢、线粒体-内质网钙耦联的调节、线粒体轴突运输和线粒体自噬等多种生理和病理过程[16]。

3. Mfn2 的功能

3.1. 维持细胞能量代谢稳态

Mfn2 的正常表达对于细胞代谢至关重要。Mfn2 缺乏会破坏线粒体融合，导致线粒体膜电位丧失、氧化磷酸化降低以及 ATP 生成减少[17]，从而促进细胞有氧糖酵解。磷酸果糖激酶 1 (PFK1)在糖酵解途径中将果糖-6-磷酸转化为果糖-1,6-二磷酸，为糖酵解中的关键酶。Mfn2 表达不足会导致 PFK1 活性增加，进一步促进细胞有氧糖酵解，从而促进血管内膜增生，而过表达 Mfn2 和 PFK1 抑制剂均可改善上述病理过程[14]。长期的脂质过载通过泛素－蛋白酶体途径诱导 K243 位点的 Mfn2 乙酰化后，诱导 Mfn2 降解，转化为脂质毒性[18]。因此，促进 Mfn2 表达可能通过提高能量代谢来维持机体稳态。

3.2. 细胞增殖

Mfn2 是一种新型增生抑制基因，在球囊损伤大鼠的动脉的血管平滑肌细胞、载脂蛋白 E 基因敲除小鼠的动脉粥样硬化动脉中，Mfn2 表达显著降低[19]。目前研究认为 Mfn2 通过以下三个方面抑制细胞增殖：一是 Mfn2 可增加细胞周期依赖性蛋白激酶抑制蛋白家族中的 P21 和 P27 表达，通过负向调整使细胞周期停滞[20]。二是通过抑制 Ras-Raf-ERK1/2 信号通路，抑制增殖相关基因表达，将细胞周期阻断在 G0/G1 期[21]，抑制细胞增殖。三是通过抑制 PI3K/Akt 信号通路，促进细胞凋亡，抑制细胞存活与增殖[22]。上述研究结果表明，通过调控 Mfn2 表达，抑制血管平滑肌细胞增殖，可抑制新生内膜的形成。

3.3. 细胞凋亡

一方面，Mfn2 可通过调节线粒体膜电位、释放细胞色素 C 等影响下游的 Bcl-2 家族蛋白和 Caspase 信号的激活与表达[23]。有研究表明 Mfn2 的过度表达可以延迟凋亡的发生[24]。另一方面，PINK1 激酶可对 Mfn2 多个位点进行磷酸化，不同的磷酸化位点可决定 Mfn2 是促进线粒体融合促进细胞修复，还是作为受体启动线粒体自噬从而清除受损线粒体[25]，这一过程是细胞是否发生凋亡的关键。最新研究发现，在癌细胞中 Mfn2 与 MARCH5、UBE2J2 可形成一个蛋白质复合物，能持续抑制凋亡，当细胞遭受应激或损伤时，复合物解离，最终导致细胞凋亡[26]。Mfn2 调控细胞凋亡是一个复杂且精密的过程，其调控细胞凋亡作用依赖于细胞的类型和所处的应激环境，在癌细胞或应激状态下的细胞内如受损的血管组织中促凋亡，在正常细胞内抗凋亡[27] [28]，使其成为重要的治疗靶点。

3.4. 内质网应激

Mfn2 也参与内质网应激(Endoplasmic Reticulum Stress, ERS)反应的调节。在机体受到各种因素刺激

后，如高血脂、高血糖、细胞内钙平衡紊乱、缺血、缺氧及化学毒物刺激，导致细胞内未折叠的蛋白增加，发生未折叠蛋白反应(UPR)，以维持内质网稳态，当超过细胞自身的代偿功能时就会诱发细胞程序性死亡，称为内质网应激[29]。ERS 与动脉粥样硬化、血管钙化等多种血管疾病发病相关。内质网与线粒体结合的部位由一系列蛋白分子连接组成，被称为线粒体–内质网膜接触位点(MAMs)，Mfn2 是构成 MAMs 的核心组成分子，参与 ERS、钙离子转运、脂质运输和代谢、ROS 产生和活性调节、自噬等多种病理生理过程[30]。在心肌细胞中，运动可促进 Mfn2 蛋白的表达，从而抑制了 Drp1、IRE-JNK 和 PERK-CHOP 信号通路的表达，有效减少了内质网应激和细胞凋亡[31]。研究表明，Mfn2 可通过增强 MAMs 偶联，减少未折叠蛋白堆积缓解内质网应激，下调 ERS 相关蛋白 CHOP、GRP78 等表达[32]，从而抑制 VSMCs 增殖抑制血管内膜增生。

3.5. 线粒体自噬

Mfn2 缺乏可引起线粒体自噬减少。作为 PINK1/Parkin 通路介导线粒体自噬的关键受体，Mfn2 表达下调导致碎片化的线粒体无法被有效自噬清除，致使受损线粒体大量蓄积并加重线粒体损伤[33]。而未被自噬清除的受损线粒体是 ROS 的主要来源，加剧氧化损伤、诱导炎症反应等[34]，再通过上述分子机制，最终导致病理性 VSMCs 大量增殖。

4. Mfn2 在新生血管内膜增生中的潜在作用机制

4.1. 减轻内皮损伤及炎症反应

内皮线粒体功能障碍是导致内皮功能异常的重要因素[35]。正常生理性层流剪切力(LSS)会使 Mfn2 蛋白表达升高，促进线粒体融合，维持内皮细胞线粒体稳态，并可减轻炎症诱导的线粒体损伤。当 AVF 建立后，吻合口处的血流动力学发生了根本性的改变。吻合口处或附近区域由于受到低剪切力的影响，这些区域血流紊乱，缺乏 LSS 的保护作用，导致线粒体稳态失调[36]。另外，Mfn2 表达下调还会诱导线粒体 ROS 蓄积。ROS 堆积可以激活内皮细胞(ECs)炎症通路，并加剧脂质过氧化以及蛋白质和核酸的氧化损伤，最终导致内皮细胞功能障碍[37]-[39]。Mfn2 在内皮细胞修复中发挥重要作用，是线粒体融合的关键蛋白。线粒体融合可维持线粒体膜电位、保障能量(ATP)供应，从而抑制内皮细胞凋亡。Mfn2 的功能缺陷，可导致内皮细胞线粒体碎片化、内皮细胞凋亡。内皮细胞凋亡不仅会使得血管屏障功能受损，还会引起 VSMCs 增殖信号暴露、促进血小板粘附和血栓形成、凋亡小体和炎症信号的释放，最终导致血管平滑肌细胞的激活，促进血管内膜增生[40]。另一方面，AVF 成形术时手术创伤可激活 TLR4/NF-κB 通路，导致促炎因子 IL-6、TNF-α 增加，从而促进内皮细胞凋亡[41]。另外，Mfn2 还可促进内皮细胞的增殖、迁移和成管能力，修复内皮功能[42]。Mfn2 还可促进内皮细胞产生一氧化碳(NO)，增加内皮型一氧化氮合酶(eNOS)功能，改善内皮依赖性血管舒张，进而保护内皮细胞[43]。因此，未来靶向激活 Mfn2 的正向调控因子上调 Mfn2 表达，将来有望减少内皮细胞凋亡、改善血管内皮功能。

4.2. 抑制 VSMCs 增殖、迁移，诱导 VSMCs 凋亡

VSMCS 的异常增殖是多种血管重塑疾病发病机制的关键过程，如动脉粥样硬化[44]、高血压[45]、血管狭窄[46]。Mfn2 是线粒体分裂和融合的重要调控因子，其不平衡可驱动 VSMCs 激活和内膜形成[47]。Mfn2 为 Ras 的负性调控因子，通过抑制 Ras-ERK1/2 信号通路，从而抑制 VSMCs 增殖和迁移[7]。过表达 Mfn2 可抑制血清诱导的 VSMCs 增殖，并阻止大鼠颈动脉球囊损伤诱导的新生内膜 VSMCs 增殖和再狭窄[48]。最新研究表明，过氧化物酶体增殖物激活受体 γ 共激活因子 1α (PGC-1α)介导的线粒体生物合成可防止血管平滑肌细胞增殖和衰老[49]。

在各种应激状态下，VSMCs 可由收缩表型转变为合成表型(去分化的 VSMCs)。一方面，去分化的 VSMCs 表达 KLF4 增加，使 VSMCs 由中膜迁移至内膜并分泌细胞外基质(ECM)，促使其分泌胶原、纤连蛋白等，最终导致管腔狭窄[50]。另一方面，Mfn2 可通过多条途径抑制 VSMCs 由收缩型向合成型转换。Mfn2 可通过抑制增殖信号通路(如前所述)，从而抑制分化的 VSMCs 转化为去分化的 VSMCs。Mfn2 还可促进收缩型 VSMCs 的标志物平滑肌 22α 蛋白(SM22α)和平滑肌肌球蛋白重链等表达[51]。也可直接调控细胞周期，通过上调 p21 和 p27 抑制 VSMCs 周期进程[52]，从而抑制血管内膜形成。

VSMCs 凋亡在血管内膜增生中具有双重作用。在 VSMCs 损伤在 AVF 建立早期阶段，Mfn2 通过抑制 Ras-PI3K-Akt 通路来诱导 VSMCs 过度增殖导致的细胞凋亡。这种适度的凋亡有助于清除部分过度增殖或受损的 VSMCs，从而限制新生内膜的总体细胞数量，抑制血管内膜增生[53]。在肺动脉高压、AVF 成熟失败或失功的晚期阶段，持续的炎症、氧化应激和异常剪切力等作用下，Mfn2 表达水平显著下调，使其功能失活，导致线粒体融合和分裂失衡，碎片化线粒体大量堆积，放大氧化应激反应，激活 VSMCs 的线粒体凋亡途径[54]。Mfn2 的持续低表达还会导致 Ras-PI3K-Akt 通路无法被抑制，同时中膜 VSMCs 在各种炎症因子等刺激下，诱导 VSMCs 转化为合成表型，代偿性、过度的向管腔内增殖和迁移[55]。因此，生理性、适度的凋亡有助于抑制过度增生，而病理性或过度凋亡则促进血管内膜增生，引起管腔狭窄甚至闭塞。综上所述，AVF 晚期治疗的重点可通过药物或基因手段恢复 Mfn2 的正常表达和功能，从根本上改善细胞健康，为逆转 AVF 的狭窄提供新的治疗思路。

4.3. 调节细胞外基质(ECM)降解与沉积

参与血管向外重构的 ECM 由基质金属蛋白酶(MMPs)、胶原蛋白及弹性蛋白等成分组成[56]。在 AVF 内膜增生过程中，TGF-β1 表达上调，一方面驱动新的胶原蛋白等细胞外基质的分泌，另一方面上调 MMPs 抑制剂 TIMPs 的表达，导致胶原降解减少，从而导致 ECM 大量沉积，导致内膜下纤维化、管壁僵硬增厚，损害 Mfn2 的表达与功能[57]。另一方面，Mfn2 可通过抑制 TGF-β1/Smad 信号，从而降低上皮–间质转化(EMT)，减少 ECM 的沉积而增加血管顺应性[58]，抑制 NIH。因此，Mfn2 可在抑制 ECM 的沉积、改善血管壁顺应性方面为 AVF 患者提供一个有前景治疗靶点。

4.4. 调节免疫炎症反应

免疫细胞参与血管重构。近年来越来越多的研究证实免疫微循环损伤在 AVF 血管内膜增生方面的重要作用。AVF 建立后可触发身体的免疫反应，包括免疫细胞的浸润和炎症因子的分泌[59]。除了上述提到的 ECM 和 VSMCs 外，NIH 的主要细胞成分中还存在巨噬细胞(Mφ)等炎症细胞[60]，而 T 淋巴细胞、NEUT、DC 及其他免疫细胞也参与 AVF 的血管重塑过程[61]。因此，免疫炎症反应在 AVF 的血管重塑过程中起着重要作用。M2 型巨噬细胞通过分泌 IL-10 和 TGF-β 促进静脉壁增厚[62]，Mfn2 功能不足可能导致 M2 极化增强[63]，进而导致 AVF 成熟失败。另一方面，有研究表明，Mfn2 可通过介导线粒体融合以满足效应 T 细胞的能量需求[64]，从而间接调控 T 细胞介导的 AVF 血管重塑。综上，未来可将 Mfn2 激动剂(如某些天然化合物)与现有的抗炎疗法联合应用以延缓血管新生内膜增生。

5. 结论与展望

对于应用动静脉内瘘的血液透析患者来说，血管通路的维护至关重要。基于上述多维度机制，Mfn2 通过以下途径抑制新生内膜增生：1) 促进线粒体融合，优化能量代谢并维持线粒体稳态；2) 增强 MAMs 偶联，减少 ERS 相关蛋白(CHOP/GRP78)产生，缓解内质网应激；3) 激活 PINK1/Parkin 通路，促进线粒体自噬以清除受损线粒体，并诱导过度增殖的 VSMCs 适度凋亡；4) 抑制 Ras-Raf-ERK1/2 通路，同时促进收缩型标志物(SM22α)表达，从而抑制 VSMCs 异常增殖及表型转化。随着对靶向基因技术和 Mfn2 作

用机制的深入研究，药物涂层球囊已广泛应用于临床中，但存在药物输送效果不理想、长期疗效证据不足等问题。目前随着极具前景的靶向纳米载体技术发展，将 Mfn2 激动剂靶向递送至 AVF 术后或狭窄病变部位有望在临床上实现，其靶向特异性高、疗效强，可减少系统性上调 Mfn2 带来的副作用。但仍需更多基础与临床研究验证其有效性和安全性，最终用于延长患者动静脉内瘘的使用寿命及减少心血管意外的发生率，降低慢性肾脏病患者的死亡率。

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