

间充质干细胞线粒体转移机制的研究进展

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摘要 线粒体是真核生物母系遗传的多功能细胞器, 不仅参与细胞能量代谢的调节, 而且参与应激细胞的存活和命运决定。线粒体转移是间充质干细胞参与组织损伤修复和伤口愈合的重要机制之一。线粒体转移的途径有很多种, 主要包括隧道纳米管、间隙连接通道、微泡、细胞融合以及胞吞作用等。多条信号传导通路可诱导隧道纳米管的形成, 使线粒体从一个细胞转移到另一个细胞。多种应激信号, 例如受损线粒体、线粒体DNA或线粒体其它产物的释放以及活性氧水平的升高等, 都能引发线粒体从间充质干细胞转移到受体细胞。该文介绍线粒体从间充质干细胞转移到邻近应激细胞的现象, 并讨论线粒体转移的可能机制及其在组织损伤等疾病治疗中的作用。

关键词 线粒体转移; 隧道纳米管; 间隙连接通道

Progress on Mitochondrial Transfer Mechanisms of Mesenchymal Stem Cell

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Abstract Mitochondria are maternally inherited multifunctional organelles, which not only regulate the energy metabolism, but also the survival and fate of stressed cells. Mitochondrial transfer is one of the emerging mechanisms through which mesenchymal stem cells (MSCs) can repair injured tissues and facilitate wound healing. Several modes of mitochondrial transfer were discovered, such as formation of tunneling nanotubes, gap junction, microvesicles, cell fusion, and endocytosis. Multiple signaling pathways can promote the formation of tunneling nanotubes for mitochondria trafficking from one cell to another. Different stress signals, such as release of injured mitochondria, mtDNA, and mitochondrial products, or the elevated reactive oxygen species promote the transfer of mitochondria from MSCs to the recipient cells. In this review, we provide an overview of the current literature on mitochondrial transfer from MSCs to neighboring stressed cells, and further discuss the possible mechanisms mediating their intercellular transmission and the therapeutic application in treatment of tissue injury.

Keywords mitochondrial transfer; tunneling nanotubes; gap junction channels

间充质干细胞(mesenchymal stem cells, MSCs)由于其独特的生物学特性, 如自我更新能力、造血支持、提供营养、激活内源性干/祖细胞、分化和转分化能力、免疫调节和炎症应答、抗细胞凋亡、抗氧化、抗纤维化和促进血管新生等, 可促进机体

多种组织损伤的修复, 已成为细胞治疗和再生医学的理想种子细胞^[1-3]。MSCs取材方便, 很容易从机体多种组织如骨髓、脂肪、牙髓、脐带和胎盘等中获取。目前, 无血清培养的多种组织来源的MSCs均已普遍应用于临床试验研究。

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MSCs免疫原性较低, 异体移植也不会发生严重免疫排斥反应, 在疾病治疗中是安全和有效的。研究表明, MSCs除通过分化或转分化作用替换受损细胞以及细胞与细胞直接接触和表观遗传调控等作用机制外, 主要通过旁分泌机制发挥作用, 参与受损组织的修复^[2,4-5]。MSCs介导的旁分泌作用可以通过释放多种细胞因子、产生胞外囊泡(主要为外泌体和微泡)以及线粒体转移等方式来实现^[3]。其中, 线粒体转移是近年来新发现的一种MSCs作用机制, 在多种组织的损伤修复中发挥重要作用^[6]。

线粒体是真核细胞中发现的最复杂的细胞器, 具有双层膜结构, 内含环状DNA, 可独立地进行基因的转录和蛋白质翻译等细胞进程, 但转录和翻译等进程仍受细胞核基因的调控, 并不断地进行融合(fusion)与分裂(fission), 是一种高度动态平衡的半自主性细胞器^[7]。哺乳动物细胞内线粒体DNA长度约为16.6 Kb, 可编码构成电子传递链上参与氧化磷酸化反应关键酶复合物的13个亚基, 以及蛋白质翻译系统包括2个核糖体RNAs(rRNAs)和22个转运RNAs(tRNAs)^[8]。线粒体功能障碍会引发活性氧分子产生的增多以及细胞凋亡途径的激活, 导致许多疾病的发生和发展, 如缺血性心脏病、肺部疾病、中风、脑损伤以及帕金森病和阿尔茨海默氏症等多种退行性疾病^[9-10]。干细胞来源的正常线粒体转移到线粒体功能障碍的应激细胞中, 可增加应激细胞内线粒体的生物合成, 重建靶细胞的有氧呼吸并抑制其凋亡, 进而恢复受损细胞正常的生物学功能^[11]。

单个线粒体的直径为0.3~1.0 μm , 细胞内线粒体的数量与细胞类型和生理状态有关, 通常高等动植物一个细胞含有成百上千个线粒体。线粒体是一种高度动态变化的细胞器, 并非都是以分散的单个形式存在, 有时在细胞内彼此连接, 呈现立体的管网状结构^[12], 通过不断地运动、分裂和融合维持线粒体网络的稳态, 以适应细胞不同生理状态对能量的需求。线粒体的融合和分裂由dynamamin类GTP酶所调节, 这两种看似相反的进程对线粒体正常功能的发挥非常重要^[13]。融合过程中, 大量线粒体之间会进行物质和遗传信息的重新整合和分配, 可避免单个线粒体功能异常而发生自噬^[13]。线粒体自噬作用是目前已知的细胞内降解线粒体的唯一机制, 是溶酶体依赖的降解过程, 可清除损伤的线粒体^[12]。细胞通过线粒体分裂和融合以及线粒体自噬等进程的

精确调控, 可改变线粒体的形态、大小、数量及其在细胞中位置的分布^[14]。

在线粒体内膜上, 电子传递链参与能量的产生, 氧分子是呼吸链电子传递的最终受体^[15]。当发生氧化磷酸化时, 如果线粒体电子传递链上的呼吸酶复合物发生电子泄漏, 就会导致活性氧自由基(reactive oxygen species, ROS)的产生^[16]。近年来研究发现, 细胞内适量的ROS可作为信号分子参与固有免疫应答反应^[17-18]。线粒体中的抗氧化酶能代谢有毒的活性氧中间产物以维持细胞内适度的氧化压力, 然而功能失调的线粒体无法有效代谢中间产物, 会导致ROS的积累并引起细胞氧化损伤^[19]。此外, 在应激状态下, 细胞的调控机制不能维持线粒体的稳态从而导致其功能障碍。

1 线粒体转移的生物学现象

Spees等^[20]于2006年首次观察到线粒体转移的现象, 在线粒体功能异常的人源上皮细胞(A549 rho cell)和标记了线粒体的MSCs共培养体系中, 原本丧失线粒体功能的人源上皮细胞中发现了含有来自供体MSCs的线粒体DNA(mitochondria DNA, mtDNA), 并且重建了正常的线粒体呼吸功能。之后, 又有多个实验室几乎同时证实了线粒体转移的现象, 而且还观察到介导线粒体转移的主要途径隧道纳米管(tunneling nanotubes, TNTs)^[21-23]。TNTs为细胞间信息传递提供了新的渠道, 细胞间可形成多条TNTs相互连接, 构成了细胞间物质和信号传递的复杂调控网络^[24]。

体外培养实验发现, 骨髓、脐带和脂肪等多种组织来源的MSCs都可以将线粒体转移到临近的应激细胞中(表1), 并协助受体细胞恢复正常的氧化呼吸功能^[25]。除干细胞可转移线粒体外, 其他类型的细胞如成纤维细胞和上皮细胞, 也具有转移线粒体的能力^[26]。线粒体功能异常会造成细胞损伤, 进而导致细胞凋亡, 通过MSCs向损伤细胞转移线粒体, 能够增加应激细胞内线粒体的生物合成, 减少氧化损伤, 并能显著改善其有氧呼吸作用和ATP的供应。线粒体转移不仅能抑制受体细胞的凋亡, 还可对损伤的细胞进行修复, 为线粒体功能异常疾病的临床研究和治疗提供了新的思路^[25]。

2 线粒体转移的途径

线粒体转移现象仅发生在靶细胞无功能性线粒

表1 多种组织来源的MSCs线粒体转移现象

Table 1 Mitochondrial transfer from multiple tissue derived MSCs

序号 No.	MSCs种类 MSCs type	受体细胞 Recipient cell	作用 Action	转移途径 Transfer mode	参考文献 Reference
1	Wharton's Jelly derived MSCs	Osteosarcoma cells devoid of mitochondria	Mitochondria function was rescued	TNTs	[25]
2	Lung-derived mesenchymal stromal cells	Human BEAS2B epithelial cells	Repair of damaged bronchial epithelial cells	TNTs, microvesicles and gap junction	[27]
3	Bone marrow derived MSCs	Macophages	Improvement of phagocytic capacity	Microvesicle	[28]
4	Adipose derived MSCs	Cardiomyocytes	Reprogram adult cardiac cells towards progenitor like state	Cell fusion	[29]
5	Induced pluripotent stem cells derived MSCs	Human airway smooth muscle cells	Attenuation of oxidative stress-induce mitochondrial dysfunction	TNTs and microvesicles	[30]

体时,或细胞处于应激、损伤等条件下。线粒体转移涉及多种途径,除主要通过TNTs转运外,还可通过间隙连接通道、胞外囊泡、细胞融合后选择性丢失供体细胞核以及细胞内吞等方式进行转运^[31]。MSCs转移功能正常的线粒体,可调控靶细胞内mtDNA的复制,调节靶细胞内其他线粒体的动态变化,维持靶细胞内线粒体的稳态,以满足靶细胞各种生物学进程所需的能量。细胞间进行细胞器的交换代表了一种特殊的细胞间通讯方式,可允许单向或双向的物质和信号交流,包括小分子物质和离子以及细胞间组分如线粒体、溶酶体、内体小泡(endosomal vesicles)和细胞膜组分等^[32]。

2.1 TNTs介导的线粒体转移

TNTs是一种介导细胞间讯息传递的线状膜性管道,由细胞膜以及纤维形肌动蛋白(f-actin)和微管蛋白(microtubulin)为主的细胞骨架成分组成^[33-34]。TNTs最初是由Rustom等^[35]在人源293细胞和大鼠PC12细胞的共培养体系中发现,之后又在免疫细胞、肿瘤细胞、神经细胞和肌肉细胞中观察到,推测TNTs很可能是哺乳动物细胞间普遍存在的一种交流方式^[36]。TNTs的长度和直径有着较大的波动范围,长度从几个 μm 到100 μm 之间,直径变化从十几个nm到1000 nm以上,有研究将其分为较细(直径 $<0.7 \mu\text{m}$)和较粗(直径 $\geq 0.7 \mu\text{m}$)两种类型^[33]。细胞间的TNTs连接具有动态性和异质性的特点,动态性是指TNTs一直处于形成和断裂的持续变化之中,其形成和消失基本只相隔几分钟^[35];异质性是指构成TNTs的成分可能同时来源于供体和受体两种细胞。MSCs与靶细胞间通过形成TNTs可高效地进行细胞器的传输,是线粒体转移的主要途径^[37](图1A)。

2.2 间隙连接通道介导的线粒体转移

间隙连接(gap junction, GJ)由间隙连接蛋白(connexin, Cx)、连接子(connexon)和间隙连接通道(gap junctional channels, GJCs)组成,是相邻细胞间进行物质交换和信号交流的重要通道^[38]。细胞膜上6个相同的Cx围绕成管状结构的连接子,相邻细胞膜上的两个连接子端对端连接形成GJ,中间形成的GJCs可允许离子(Na^+ 、 K^+ 、 Ca^{2+} 等)、第二信使[如三磷酸肌醇(inositol 1,4,5-triphosphate, IP3)、环磷酸腺苷(cyclic adenosine monophosphate, cAMP)、环磷酸鸟苷(cyclic guanosine monophosphate, cGMP)]以及固醇、磷脂等其它小分子跨细胞进行交换^[38-39]。在脊椎动物细胞中,Cx是由多基因家族编码的具有同源性的跨膜蛋白,目前已发现20多种Cx亚型,其中Cx43是表达最广泛、研究最彻底的一种Cx亚型,参与了一系列的生理进程,例如物质交换、囊泡运输、线粒体呼吸和离子转运等^[40]。活细胞成像研究发现,骨髓来源的MSCs与损伤的肺泡上皮细胞之间形成了基于Cx43构成的GJCs, MSCs释放包裹线粒体的囊泡通过GJCs到达肺泡上皮细胞,之后通过内吞作用被摄取^[41]。线粒体通过GJCs转移到肺部上皮细胞是MSCs治疗肺损伤的重要机制之一^[42](图1B)。

2.3 微泡介导的线粒体转移

MSCs可通过微泡将线粒体转移至其它细胞。微泡是直径介于100~1 000 nm之间的一种胞外囊泡,从细胞质膜上脱落释放产生,也称为脱落的囊泡,其产生过程与胞质内钙离子内流和细胞膜骨架的重构有关^[43]。微泡介导线粒体转移,首先MSCs产生的线粒体和mtDNAs会被包装到含有自噬相关蛋白轻链3的囊泡(autophagy marker light chain 3-containing

vesicles)中,然后囊泡迁移到细胞周边并整合到外向的芽泡中。当MSCs受到生物信号(例如白介素、肿瘤坏死因子、内毒素和凋亡蛋白因子等)或理化刺激(例如低氧环境、氧化应激和胞质内钙离子浓度增加等)时,细胞骨架发生重塑,以出芽的方式从细胞质膜上脱落产生微泡^[44]。微泡可直接与靶细胞的质膜相互融合,或被靶细胞通过内吞作用而摄取,将微泡内的线粒体和mtDNA等成分转移至靶细胞的细胞质中^[45](图1C)。

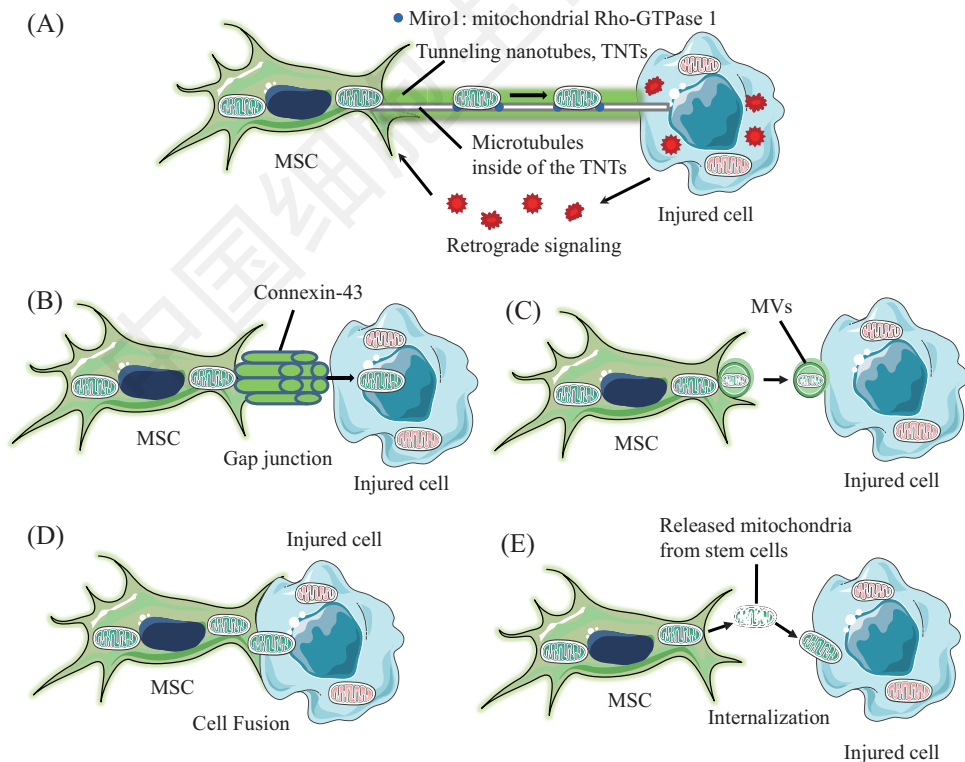
2.4 细胞融合介导的线粒体转移

细胞融合(cell fusion)是指两个或多个独立的细胞通过细胞膜的融合,形成一个细胞的过程,融合后的细胞具有亲本细胞的遗传信息,共用细胞器和其它胞质组分^[46]。通过对线粒体DNA和细胞核DNA多态性的研究发现,细胞融合不是线粒体转移的主要途径^[20]。在高等真核生物正常生理条件下,细胞融合发生的概率很低,但作为细胞间一种基本的生理活动,受到一系列作用元件精密的调控,确保只有在特定的条件下才可以发生^[47](图1D)。细胞融合现象

包括永久性融合和短暂性融合^[29]。发生永久性细胞融合后,杂交细胞共用细胞质组分并选择性丢失供体细胞核,受体细胞核重编程后表现出组织特异性干/祖细胞的特性^[48];短暂性细胞融合,允许瞬时的细胞间物质和信号的交换,包括供体细胞线粒体的转移^[29]。终末分化的体细胞与MSCs融合后可介导体细胞的重编程,有助于组织的再生,目前在骨骼肌、肝脏、肺脏、心脏、肠道、皮肤、脑和视网膜等多种组织和器官中都观察到细胞融合的现象^[49-50]。

2.5 细胞内吞介导的线粒体转移

细胞内吞(endocytosis)是真核细胞通过细胞膜内陷形成囊泡,将胞外物质摄取到细胞内的过程,主要包括吞噬作用(phagocytosis)和胞饮作用(pinocytosis)两种类型^[51]。MSCs在炎症因子的刺激下可释放线粒体,研究表明,干细胞释放的线粒体可被宿主细胞通过内吞作用摄取^[52-53](图1E)。大型胞饮作用(macropinocytosis)通过质膜皱褶包裹内吞物形成囊泡完成胞饮作用,是胞饮作用的一种方式^[54]。对外源性线粒体进行标记并利用活细胞荧光成像和



A: 隧道纳米管介导的线粒体转移; B: 间隙连接介导的线粒体转移; C: 微泡介导的线粒体转移; D: 细胞融合介导的线粒体转移; E: 内吞作用介导的线粒体转移。

A: tunneling nanotubes mediated mitochondrial transfer; B: gap junction mediated mitochondrial transfer; C: microvesicles mediated mitochondrial transfer. D: cell fusion mediated mitochondrial transfer; E: endocytosis mediated mitochondrial transfer.

图1 线粒体转移的主要途径及机制

Fig.1 Multiple modes and mechanisms of mitochondrial transfer

三维重建成像等技术发现,从MSCs分离出的结构完整并且功能正常的线粒体,能够被体外培养的心肌细胞通过大型胞饮作用摄取^[52]。体外培养的心肌细胞可通过微丝依赖的细胞内吞摄取线粒体,随着共培养时间的延长,细胞内吞作用摄取的线粒体数量会逐渐增多^[53]。

3 影响线粒体转移的调控机制

线粒体转移首先需要应激细胞发出刺激信号, MSCs接收局部微环境的刺激信号后进行线粒体的大量合成,合成的线粒体在特定的环境下选择不同的途径进行转移。研究发现,在肺部支气管上皮细胞^[41]、肾小管上皮细胞^[55]、血管内皮细胞^[56]、角膜上皮细胞^[57]和大脑皮质神经元^[58]等类型的细胞中,线粒体主要通过隧道纳米管的方式进行转移;心肌细胞主要通过和MSCs进行细胞融合完成线粒体的转移,并导致心肌细胞重编程呈现出心肌祖细胞的特性,进而完成损伤心肌细胞的修复^[29];线粒体通过微泡进行转移主要发生在涉及免疫应答的情况下,如在抗微生物感染的进程中^[28]。至于何种刺激信号可诱导何种途径的线粒体转移目前仍不清楚。

3.1 触发线粒体转移的早期信号

线粒体转移仅发生在靶细胞无功能性线粒体或靶细胞处于应激状态时(例如炎症或细胞损伤),暗示应激状态下的细胞通过病理性刺激,是触发MSCs来源线粒体转移的关键信号^[41]。当发生严重组织损伤时,许多线粒体相关组分会释放到损伤的细胞外,这些组分被称为线粒体损伤相关的分子模式(damage associated molecular patterns, DAMPs),包括mtDNA、*N*-formyl peptides、胞外ATP、TFAM和心磷脂(cardiolipin)等,它们聚集在损伤组织的周围或穿过毛细血管汇入血流^[59-60]。此外,在急性组织损伤或炎症状态下,释放到损伤细胞外的线粒体本身也可以作为DAMPs^[61-62]。损伤细胞释放的线粒体或mtDNA作为局部微环境的求救信号,除可被固有免疫细胞通过特异性的受体识别引发早期的免疫应答反应外,还能够被MSCs所感知,触发MSCs抗细胞凋亡的功能,诱导MSCs产生具有保护功能的血红素氧合酶1(heme oxygenase-1, HO-1)并刺激线粒体的生物合成^[61]。

除DAMPs外,应激或炎症状态下,细胞释放的ROS也能够刺激线粒体从供者细胞向受者细胞的转

移^[57]。应激细胞通过释放高水平的ROS作为求救信号,诱导MSCs转移线粒体可下调应激细胞内的氧化压力^[11]。此外,应激细胞线粒体释放的细胞色素c(cytochrome c, Cyt c)也能够触发线粒体的转移^[63]。紫外线照射导致损伤的PC12细胞,在细胞凋亡的早期阶段通过释放Cyt c可诱导与其共培养的MSCs之间形成TNTs, MSCs转移正常功能的线粒体从而挽救损伤的PC12细胞^[63]。DAMPs、ROS和Cyt c等多种信号触发了MSCs来源的线粒体转移,但触发转移的详细机制及下游信号是如何进行转导的,目前仍不清楚。

3.2 MSCs释放线粒体的调控机制

MSCs接收到应激细胞触发的线粒体转移信号之后,首先会对线粒体进行筛选并从细胞内释放。MSCs只转移功能正常的线粒体到受体细胞,mtDNA突变而导致功能异常的线粒体不会发生转移^[64]。MSCs释放线粒体之前,会通过线粒体自噬的方式清除自身功能异常的线粒体,并把发生自噬的线粒体和溶酶体等细胞器通过囊泡定向输送到巨噬细胞进一步清除^[65]。MSCs清除自身功能异常的线粒体,对于调节自身氧化压力和细胞的存活起到重要作用。从这一角度来讲, MSCs转移线粒体不仅仅是一种单纯的利他行为,对自身而言也是一种重要的保护机制^[65]。

目前已发现,线粒体在细胞内的转运有3种调节方式,可能与供体细胞内线粒体的释放有关。第1种是微管相关蛋白(microtubule-associated proteins, MAPs)介导的线粒体在细胞内的移动^[66]。线粒体在细胞内的移动主要依赖微管等细胞骨架成分和分子马达蛋白,也是线粒体在细胞内转移和重新分布的主要方式^[66-67]。第2种是突触活动依赖性的调节。线粒体首先被转移至激活的突触,供体和受体细胞内的信号会控制线粒体移动的速度并将其募集到供体细胞的特定位点^[68],线粒体在细胞内的移动仍然需要驱动蛋白的协助,而且这一过程是钙离子浓度依赖的^[69]。第3种是神经信号介导的调节。在背根神经节神经元中,神经生长因子(nerve growth factor, NGF)可以作为刺激信号,使轴突线粒体在细胞外来源的NGF附近积累^[70]。细胞骨架蛋白微丝参与了神经信号介导的细胞内线粒体的转运。

3.3 TNTs内线粒体转移的调控机制

供体细胞和受体细胞间形成TNTs是线粒体转

移的主要途径。Miro1是一种钙敏感性衔接蛋白(线粒体外膜的Rho-GTPases)^[71], 能使线粒体附着于KIF5肌球蛋白上, 在一系列辅助蛋白如Miro2、驱动蛋白TRAK1/2、肌球蛋白Myo10/19等的帮助下, 协助线粒体沿着TNTs内的微管移动^[26]。Miro1的缺失并不影响TNTs的形成, 但很大程度上降低了线粒体在TNTs内转移的速度^[72]; 过量表达Miro1的MSCs表现出更强的线粒体转移能力和细胞损伤修复能力^[73]。线粒体基质内Ca²⁺的含量与线粒体移动速度有关, Miro1主要通过调节线粒体对Ca²⁺的摄取从而影响线粒体在TNTs内的移动速度^[74](图1A)。

能够刺激TNTs形成的物质主要包括肿瘤坏死因子 α (tumor necrosis factor, TNF- α)^[75]、ROS^[57]和M-Sec^[76]等。TNF- α 预处理后MSCs表达的TNF- α IP2(TNF- α induced protein)显著增加, 通过TNF- α /NF- κ B/TNF- α IP2信号通路可诱导TNTs的形成^[75]。应激细胞释放的ROS也能够激活NF- κ B/TNF- α IP2信号通路, 诱导TNTs的形成^[57]。M-Sec是一种哺乳动物表达的蛋白, 可刺激较细(小于0.7 μ m)TNTs的形成, 这类TNTs内只含有微丝不含有微管等细胞骨架成分^[76]。Cdc42是一种小分子的GTPase, 供体细胞的细胞膜凸起后在TNTs的延伸过程中起到重要作用^[76]。在骨髓来源的MSCs和多发性骨髓瘤细胞共培养的研究中发现, CD38介导了TNTs的形成和线粒体的转移^[77]。此外, 对星形胶质细胞的研究发现, P53的激活对TNTs的形成起到重要作用, 包括EGFR、Akt、PI3K和mTOR等信号的激活都参与到TNTs的形成过程^[78]。

线粒体在TNTs内的运输是双向的, 功能正常的线粒体可以从MSCs转移到受体细胞内, 应激状态下受体细胞内损伤的线粒体也可以通过TNTs转移到MSCs^[61], 并激活压力诱导的HO-1信号通路, 通过线粒体自噬的方式被MSCs清除^[79]。除损伤的线粒体外, 应激细胞还可通过TNTs向MSCs转移ROS和Ca²⁺等物质以及应激细胞内AMP/ATP和NAD⁺/NADH的比值等逆行信号(retrograde signaling)^[26](图1A)。在星形胶质细胞的研究中发现, CD38也可以作为逆行信号增强线粒体的转移^[80]。TNTs内的逆行信号一方面可通过上调与线粒体生物合成相关的蛋白PGC-1 α (proliferator activated receptor gamma coactivator-1 α)表达水平, 刺激MSCs内线粒体的生物合成和转移^[81], 另一方面可激发MSCs抗细胞凋亡和细胞损伤

修复的功能^[82]。

4 线粒体转移在疾病治疗中的作用

MSCs能够感知应激细胞释放的线粒体等DAMPs, 并激发其损伤修复的特性^[61]。无论在细胞水平的体外共培养实验中, 还是模式动物的组织损伤实验中, MSCs转移的线粒体都具有显著的抑制凋亡并挽救应激细胞正常生理功能或组织损伤修复的作用。第一例应用线粒体转移的临床试验报道, 5位心肌缺血再灌注损伤的儿科患者通过自体来源的线粒体移植后, 4位患者的心肌的收缩功能得到明显改善^[83]。

体外共培养实验中, MSCs与心肌细胞^[84]、内皮细胞^[56]、支气管上皮细胞^[85]、角膜上皮细胞^[57]和神经元细胞^[58]等共培养, 通过对培养的细胞进行各种刺激如缺氧、营养耗竭或暴露于烟雾等造成损伤, 会观察到MSCs向应激细胞转移线粒体的现象。线粒体转移后损伤细胞凋亡的现象被明显地抑制, 损伤细胞的能量代谢和生成的ATP显著增加, 并逐渐恢复各项生理功能。多种疾病的动物模型实验中也观察到MSCs转移线粒体的现象, 例如心肌缺血模型^[86]、LPS诱导的急性肺损伤^[41]、鱼藤酮诱导的支气管上皮细胞损伤^[72]、鱼藤酮诱导的兔角膜上皮细胞损伤^[57]。动物疾病模型的体内实验进一步证实, 移植外源的MSCs也可以向损伤的组织或细胞转移功能正常的线粒体, 通过增加应激细胞内线粒体的生物合成, 恢复应激细胞的氧化磷酸化进程以及ATP的生成, 起到组织损伤修复的作用。

体外和体内实验研究均表明, MSCs向巨噬细胞转移线粒体有助于巨噬细胞表型的转变^[87-88]。在急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)模型中, MSCs来源的线粒体转移到巨噬细胞, 能提高巨噬细胞的氧化磷酸化水平并增强其吞噬功能^[88], 巨噬细胞倾向于分化成具有抗炎作用的M2型^[28]。然而, 并非所有的线粒体转移现象都是有利的, MSCs或宿主细胞来源的线粒体可以转移到多种恶性肿瘤细胞中, 例如乳腺癌细胞、卵巢癌细胞、多发性骨髓瘤细胞、黑色素瘤细胞、急性白血病细胞和胶质母细胞瘤, 可促进癌细胞的发生发展、迁移以及对化疗的耐药性等^[89-94]。抑制线粒体转移可以作为癌症潜在的治疗靶点, 例如可选择性阻断TNTs的形成抑制线粒体转移。

5 展望

MSCs能够感受到处于应激状态或损伤细胞发出的求救信号,并与之建立复杂的细胞间通讯进行有效的物质和信息交流,进而通过改变细胞代谢水平对损伤或应激细胞进行修复,在多种动物的组织损伤修复疾病模型中具有显著的治疗效果。从MSCs分离出来的线粒体做为药品直接导入病变组织模拟体内线粒体转移可能会是未来一种新颖的疾病治疗方式^[95],但应用到临床之前仍有许多问题需要深入研究。MSCs多种作用机制参与组织损伤修复,例如旁分泌作用、转分化后细胞替代以及细胞融合介导的重编程等^[6],线粒体转移是否与其他作用机制产生协同效应?如何选择或改造可高效分离高质量线粒体的MSCs?由于细胞内在的呼吸状态存在差异,不同组织来源的MSCs其转移线粒体的能力和治疗效果也不尽相同。研究表明,脂肪和骨髓来源的MSCs具有较强的线粒体转移的特性,然而牙髓和脐带来源的MSCs由于其线粒体具有更强的有氧呼吸能力,转移相同数量的线粒体表现出更强的治疗效果^[96]。利用分离的线粒体治疗特定疾病所需的最佳数量以及保护线粒体活性的方法和合适的输注途径等都亟待临床试验进行明确。

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