线粒体移植疗法

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摘要 线粒体移植(mitochondrial transplantation)曾指利用显微操作, 将分离获得的正常线粒体注射到卵细胞的辅助生殖技术。近年兴起的, 将线粒体直接注射到组织器官的受损部位, 或注射到血液循环系统, 进而发挥治疗作用的技术, 同样被称为线粒体移植。在细胞研究水平, 则是直接将线粒体与培养细胞共同孵育。这些技术方法也统称为线粒体疗法。该文系统综述了线粒体移植在心、脑、肝、肾、肺、骨骼肌等多种组织器官损伤模型中, 在小鼠、大鼠、兔、猪等多种实验动物模型中的研究成果, 以及在心脏病患儿体内的初步临床研究成果; 介绍了学界提出的线粒体进入细胞、产生ATP等作用机制, 及对此机制的相关质疑; 同时介绍了自己课题组关于线粒体移植治疗皮肤急性光损伤和烧伤的研究成果, 提出并讨论了线粒体可能不需要进入细胞即可发挥作用的假说。该文提出线粒体移植机制的内化机制和非内化机制概念, 为深化线粒体移植机制研究指出新方向。

关键词 细胞器; 线粒体; 线粒体移植; 线粒体移植疗法; 线粒体疗法; 缺血再灌注损伤

Mitochondrial Transplantation Therapy

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Abstract Mitochondrial transplantation was ever referred to the assisted reproductive technology that injects isolated normal mitochondria into oocytes using micromanipulation. While, in the recent years, the technique of injecting healthy mitochondria directly into damaged tissues or organs, or injecting into the blood circulation, and subsequently exerting a therapeutic effect is also named as mitochondrial transplantation. In the cultured cell models, mitochondria are directly incubated with cells. This technique can also be termed as mitochondrial therapy. In the present review, the mitochondrial transplantation in diverse tissue and organ injury models, including but not limited to heart, brain, liver, kidney, lung, and skeletal muscle, in experimental animal models such as mice, rats, rabbits, and pigs, as well as preliminary clinical studies conducted on children with heart diseases are introduced. The proposed internalization mechanism, which is mitochondria entering cells to produce ATP, and its limitations are also introduced and discussed. Finally, a hypothesis that mitochondria may not need to enter the cell to function is proposed and named as non-internalization mechanism corresponding to the former internalization mechanism. This review puts forward a new direction for deepening the study of mitochondrial transplantation and the related mechanisms.

Keywords organelle; mitochondria; mitochondrial transplantation; mitochondrial transplantation therapy; mitochondrial therapy; ischemia-reperfusion injury

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“线粒体移植”是指将分离获得的线粒体注射到组织器官的受损部位，或者注射到血液循环系统，从而发挥疗效的技术；在细胞培养水平，则是指将分离获得的线粒体与培养细胞共同孵育，来研究线粒体移植效果的技术。其对应的英文名词是MT(mitochondrial transplantation)。检索PubMed数据库，发现该英文名词首次出现在2016年3月发表的文献中[1]。而中文“线粒体移植”名词早在2003年7月即被孔令红等[2]报道，译为mitochondria transfer，同年9月，该组又发表论文，将其译为mitochondrial transplantation[3]。但是，这些早期中文文献报道的“线粒体移植”，与本文综述的线粒体移植并非同一概念。早期中文文献特指用显微注射方法，将分离获得的线粒体注射到卵细胞，从而实现辅助生殖的技术。而本文介绍的线粒体移植则是指段首所述的新技术。直到2018年3月，类似的中文文献才见报道[4]。实际上，这些用分离得到的线粒体进行疾病治疗的技术，可以被统称为线粒体疗法(mitochondrial therapy)。但是，一个名词概念的形成与其历史发展密切相关，相信随着该技术的逐渐成熟，学界会给出一个较为规范的统一称谓。

相比于器官、组织、细胞移植，线粒体移植是细胞器的移植，属于亚细胞水平移植范畴，是一类新型移植技术。该技术近年来逐渐成为研究热点，取得了较大研究进展。本文将对这些成果进行综述，并针对机制方面尚存问题进行讨论。

1 线粒体移植疗效研究成果

2009年，MCCULLY等[5]报道，将线粒体注射到兔心脏缺血部位，可见显著的心脏保护作用，这是MT对实验动物疗效的首次报道。截至目前，在心[5]、脑[6]、神经系统[7]、肺[8]、肾[9]、肝[10]、骨骼肌[11]、皮肤[12]等组织器官损伤，以及炎症[13]、肿瘤[14]等疾病方面都发现了MT的治疗效果。

1.1 治疗心血管疾病

MT对心脏损伤疗效的研究，以MCCULLY课题组的文献最多。该组已在兔[5]、猪[15]、小鼠[16]、大鼠[17]等实验动物上，揭示了MT对心肌缺血再灌注损伤的疗效，试验了将线粒体直接注射到损伤区域[5,15]和注入冠状动脉[16-17]等不同方法，也试验了从左心室[5]、胸大肌[15,17]、腓肠肌[16]等不同肌肉组织分离线粒体，均取得了很好的效果。特别是于2017[18]和2021[19]年两次报道了儿童心脏病的临床试验疗效。该组以猪为模型，较为全面地试验了MT发挥作用的诸多情况，比如发现：相对于多数实验在重灌注之前进行MT，该组在重灌注120 min后，再进行MT，也有效[20]；在缺血前实施MT有效[21]；针对循环死亡后的心脏，无论是成年猪的心脏[22]还是新生猪或者幼年猪的心脏[23]，MT均有效；针对右心室肥厚和衰竭模型，MT同样有效[24]。这些研究揭示MT应用的灵活性和疗效的广泛性。

两次MT临床研究针对的均为心脏遭受缺血/重灌注损伤儿科患者，结果均支持此技术的可行性及有效性[18-19]。表1展示了MT对心脏疾病疗效的研究成果，其中除部分小鼠[28-29]和大鼠[30-31]研究外，均为MCCULLY课题组的贡献。

1.2 治疗脑及脊髓等神经系统疾病

MT对脑和脊髓等神经系统相关疾病的疗效研究成果也较丰富(表2)，主要以大鼠和小鼠为动物模型。

大鼠模型研究成果主要涉及脊髓损伤[7,32]、脊髓缺血[33]、脑卒中[6,34-35]、视网膜变性[36]、老年大鼠的焦虑和抑郁样行为[37]等；线粒体来源有培养细胞如PC12[7]、人脐带间充质干细胞[34]、N2a细胞和mNSC细胞[35]等，以及比目鱼肌[7,32-33]、胸大肌[6]、肝脏[36]、脑组织[37]等；移植方法包括直接注射到脊髓损伤部位的中外侧灰质[7]或其损伤部位[32]、颈内动脉[33,35]、左侧脑室[6]、右侧脑室[34,37]、眼球玻璃体腔[36]等。

小鼠模型神经系统MT研究成果主要涉及抑郁[39]、脑功能障碍[40]、创伤性脑损伤[41]、脑皮质缺血导致的少突胶质细胞退化[42]以及年龄相关的认知功能下降[43]等；线粒体来源有海马体[39]、胸大肌[40]、肝脏[41-43]；移植途径有静脉注射[39]、左侧脑室注射[40]、大脑皮层注射[41-42]和双侧海马体注射[43]以及通过光生物调节作用协助进入等[38]。总之，MT对某些神经系统损伤和疾病表现出了明显的疗效。

1.3 治疗肺部疾病

MT对肺损伤疗效主要是华中科技大学HU课题组[8,44]和MCCULLY课题组[45]的工作。前者以大鼠为模型，研究了线粒体移植对气道高反应性[8]和缺氧性肺动脉高压[44]的疗效，分别从气道上皮[8]和培养的肺动脉和股动脉平滑肌细胞[44]分离线粒体，通过气道引入[8]和尾静脉注射[44]形式进行移植。后者以小鼠为模型，报道了MT增强缺血再灌注损伤后肺活力，

表1 线粒体移植治疗心脏相关疾病研究成果

Table 1 Research results of mitochondrial transplantation in the treatment of heart-related diseases

动物模型 Animal model	疾病/损伤模型 Disease/injury models	线粒体来源 Sources of mitochondria	移植途径 Transplant route	治疗效果 Treatment effect
Rabbit	Ischemia/reperfusion injury[5,25]	Left ventricle[5] Pectoralis major[25]	Inject into the ischemic area[5,25]	Significantly enhance functional recovery and cell viability after ischemia[5,25]
Pig	Ischemia/reperfusion injury[15,20-22,26] Right ventricular hypertrophy and failure[24]	Pectoralis major[15,20-22,26] Gastrocnemius muscle[24]	Inject into the ischemic area[15] Inject into coronary artery[20-22,26] Inject into the free wall of the right ventricle[24]	Significantly enhance cellular activity after ischemia-reperfusion injury[15] Reduce infarct size[20-22,26] Promote physiological adaptation of the right ventricle[24]
Mouse	Ischemia/reperfusion injury[27-28] Myocardial infarction[29]	Gastrocnemius muscle muscle[27] Mouse primary myocardial cells[28] Mesenchymal stem cells and skin fibroblasts[29]	Inject into coronary artery[27] Left ventricular myocardium[28] Periinfarction area[29]	Limit the infarct size after ischemia-reperfusion injury[27-28] Enhance vascular density, inhibit cell apoptosis, and improve cardiac function[29]
Rat	Ischemia/reperfusion injury to the heart of diabetes rats[17] Right ventricular pulmonary hypertension[30] Cardiac arrest[31]	Pectoralis major[17,31] Soleus muscle[30]	Inject into coronary artery[17] Internal jugular vein injection[30] Intravenous injection[31]	Enhance recovery after heart ischemia in diabetes[17] Improvement of overall right ventricular function[30] Improve survival and neurological recovery in post-CA rats[31]
Human	Pediatric patients with ischemia/reperfusion injury[18] Children with cardiogenic shock after ischemia/reperfusion injury[19]	Rectus abdominis[18-19]	Intramyocardial injection[18] Inject diredectly into the damaged myocardium through the epicardium[19]	Patient disengagement from ECMO, enhance cardiac strain[18-19]

促进组织损伤恢复, 线粒体源于腓肠肌, 试验了经肺动脉或气管雾化气溶胶两种形式的移植效果[45]。

1.4 治疗肾损伤

MT对肾损伤的疗效报道可见于大鼠和猪研究模型。MCCULLY组[9]针对猪缺血再灌注损伤模型, 将分离自胸锁乳突肌线粒体单剂注射到肾动脉, 使肾小球滤过率、尿量、血清肌酐、血尿素氮等指标均显著改善, 增强了肾功能, 减轻了急性肾损伤。伊朗研究人员JABBARI等[46]以大鼠为模型, 将源于胸大肌的线粒体注射到肾动脉, 观察到显著的减轻肾缺血再灌注损伤的效果。土耳其研究人员以大鼠为模型, 将源于间充质干细胞的线粒体直接注射到肾皮质, 观察到显著的减轻肾缺血再灌注损伤[47]和阿霉素导致的肾损伤[48]疗效。

1.5 治疗肝损伤

西南大学FU课题组[10]用CCl_4诱导小鼠肝损伤模型, 将来自健康小鼠肝脏的线粒体通过静脉注射到模型小鼠, 促进后者ATP生成, 减少自由基损伤, 显著改善了肝功能并防止组织纤维化。土耳其学者ULGER等[49]用对乙酰氨基酚(acetaminophen)诱导大鼠肝损伤, 继而将分离自体外的大鼠间充质干细胞线粒体注射到脾脏, 经门静脉循环输送到肝脏, 改善了肝脏受损组织结构, 降低了细胞凋亡和氧化应激水平。

1.6 治疗肌肉损伤和疾病

MCCULLY等[11]用止血带, 在小鼠左后肢, 构建骨骼肌缺血再灌注损伤模型, 将分离的同种异体骨骼肌线粒体注射到造模部位, 使得肌肉梗死面积减小、细胞凋亡水平下降, 证明MT能改善急性肢体缺血损伤。ALWAY等[50]将$BaCl_2$注入小鼠腓肠肌构建创伤性肌肉损伤模型, 将线粒体注入尾静脉, 发现MT能够提高受伤后肌肉再生和功能恢复的速度。LEE等[51]报道在注射胶原酶诱导的肌腱病大鼠模型中, 向跟腱处注射线粒体(分离自培养的大鼠成纤维

表2 线粒体移植治疗脑及其他神经系统疾病研究成果

Table 2 Research results of mitochondrial transplantation in the treatment of brain and other neurological diseases

动物模型 Animal model	疾病/损伤模型 Disease/injury models	线粒体来源 Sources of mitochondria	移植途径 Transplant route	治疗效果 Treatment effect
Rat	Spinal cord injury[7,32,38] Spinal cord ischemia model[33] Cerebral stroke[6,34-35] Retinal degeneration[36] Anxiety and depression like behavior in elderly rats[37]	PC12 cells or soleus muscle[7] Soleus muscle[32-33] Pectoralis major[6] Human umbilical cord derived mesenchymal stem cells[34] Mouse brain neuroma cell line N2a and mouse neural stem cell line mNSC[35] Liver[36] Healthy young rat brain[37] Blood[38]	Inject into the lateral gray matter around the injured spinal cord[7] Inject into the spinal cord injury site [32] Inject into the left cerebroventricular[6] Inject into the right cerebroventricular[34,37] Inject into the internal carotid artery[33,35] Inject into the vitreous cavity[36] PBM (photobiomodulation) promotes MT[38]	Help maintain normal neural energy, but does not produce long-term protective effects[7] Reduce cell apoptosis and inflammatory response[32] Reduce the area of cerebral infarction[6,34-35] Reduce photoreceptor degradation[36] Improve anxiety and depression like behavior[37] Promote tissue repair and motor function recovery[38]
Mouse	LPS induced depression model[39] Sepsis related brain dysfunction[40] Traumatic brain injury[41] Focal cortical ischemia induced oligodendrocyte degeneration[42] Age related cognitive decline[43]	Hippocampus[39] Pectoralis major[40] Liver[41-43]	Intravenous injection[39] Inject into the left cerebroventricular[40] Inject into the cerebral cortex[41-42] Bilateral hippocampal injection[43]	Improve oxidative stress and LPS induced depressive behavior[39] Promote the transformation of microglia and improve brain dysfunction[40] Stimulate microglia activation and improve damage[41] Reduce apoptosis of oligodendrocyte group cells and promote proliferation[42] Improve cognitive function and exert anti-aging effects[43]

细胞), 发现MT对肌腱病具有治疗效果。

1.7 治疗皮肤疾病

CHANG课题组[12]报道, 将小鼠肝脏线粒体用冲压式多针注射器注射到衰老小鼠皮下, 可改善衰老相关的脱毛。我组用紫外线UVC辐照HeLa细胞建立细胞损伤模型, 从未受辐照的HeLa细胞中分离线粒体, 经共同孵育实施线粒体移植, 结果显示MT对紫外辐照损伤细胞的线粒体膜电位、细胞周期及凋亡有明显改善作用[52]。在此基础上, 进一步发现了MT对UVC辐照小鼠皮肤急性光损伤的疗效(尚未发表)。

1.8 治疗炎症相关疾病

韩国学者HWANG等[53]将源于L6大鼠成肌细胞系和脐带间充质干细胞的线粒体, 静脉注射到败血症模型大鼠中, 发现MT对败血症具有治疗效果。WANG课题组[13]将源于异体胸大肌的线粒体, 尾静脉注射到败血症小鼠模型中, 同样发现了MT对败血症具有治疗效果。另一组韩国学者LEE等[54]将分离自体外的大鼠L6细胞的线粒体, 注射到碘乙酸钠诱导的关节炎模型大鼠的关节处, 发现MT对骨关节炎具有治疗效果。

1.9 治疗肿瘤

前述MT各种疗效均针对不同组织或器官的多种类型的损伤, 这从线粒体产能和信号中枢作用而言, 是符合逻辑的。而关于MT抗肿瘤的报道, 从逻辑上较难理解。我们用人宫颈癌HeLa细胞为模型, 发现MT能有效减轻紫外线对HeLa细胞的致死作用, 而线粒体与未经辐照的HeLa细胞共孵育, 却并未表现出对HeLa细胞生长的影响, 即未见体外抗肿瘤作用[52]。CHEN等[55]将来源于骨肉瘤143B细胞的健康线粒体, 与乳腺癌细胞系MCF-7共孵育, 结果显示MT诱导细胞凋亡, 抑制细胞增殖, 降低氧化胁迫, 使癌细胞MCF-7对抗癌药多柔比星和紫杉醇更加敏感。SUN等[56]将源于正常人星形胶质细胞的线粒体, 与人胶质瘤U87细胞共孵育, 发现MT可增加

三羧酸循环相关基因和蛋白的表达水平, 增加有氧呼吸, 降低糖酵解, 激活线粒体凋亡通路, 抑制U87细胞增殖; 在异体移植肿瘤裸鼠模型中, MT抑制胶质瘤生长; 且在体外和体内均可增强辐射敏感性。FU课题组[14]在小鼠肝癌细胞系H22及其植瘤小鼠模型上, 发现分离自肝脏的线粒体可在体外和体内实验中, 通过阻滞细胞周期和诱导凋亡, 延迟H22细胞增殖和肿瘤生长; 且来源于雌鼠肝脏的线粒体抑瘤活性优于雄鼠。

如上所述, MT在多达9大类组织器官损伤或疾病等情况下呈现明显疗效。这些研究成果的大量涌现, 表明MT研究进入到了相对成熟期。我组近期研究发现, MT对小鼠皮肤急性光损伤和烧伤均表现出较好疗效(尚未发表)。可以预期, MT应用领域还将不断拓展, 这也凸显了MT机制研究的紧迫性。

2 线粒体移植机制争议

现有MT机制理论聚焦线粒体产能, 认为移植线粒体进入受体细胞, 取代或修复受损线粒体, 提高ATP合成能力, 促进细胞恢复健康, 减轻组织损伤或治愈疾病。该理论基于线粒体主要功能, 在逻辑上是成立的, 也有相关研究支撑。MCCULLY团队[57]在2015年即已发表论文提出该机制, 其后多有类似文献陆续发表[35,58-61]。而且, 针对线粒体进入机体可能引发免疫反应的问题, MCCULLY团队[15,25]也给出了否定的回答。至此, 关于MT的疑虑似乎都得到了解决。然而, 伴随着研究成果的相继发表, 对MT的质疑也不断出现(表3)。

表3总结了针对MT最具代表性的4点质疑, 也是MT研究需要攻克的重点机制难题。略作几点讨论。

数量过少与起效过快。基于线粒体进入细胞数量过少的前因, 很难支持其10 min迅速起效的后果。因此, MT功效是否缘于其进入细胞发挥作用仍存疑虑。MCCULLY团队[25]也曾怀疑线粒体进入细胞是否必要, 探讨可能存在线粒体在细胞外即发挥支持心肌恢复功能的作用, 但并无后续研究的支持。

高钙环境失活线粒体。细胞外液和血液中钙离子浓度远高于细胞内。德国学者专门报道线粒体不能在移植过程的高钙环境中存活[63]。然而, 我组研究虽未测定线粒体呼吸活性, 但发现经高钙缓冲液处理的线粒体, 仍具有移植活性[52], 这说明结构完整性可能比呼吸活性对移植效果更为关键。而且, 诸多研究不断报道经血液注射的方法对于心[16,20-21,26]、脑[35]、脊髓[33]、肺[44-45]、肾[9,46]、肝[10,49]、抑郁[39]、败血症[13,53]、黑色素瘤[64]等组织器官损伤和疾病模型均有显著疗效。这表明线粒体不仅“有办法”适应血液的高钙环境, 而且有相应的机制“穿过血管, 到达损伤部位, 进而发挥作用”。这无疑为MT机制研究提供了更多的可能和挑战。

进入细胞机制多样。如表3所示, 胞吞、大胞饮、胞间连接等多种内化机制都有报道, 是缘于不同实验模型的组织或种属特异性, 还是因为现有研究未能揭示真实机制, 有待进一步深入细致的研究来确定。

表3 针对线粒体移植作用和机制的质疑

Table 3 Questioning the role and mechanism of mitochondrial transplantation

疑点 Doubtful points	质疑内容 Question content	提示其他机制 Prompts other mechanisms
Insufficient quantity	How can MT undertake the task of producing a large amount of ATP when the number of mitochondria into cells is too small[62]	Is there any other regulatory mechanism that differs from the direct production of ATP by transplanted mitochondria, such as promoting the activity of existing mitochondria
Acting too fast	Mitochondria injected into the myocardium takes effect within 10 minutes, but it takes 2-8 hours for mitochondria to enter the cells before being observed[25]	Is entering the cell a necessary condition for its function Is there a mechanism that does not require entry into cells
High calcium environment	Extracellular/blood high calcium environment leads to mitochondrial inactivation[63], how to explain the injection of mitochondria into arteries or venous vessels also shows a therapeutic effect	May MT not require mitochondria to have respiratory activity? May mitochondria maintain transplantation efficiency in some form
Entering cells	The specific mechanisms of endocytosis[56-57], macropinocytosis[58,60], intercellular junction[35] are constantly controversial	Is there a unified mechanism for entering cells? Does it not need to enter the cell

3 线粒体移植作用机制思考

3.1 内化机制与非内化机制

我们把线粒体进入细胞的过程称为内化过程, 相应的机制被称为内化机制。同时, 前述进入细胞的线粒体数量过少, 但起效过快的矛盾, 提示可能存在不需要进入细胞即可发挥功效的机制, 即非内化机制。因此, MT作用机制可分为内化机制和非内化机制两类。

内化机制发挥疗效作用的理论基础, 建立在线粒体产生ATP的功能之上。对应的非内化机制, 建立在线粒体不需要进入细胞的假设之上, 认为线粒体仅凭与细胞表面特定物质的相互作用, 即可将信息传入细胞, 刺激细胞产生自救。

3.2 两类机制共存?

内化机制已有一些实验结果的支持, 虽然具体的内化途径如胞吞、大胞饮、细胞连接等并未统一, 但该机制的理论基础均建立在线粒体产能这一共性之上。既有理论基础, 又有实验结果的支持, 内化机制是逻辑自洽的。其挑战同样源于实践发现, 线粒体进入细胞数目过少, 而起效却过快, 似乎提示还有另外的机制, 即非内化机制。

这些实践结果的指向, 是否预示着内化机制和非内化机制在MT过程中共同发挥作用? 例如, 非内化机制因其不需要进入细胞, 而通过信号转导发挥作用, 对于心肌细胞恢复功能方面更有立竿见影的效果。而内化机制涉及线粒体进入细胞、线粒体分裂或融合、线粒体产能, 更适合需要修复时间较长的损伤。此外, 我组近期研究发现, 从昆虫细胞和线虫中提取的线粒体对小鼠皮肤急性光损伤表现出一定疗效(尚未发表), 这提示线粒体移植机制可能存在保守性, 这为机制研究提供了新方向。当然, 非内化机制目前还只是推理假设, 需要扎实的实验支撑, 这应该是该领域未来的研究方向之一。

4 小结与展望

本文系统介绍了MT在多种组织器官损伤以及对炎症、肿瘤等多种疾病的疗效, 提出了内化机制、非内化机制的概念, 探讨了两种机制可能在不同组织器官损伤和不同疾病的不同阶段, 共同或单独发挥作用的观点。MT研究正处于蓬勃发展阶段, 将这一技术推广到不同的疾病模型中, 显示出极大的潜力, 未来研究MT适应症仍然是本领域发展的重点方向之一。此外, MT机制研究是当前的难点, 如何解析线粒体与细胞的相互作用, 既意义重大, 又充满挑战。随着机制的解析, MT研究必将展现出更加宽广的前景。

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