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内皮间质转化在心肌纤维化中的机制及应用

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[摘 要] 内皮间质转化(endothelial-mesenchymal transition，EndMT)是指在多项影响因素的作用下，内皮细胞的结构和功能向间质细胞转变。研究显示在内皮的功能调节、心肌细胞、血管及心脏瓣膜等的发育和结构重塑等方面都有EndMT参与，表明心血管疾病领域在该方面投入更多研究的意义逐渐凸显。了解EndMT过程中信号转导通路，有助于进一步认识EndMT引起心肌纤维化(myocardial fibrosis，MF)的机制，为探索干预MF的治疗方案提供更多依据。

[关键词] 内皮间质转化；心肌纤维化；信号转导通路

Mechanisms of endothelial-mesenchymal transition induced myocardial fibrosis and its application

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Abstract Endothelial-mesenchymal transition (EndMT) results from the induction of some transcription factors, leading to a shift in cytoskeletal dynamics and a change of morphology and physiology from epithelial to the mesenchymal phenotype. Previous studies in recent years showed that EndMT participates in endothelial function regulation, development and remodeling of myocardial cells, vascular and heart valves, which indicates the essence of research on EndMT in cardiovascular diseases. Therefore, to understand the mechanisms and signal pathways of EndMT may provide therapeutic strategies and perspective for treating the diseases.

Keywords endothelial-mesenchymal transition; myocardial fibrosis; signal pathways

心肌纤维化(myocardial fibrosis，MF)是指心肌细胞外基质胶原纤维过量沉积，正常的心肌结构遭到破坏，心脏微循环减少，导致心脏舒缩功能减低、心力衰竭、心律失常等，甚至猝死。研究[1]表明：引起MF的成纤维细胞来源于原位静止的纤维母细胞、骨髓来源的成纤维细胞及发生上

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皮间质转化的上皮细胞等。然而，内皮间质转化(endothelial-mesenchymal transition，EndMT)参与了MF过程，并有研究[2]推测约30%的成纤维细胞来源于内皮细胞的EndMT；而当MF程度较低时，EndMT的发生也相应较少。

Zeisberg等[3]发现：纤维化的心脏中约1/3的间质细胞来源于内皮细胞的EndMT，并首度在小鼠体内发现心肌的血管内皮细胞能够通过EndMT形成成纤维细胞，促进MF发生和发展。Widyantoro等[4]发现：内皮细胞产生的Endothelin-1(ET-1)通过链霉素诱导的糖尿病小鼠模型的EndMT，促进MF；糖尿病小鼠的心功能下降，血管周围纤维化增强，敲除ET-1后抑制内皮细胞EndMT的同时显著改善MF，上述过程涉及TGF-β-Akt-Snail信号通路。Aisagbonhi等[5]也在小鼠心肌梗死模型中证实了心肌血管EndMT的存在。

本文对EndMT引起MF的机制进行综述，旨在更加全面地了解EndMT介导的MF的发生过程，进一步认识EndMT引起MF的机制，以期对其基础研究、诊断和治疗产生一定的启示意义。

1 EndMT 的基本内容

EndMT是指在病理或生理状态下，内皮细胞结构和功能都呈现显著变化，最终表达成纤维细胞特征的过程。其具体过程为：细胞内骨架蛋白重新排列，外形逐步变成长梭形，内皮细胞的特异性标志物，如血管内皮钙黏蛋白、血管内皮生长因子受体、血小板内皮细胞黏附分子等表达降低甚至丧失，而成纤维细胞特异性标志物表达增加，如α-平滑肌肌动蛋白(α-smooth muscle actin，α-SMA)、成纤维细胞特异性蛋白1(fibroblast specific protein 1，FSP1)、波形蛋白、钙调蛋白等[6]。

张晶晶等[7]在研究胚胎期心脏瓣膜发育时，最初在脊椎动物胚胎发育时期发现：心内膜细胞首先表达内皮细胞标志物，在之后的瓣膜发育成熟过程中，内皮细胞标志物表达减少直至最后消失，间质细胞标志物表达反倒增加。此外，EndMT在主动脉和肺动脉的发育过程中同样起到极其关键的作用。越来越多的研究[8-13]报道：EndMT参与心、肺、肾等重要器官纤维化，在心肌、血管及瓣膜重塑等方面发挥不可忽视的作用。

2 EndMT 引起 MF 的分子机制

EndMT引起MF是由多种因素诱导产生的，包括生长因子[14-16]、炎症细胞因子[17-19]、蛋白酶及多肽[20-23]等。上述因素虽不胜枚举，但其诱导EndMT的发生进而引起MF的过程相对一致。

2.1 TGF-β 信号转导途径

转化生长因子β(TGF-β)是一类多功能的蛋白超家族，在哺乳动物中存在TGF-β_1，TGF-β_2和TGF-β_3，起调节细胞生长、分化和凋亡等多种生理作用，参与维持内环境稳态，并修复受损组织等生理过程，同时TGF-β也参与心血管疾病[24]、癌症[25]和组织器官纤维化[26]等各种疾病的发生。

TGF-β在体内是以无活性的前体蛋白分泌出细胞，经血小板反应素、纤维蛋白溶酶、MMPs等激活后，TGF-β与TGF-β受体结合后引起后者磷酸化，继而特异性识别和磷酸化Smad蛋白；随后，存在于细胞质中的Smad2蛋白将信号由细胞膜传导至细胞核，调节目的基因的转录[27]。然而，大量研究表明[28-31]：TGF-β_2在EndMT中作为中心关键分子发挥功能。TGF-β_2诱导内皮细胞向间质细胞转化，内皮细胞标志物如claudin-5等的表达下降，间质细胞标志物如SMA，SM22α等的表达升高；且EndMT和上皮间质转化共用一个信号转导网络来调节内皮细胞和间质细胞标志物表达的变化。Chen等[15]证实：碱性成纤维生长因子(baseline fibroblast growth factor，bFGF)能够通过调节Let-7微小RNA的表达激活TGF-β信号，参与对EndMT的调节过程。利用HGF转基因小鼠、人冠状动脉内皮细胞和人心肌成纤维细胞。

2.2 Notch 信号转导途径

Notch信号通路参与多种心血管疾病、神经系统疾病、免疫功能调控及肿瘤、遗传性疾病等的发生发展过程[32-34]。当Notch受体与配体结合后，肿瘤坏死因子α-转化酶(tumor necrosis factor-α-converting enzyme，TACE)在细胞外酶解Notch受体，再由γ-分泌酶/早老素(presenilin-1)水解，释放Notch胞内段(notch intracellular domain，NICD)，转运至细胞核内，通过RAM区和ankyrin重复序列，与DNA结合蛋白相互作用，调控下游转录因子表达水平[35]。研究[36]证明：使用γ-分泌酶抑制剂(又称DAPT)阻断Notch通路后，α-SMA的表达量增加，引起内皮细胞向成纤维细胞分化。当激活Notch4或Notch1表达时，微血管内皮细胞(human microvascular endothelial cell，HMEC)发生明显的非TGF-β-Smad2依赖性EndMT，而Notch配体Jagged-1促进了上述作用[37]。松弛肽可通过增加

Notch1的表达抑制TGF-β诱导的EndMT，从而缓解MF并提高心功能[38]。高剂量葡萄糖可诱导Notch2的表达，从而促进人主动脉瓣内皮细胞的EndMT的发生，引起内皮钙黏蛋白和CD31表达下调，FSP-1和α-SMA表达上调，而过表达miR-18a-5p可以抑制Notch2的表达和EndMT的发生，提示miR-18a-5p/Notch2信号通路会是糖尿病性MF的新型潜力治疗靶点[39]。

2.3 Wnt 信号转导途径

Wnt蛋白是一种富含半胱氨酸残基的分泌型糖蛋白，由350~400个氨基酸组成，在多种组织和细胞中均有表达。Wnt蛋白Wnt信号转导途径激活的重要起始信号主要通过自分泌或旁分泌的方式激活膜受体进而发挥作用[40-41]。Wnt信号通路成员主要包括Wnt蛋白家族、Frizzled/低密度脂蛋白受体相关蛋白(low density lipoprotein receptor-related protein，LRP)等调控机体多种生理过程。Wnt-β-catenin通路是经典的Wnt信号转导途径，β-catenin通过形成E-cad/β-cat复合体参与细胞间的黏附，一旦β-catenin被磷酸化，E-cad/β-cat复合体的结构遭到破坏，细胞间的黏附力下降，从而介导细胞的转化过程[42-44]。

当没有Wnt信号时，β-catenin与细胞质中的结肠癌抑制因子(adenomatous polyposis coli，APC)、轴蛋白(Axin)和糖原合成酶激酶3β(glycogen synthase kinase 3β，GSK3β)相互作用，形成“APC-Axin-GSK3β”复合物，同时将β-catenin降解并保持较低水平，且不能进入细胞核内。当参与Wnt信号通路的受体蛋白Frizzled受体被Wnt配体激活后，引起LRP磷酸化，形成FZ/LRP复合物，随后胞质中的散乱蛋白(disheveled，Dsh)被募集到胞膜，使GSK3β磷酸化，进而导致“APC-Axin-GSK3β”复合物解体，抑制β-catenin降解，导致β-catenin在细胞质内大量聚集并进入细胞核。进入细胞核后β-catenin可激活T细胞因子/淋巴样增强因子，抑制其对组蛋白脱乙酰基酶抑制复合物的形成，从而解除对Wnt靶基因的抑制作用[42-44]。

研究[10]发现：在人类纤维化疾病的组织样本中，Wnt蛋白表达增加。急性心肌梗死时心外膜的Wnt1表达上调，梗死区成纤维细胞Wnt1表达也增加。在β-catenin基因敲除的小鼠胚胎模型[44]中，TGF-β诱导内皮细胞生成α-SMA阳性细胞的数量减少，TGF-β_2诱导EMT的过程中伴有β-catenin转录的激活，阻断β-catenin的转录可抑制TGF-β_1诱导EMT。Cheng等[45]研究发现：Wnt7b-Msx2可有效减少主动脉内皮细胞EndMT的发生，而DKK1通过ALK/Smad依赖性机制逆转上述效应，促进EndMT的发生，增强主动脉内皮细胞纤维化；小鼠心肌梗死4 d后，经典的Wnt通路激活，通过细胞谱系追踪的方式发现，α过细胞谱和Wnt双阳性间质细胞来源于发生EndMT的内皮细胞，这些细胞参与纤维化和疤痕组织的生成。这些发现为心肌梗死后的心肌修复提供了新的思路[5]。

3 EndMT 相关的 MF 治疗方式及研究前景

目前，血管紧张素转化酶抑制剂(angiotensin converting enzyme inhibitors，ACEI)及血管紧张素受体拮抗剂(angiotensin II receptor blockers，ARB)已被广泛应用于多种心血管疾病中。

Sepehri等[46]研究表明：洛沙坦可降低TGF-β表达，抑制I，III型胶原和纤连蛋白的合成。而TGF-β_1抑制剂曲尼司特通过抑制心肌细胞TGF-β_1的表达，阻止心肌梗死后心肌的纤维化进程和心肌成纤维细胞胶原蛋白合成[47]。Yu等[48]研究证明：ACEI类药物依那普利可通过阻断TGF-β信号转导通路，抑制由血管紧张素II诱导的成纤维细胞的增殖及细胞外基质沉积。非肽类蛋白酶抑制剂卡莫司他可阻止TGF-β_1的激活而发挥抗MF的作用[49]。曹蕾等[50]研究报道：3-羟基-3-甲基戊二酰辅酶A(HGM-CoA)还原酶抑制剂类调脂药物阿托伐他汀治疗高血压大鼠8周后，治疗组大鼠心肌内TGF-β_1 mRNA，Smad3 mRNA明显低于对照组，Smad7 mRNA明显高于对照组，说明阿托伐他汀可能是通过下调心肌TGF-β_1，Smad3和上调心肌Smad7改善高血压大鼠的心室重构。另外，中国传统医学在治疗MF方面也有确切的疗效。Fu等[51]研究发现：苦参中的主要成分氧化苦参碱可通过抑制TGF-β_1/Smad2，3，4来降低心肌成纤维细胞的增殖。

4 结语

MF是心脏重构的最主要表现之一，与心脏重塑与心脏收缩和舒张功能障碍密切相关，是导致心力衰竭发生的重要机制。因此预防和逆转MF进程是心血管诊治基础研究和临床应用研究的一个重要目标。目前已有多靶点药物用于治疗MF，但如何在毒副作用最小的情况下预防和治疗MF仍是现阶段亟待解决的问题。

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