·REVIEWS· ·综 述·

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转化生长因子β通路对血管再狭窄的影响及其机制

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[摘 要] 转化生长因子β(transforming growth factor-β，TGF-β)是血管再狭窄中重要的调控分子，在血管再狭窄的发生、发展中发挥关键作用。TGF-β是TGF-β超家族成员之一，可与TGF-β受体相结合，通过经典的依赖Smad蛋白通路或非经典通路将膜外信号转导到膜内，从而调控细胞的生长、增殖、分化和凋亡的过程。血管再狭窄至今仍是心脑及外周血管疾病中难以攻克的世界性难题之一，其发生、发展机制具有多样性和复杂性。预防术后血管再狭窄或延长血管通畅时间具有重要的临床意义。TGF-β通路在不同细胞类型中表现出多样性，探讨TGF-β在不同细胞类型中的作用及其对血管再狭窄的具体影响有助于为TGF-β与血管再狭窄的相关研究提供依据和策略。

[关键词] 转化生长因子β；血管再狭窄；血管平滑肌细胞；间充质细胞；间充质干细胞；内皮-间充质转化

Impact of the transforming growth factor-β pathway on vascular restenosis and its mechanism

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ABSTRACT As a crucial regulatory molecule in the context of vascular stenosis, transforming growth factor-β (TGF-β), plays a pivotal role in its initiation and progression. TGF-β, a member of the TGF-β superfamily, can bind to the TGF-β receptor and transduce extracellular to intracellular signals through canonical Smad dependent or noncanonical signaling pathways to regulate cell growth, proliferation, differentiation, and apoptosis. Restenosis remains one of the most challenging problems in cardiac, cerebral, and peripheral vascular

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disease worldwide. The mechanisms for occurrence and development of restenosis are diverse and complex. The TGF-β pathway exhibits diversity across various cell types. Hence, clarifying the specific roles of TGF-β within different cell types and its precise impact on vascular stenosis provides strategies for future research in the field of stenosis.

KEY WORDS transforming growth factor-β; vascular restenosis; vascular smooth muscle cell; interstitial cell; mesenchymal stem cell; endothelial-mesenchymal transition

血管再狭窄是一种常见的心血管疾病，其病理过程涉及多种细胞类型和复杂的信号转导网络。血管再狭窄通常发生在血管损伤、手术或动脉粥样硬化等情况下，导致血管管腔的狭窄和堵塞，严重威胁患者的健康[1]。明确其主要发病机制和影响因子十分重要。转化生长因子β(transforming growth factor-β，TGF-β)因在再狭窄组织中的高表达成为了研究的焦点之一[2]。TGF-β是一种多功能细胞因子，在细胞生物学过程中发挥关键作用[3]。然而，不同细胞类型对TGF-β的响应方式不同，这增加了TGF-β在血管再狭窄中作用的相关研究的复杂性。血管平滑肌细胞(vascular smooth muscle cell，VSMC)、内皮细胞、间充质细胞等多种细胞类型在血管再狭窄的发病机制中发挥关键作用，并且与TGF-β信号通路密切相关[4-8]。本文总结TGF-β在不同细胞类型中对血管再狭窄的调控机制，分析相关信号通路的激活方式，旨在为未来的研究提供有关血管再狭窄的发病机制和潜在治疗策略的相关依据。

1 TGF-β信号通路简介

1.1 TGF-β

TGF-β超家族主要由TGF-β、活化素、生长分化因子(growth differentiation factor，GDF)、抑制素、缪勒氏管抑制质(Müllerianinhibiting substance，MIS)和骨形成蛋白(bone morphogenetic protein，BMPs)等组成，具有调节细胞内环境平衡、胚胎发育、细胞分化、增殖、免疫监视、血管生成和凋亡等重要作用[3]。TGF-β有6种不同的亚型，TGF-β1~3主要在哺乳动物中表达，TGF-β4~6主要在禽类、两栖类及鱼类中表达。在人体中3种TGF-β亚型在不同部位表达情况不同：TGF-β1表达于上皮细胞、平滑肌细胞、造血细胞和成纤维细胞；TGF-β2表达于上皮细胞和神经元；TGF-β3主要表达于间充质细胞[9]。而存在于细胞内的TGF-β并非以活性形式释放到细胞外，需要与潜伏期相关肽(latency associated peptide，LAP)结合以非活化复合体的形式分泌，并且LAP可以与潜在转化生长因子β结合蛋白(latent transforming growth factor beta binding proteins，LTBP)共价键结合，从而形成潜伏三聚体。潜伏三聚体中的LTBP可被细胞外基质中蛋白酶所降解，从而使LAP与TGF-β解离，游离的TGF-β与TGF-β受体相结合发挥生理效应[10]。TGF-β受体根据所发挥的作用不同分为3类，即I型受体、II型受体和III型受体。在哺乳动物体内，已知有7种I型受体、5种II型受体和2种III型受体，其中2个I型受体(TGF-βRI)与2个II型受体(TGF-βRII)组合形成异四聚体，与TGF-β结合，从而激活下游的Smad蛋白，将膜外的生物信号转入膜内，进而调控细胞生长、增殖、分化及凋亡等过程[11-13]。

1.2 TGF-β信号通路

TGF-β与TGF-βRII结合后可以招募并磷酸化TGF-βRI，而磷酸化的TGF-βRI可以激活下游Smad蛋白家族。其中Smad家族按照功能的不同可以分为3个亚家族：1)受体相关型Smad(R-Smad)，包括Smad1、2、3、5和8。2)共同通路型Smad(Co-Smad)，即Smad4。3)抑制型Smad(I-Smad)，包括Smad6和Smad7。尽管Smad家族成员丰富，但不同的配体结合TGF-β受体后激活的Smad蛋白有所不同，如Smad1/5/8主要被MIS及BMP的信号所激活，而TGF-β主要激活Smad2和Smad3。激活的Smad2和Smad3被TGF-βRI磷酸化并从受体膜内侧解离，解离的Smad2/3与胞内的Smad4结合形成三聚体，并从胞内转移至核内，在核内与靶基因启动子区域的Smad结合元件(Smad-binding element，SBE)结合，调节靶基因的转录，这就是经典的依赖Smad蛋白通路[14]。此外，TGF-β也可通过不依赖Smad但依赖于特定细胞类型的信号通路来转导信号，如c-Jun氨基末端激酶(c-Jun N-terminal kinase，JNK)/p38、丝裂原活化蛋白激酶/细胞外调节蛋白激酶(mitogen-activated protein kinase/extracellular regulated protein kinases，MAPK/ERK)、Rho样GTPase和磷脂酰肌醇3激酶/蛋白激酶B(phosphoinositide 3-kinase，PI3K)/Akt信号通

路，可参与上皮-间充质转化(epithelial-mesenchymal transition，EMT)以及其他一些生理活动[15]。TGF-β信号通路在疾病中有不同的作用，这些信号通路的异常会导致不同疾病。如TGF-β/Smad通路既有抑制肿瘤的作用又有促进肿瘤发生的作用[16]。TGF-β/Smad信号通路通过抑制细胞增殖、维持组织结构、抑制基因组不稳定、诱导衰老和凋亡而发挥抑制肿瘤的作用；相反，许多晚期肿瘤失调会引起TGF-β信号通路过度表达，这可能在细胞基质区室(抑制免疫监视、增强血管生成)和癌细胞(诱导EMT、增强迁移和侵袭)中发挥促肿瘤作用，促进肿瘤的侵袭和转移[17]。

2 TGF-β信号通路与血管再狭窄

血管成形术和支架置入术是血管狭窄性疾病的有效治疗手段。从1977年首次使用普通球囊血管成形术到如今最新一代的药物洗脱支架和药物涂层球囊的出现，使得1年内血管再重建率从原先的40%降低到了现在的2%[18]。但术后并发症即血管再狭窄仍然是一个重要的临床问题，与内膜增生、血栓形成等密切相关。尽管目前已有研究[19-21]对TGF-β信号通路在不同细胞类型中的影响进行剖析，但尚未进行系统归纳，仍需进一步了解TGF-β信号在血管再狭窄中的作用。

2.1 TGF-β对平滑肌细胞的影响

VSMC是一种高度分化的细胞类型，大部分位于弹性动脉的中层。与大多数分化的细胞不同，VSMCs保持表型可塑性。在细胞因子、细胞外基质相互作用、损伤刺激和机械力作用下，VSMCs可以在分化(也称为“收缩”)状态和去分化(也称为“合成”)表型之间转化[22-23]。分化的VSMCs表型的特点是收缩基因表达水平高，增殖、迁移和细胞外基质合成率低。相反，去分化的VSMC增加了细胞外基质的产生、迁移和增殖的速率，以及减少收缩基因的表达。VSMC表型转化对解决血管损伤至关重要。损伤后，VSMC立即去分化以促进血管修复；一旦损伤得以解决，健康的VSMC恢复到非增殖、收缩的表型，从而维持正常的血管生理[24-25]。已有研究[26]表明：TGF-β可以促进VSMC向合成表型转化，可通过经典的依赖Smad蛋白通路诱导Smad2和Smad3蛋白磷酸化，磷酸化的Smad2可以作用于VSMC中*COL1A2*(collagen type I alpha 2 chain)基因，从而提高VSMC的I型胶原蛋白表达，磷酸化的Smad3可以促进神经纤毛蛋白2(neuropilin 2，NRP2)的上调。NRP2的表达增加可使VSMCs转变为促进内膜增生的表型，减少α-平滑肌肌动蛋白(α-smooth muscle actin，α-SMA)表达，包括增殖、迁移和去分化[27-28]。此外，TGF-β也可以通过Smad非依赖途径促进VSMCs的表型转化，如基质细胞衍生因子-1α/CXC趋化因子受体4，stromal cell-derived factor-1α/CXC chemokine receptor type 4，SDF-1α/CXCR4)通路可能通过激活ERK信号通路，帮助VSMC转化为合成表型[29]。TGF-β除诱导VSMCs发生表型转化外，还可通过诱导血小板衍生因子(platelet-derived growth factor，PDGF)-AA间接促进VSMC有丝分裂，与PDGF-BB协同促进VSMC的增殖[30]。TGF-β还可与成纤维细胞生长因子(fibroblast growth factor 2，FGF-2)和表皮细胞生长因子(epidermal growth factor，EGF)结合促进VSMC的DNA合成[31]。除了促进VSMC数目的增多，TGF-β还可通过上调$\alpha_v\beta_3$整合素的表达，增强VSMC从中膜向内膜迁移[32]。因此，TGF-β可以通过影响VSMC的表型转化、增殖和迁移能力，从而引起血管内膜增生及再狭窄发生。

2.2 TGF-β对间充质细胞的影响

存在于血管外膜的间充质细胞主要包括成纤维细胞和肌成纤维细胞，其中成纤维细胞表达成纤维细胞特异性蛋白1(fibroblast-specific protein，FSP-1)[33]，而肌成纤维细胞则通过FSP-1/α-SMA与波形蛋白的共表达从而在免疫组织学上与成纤维细胞进行区分[34]。正常情况下这2种细胞主要聚集在中膜外侧和外膜中，但当血管内部弹力层破坏时，在细胞因子的介导下，成纤维细胞和肌成纤维细胞可以迁移到新生内膜，此外来自血管内侧的内皮细胞也可以通过内皮-间充质转化(endothelial-mesenchymal transition，EndMT)生成肌成纤维细胞，一同分泌TGF-β[35-36]。研究[37]表明：在再狭窄的斑块中可见星状细胞、成纤维细胞和肌成纤维细胞的增殖增加；且与新生斑块相比，再狭窄产生的斑块中这些细胞的增殖和凋亡活性更强。TGF-β可通过诱导α-SMA的激活从而促进成纤维细胞向肌成纤维细胞的转分化，有助于细胞外基质(extracellular matrix，ECM)的合成[38]。并且在ECM中III型胶原的密度显著增加，而成熟型I型胶原密度降低，进而促进新生内膜增生及血管病理性重塑，导致血管再狭窄[37, 39]。

2.3 TGF-β对间充质干细胞的影响

间充质干细胞(mesenchymal stem cells，MSCs)是具有体外扩增、自我更新、低免疫原性和免疫调节特性的一类干细胞，在特定的条件下可以分化为多

种细胞。1970年，MSCs首次在骨髓中发现[40]，广泛存在于体内多种组织，如脂肪、滑膜、骨髓[41]和肺[42]等。因MSCs具有降低炎症水平、促进心肌细胞分化和血管生成、增加细胞抗凋亡及抗纤维化能力、提供心脏保护及防止心脏重塑能力，被广泛用于细胞移植来达到治疗心血管疾病[43-44]。血管成形术后引起的机械性损伤会引起局部的血管壁炎症，使得多种细胞因子和生长因子过度释放，其中包括PDGF-BB，这会导致平滑肌细胞的过度增殖、表型转换，从而引起新生内膜增生[45]。新生的内膜细胞高水平表达MSCs的标志物(巢蛋白[46]和CD29[47])，而MSCs可以通过旁分泌一氧化氮[48]、前列腺素E2[49]和肿瘤坏死因子-α刺激基因/蛋白6(tumor necrosis factor-α stimulated gene/protein 6，TSG-6)达到抑制炎症细胞因子[如白细胞介素-6、单核细胞趋化蛋白-1(monocyte chemoattractant protein-1，MCP-1)和细胞间黏附分子-1(intercellular adhesion molecule-1，ICAM-1)]转录的作用，并减少VSMC的增殖和迁移，从而限制新生内膜的过度增殖[50]。而TGF-β则可以动员MSCs从骨髓进入外周血，通过表达SDF-1α诱导MSCs的趋化和迁移至内膜损伤部位[51]，并刺激其增殖和分化为含有VSMC样和间充质样细胞表型的新内膜细胞，进一步加重细胞外基质沉积，从而形成新生内膜[47]。

2.4 TGF-β对内皮细胞的影响

内皮细胞在新生内膜增生中有重要作用。内皮细胞的损伤或破坏会导致内膜增生继而发生血管再狭窄。此外，在血管损伤过程中，内皮细胞可通过EndMT促进新生内膜的增殖，并可作为VSMC的来源。EndMT是EMT的一种特殊形式。内皮细胞可以通过EndMT失去其内皮特异性标志，如vWF、CD31，获得间充质标志物(α-SMA和钙调蛋白)，失去细胞-细胞连接，并获得侵袭性和移行性[52]。尽管EndMT是胚胎早期心脏发育、组织再生和伤口愈合的关键过程，但已有研究[53-54]表明：经历了EndMT的内皮细胞是肌成纤维细胞的重要来源，从而导致支架内再狭窄和血管纤维化。并且内皮细胞分泌TGF-β1可以通过激活Notch信号通路从而诱导EndMT产生[52]。此外，同种异体移植血管的内皮细胞凋亡可以分泌TGF-β1诱导Smad3、PI3K/Akt/mTOR和MAPK/ERK信号通路激活，抑制内皮细胞的上皮标志物表达和调节细胞生长及迁移，从而促进EndMT发生，导致移植物的内膜新生和动脉硬化，引起血管再狭窄[55]。

3 TGF-β的调节作用

TGF-β是一种强大的多功能调节因子，可调节多种血管细胞的活动，包括平滑肌细胞的增殖和细胞外基质的分泌、外膜成纤维细胞表型转化等。活性的TGF-β通过与TGF-βRII结合，启动细胞信号的转导，然后招募并磷酸化TGF-βRI，引起胞内段TGF-βRI上的丝氨酸-苏氨酸激酶激活，进而促进Smad2/3的磷酸化。磷酸化的Smad2和Smad3与Smad4形成复合体并进入细胞核，该复合体通过与转录因子相互作用或直接与DNA结合来调节基因的表达，这就是TGF-β经典的依赖Smad通路[56]。而有研究[57]表明在再狭窄组织中3种不同亚型的TGF-β均表达上调。TGF-β作为一个体内重要的细胞因子，由不同的细胞分泌，作用于构成血管的不同细胞，从而修复受损的血管，或者引起血管内膜过度增生(图1)。狭窄的血管接受血管成型术或支架置入术后所期望的是使血管成形术过程中受损的内皮修复或者置入的支架内层形成内皮化，适应宿主的血管生理情况。此时TGF-β可发挥以下重要的功能：1)TGF-β可通过Smad依赖及非依赖途径促进平滑肌细胞表型转换，增强其迁移能力，使平滑肌细胞从中膜迁移入受损的内膜，促进其增殖和分泌的功能，使受损的内膜中细胞成分和基质成分增加，促进内膜修复。2)TGF-β还可作用于间充质细胞，使成纤维细胞向肌成纤维细胞转分化，从而促进细胞外基质的合成，促进血管重塑。3)TGF-β通过骨髓动员MSCs，并募集其黏附在受损的血管壁上，刺激其转分化为VSMC样和间充质样的新内膜细胞，分泌细胞外基质，促进内膜新生。4)TGF-β在内皮细胞的EndMT发生、发展中起关键作用，可抑制内皮细胞上皮标志物的表达，促进其迁移和增殖，从而促进新生内膜生成。然而，TGF-β过度释放可过度激活体内自适应的过程，会导致血管发生病理性重塑，引起血管再发狭窄。

4 结语与展望

TGF-β在不同细胞类型中的作用仍需要进一步研究和探索。尽管TGF-β在血管内再狭窄中起着重要作用，但在血管成形术或支架置入术的初期阶段，其过度释放可过度激活体内自适应的过程从而导致血管发生病理性重塑不容忽视。因此，能否使TGF-β在手术后的初期维持一个有效水平，并在此后快速代谢从而维持一个较低水平是更需要解决的一个问题。TGF-β介导的血管再狭窄的发生、发展机制十分

复杂，针对其中经典的依赖Smad蛋白通路研究较丰富，在再狭窄的发生、发展过程中TGF-β非经典通路的作用正在逐渐被重视，因此TGF-β非经典通路是一个有研究价值的方向。TGF-β在血管再狭窄领域中仍有广泛的研究空间，而其中最重要的是如何将研究的结果转化为临床上治疗的手段，这是今后研究所需要攻克的重点及难点。

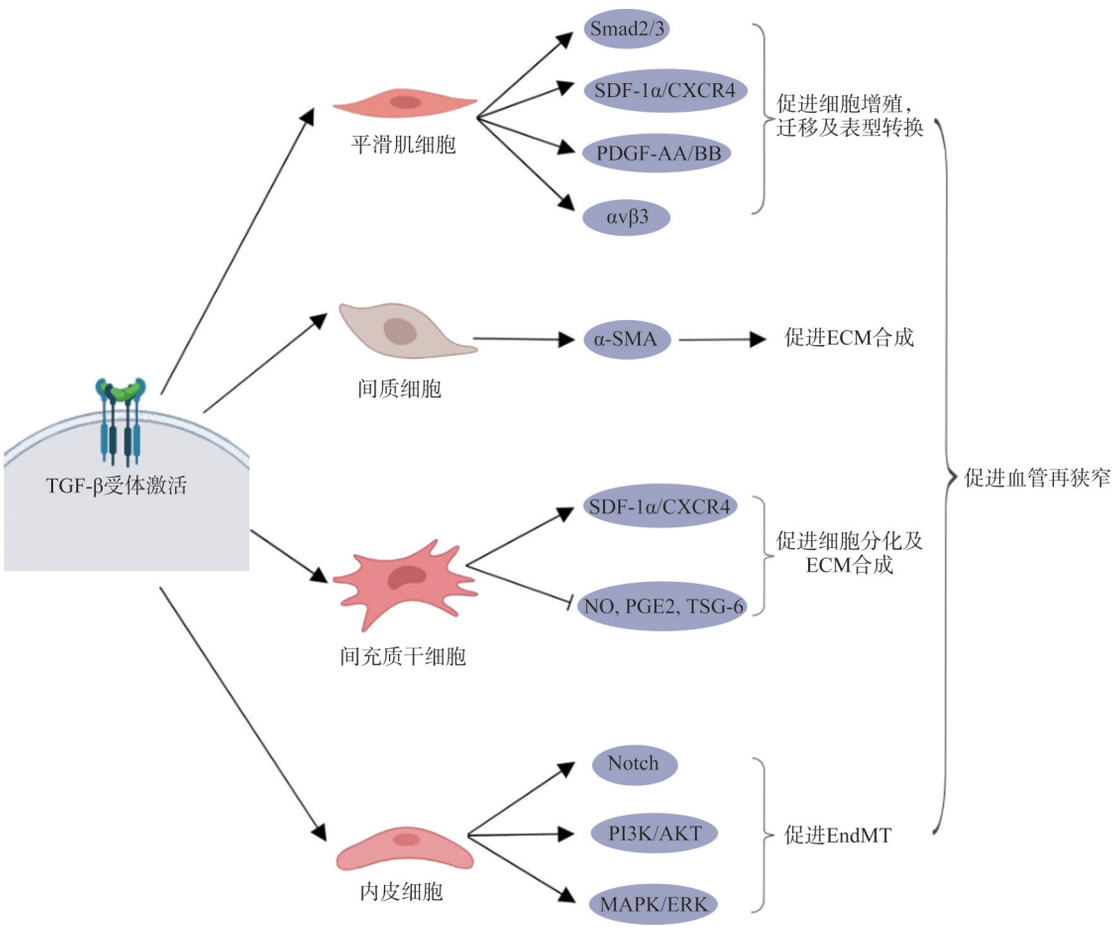

图1 TGF-β通路在不同细胞中引发再狭窄的作用机制

Figure 1 Mechanism of TGF-β pathway inducing restenosis in different cell types

TGF-β: Transforming growth factor-β; SDF-1α/CXCR4: Stromal cell-derived factor-1α/CXC chemokine receptor type 4; PDGF-AA/BB: Platelet derived growth factor-AA/BB; α-SMA: α-Smooth muscle actin; NO: Nitric oxide; PGE2: Prostaglandin E2; TSG-6: Tumor necrosis factor stimulated gene-6; PI3K: Phosphoinositide 3-kinase; MAPK/ERK: Mitogen-activated protein kinase/extracellular regulated protein kinases; ECM: Extracellular matrix; EndMT: Endothelial mesenchymal transition.

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