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血管平滑肌细胞凋亡在血管再狭窄中作用的研究进展

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[摘 要] 血管平滑肌细胞构成新生内膜增生的重要部分，且在血管腔内治疗术后再狭窄的心血管疾病的发生和发展中具有重要作用。血管平滑肌细胞凋亡能有效抑制血管球囊损伤和血管旁路移植术后新生内膜增生，从而可为血管术后再狭窄提供治疗手段。

[关键词] 血管平滑肌细胞；血管再狭窄；凋亡

Role of vascular smooth muscle cell apoptosis in vascular restenosis

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Abstract Vascular smooth muscle cell is an important cell component of neointimal hyperplasia and plays a crucial role in the development and progression of vascular restenosis, which usually results from balloon angioplasty, stenting and other vascular diseases. Vascular smooth muscle cell apoptosis can effectively reduce vascular restenosis and in turn to inhibit neointimal hyperplasia, which may provide a way to treat vascular restenosis.

Key words vascular smooth muscle cell; vascular restenosis; apoptosis

经皮血管腔内治疗术后出现的血管再狭窄(restenosis，RS)问题严重影响着患者的远期通畅率及生活质量，术后6月RS率36.8%，12月RS率达到53.3%[1]。因此，如何解决RS问题已经成为广大血管外科医生共同关注的临床难题。近年来认为血管平滑肌细胞(vascular smooth muscle cell，VSMC)凋亡在血管重构、动脉硬化、血管成形术后RS中起着重要作用[2]。本文主要对VSMC凋亡在RS中的作用机制及治疗新进展进行综述。

1 RS机制

血管腔内径小于原先的50%称血管狭窄[3]。而引起血管狭窄最常见的原因是血管动脉硬化。RS的本质为在动脉硬化病变基础上对血管壁内皮损

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伤发生适应反应，从而导致管腔狭窄的表现[4]。RS病理表现是新生血管内皮细胞表型改变、细胞外基质聚集和纤维化、VSMC增殖及凋亡。新生内膜增生是RS机制中重要的环节，球囊扩张对血管壁的直接损伤、损伤后的低血流动力学状态均会导致新生内膜增生。而导致新生内膜增生的重要原因是由于VSMC增殖及伴随着的VSMC凋亡不足[5]。糖尿病、高血压病、高脂血症病人中RS发生率较高，因此RS产生的机制在不同病人中存在差异[2]。

2 VSMC凋亡与RS

VSMC的凋亡贯穿整个血管形成、损伤后重构，是造成动脉粥样硬化、血管再阻塞及高血压的重要病理变化的原因[6]，并在血管结构及功能上起着决定性作用。促凋亡与抗凋亡两种途径的不平衡，是新生内膜形成的细胞学基础，因而VSMC凋亡的相对不足是RS发生的重要原因之一[7]。凋亡可以减少细胞整体数量，进而减轻内膜增生，所以促进VSMC凋亡是治疗血管球囊扩张术后RS的重要手段。最近有研究[8]表明：凋亡可减少过度增殖的VSMC，从而能够有效保护血管受损伤后RS问题。当动物体内特别是局部血管受到外来应激刺激时，会诱导VSMC凋亡；而细胞的凋亡受多种信号途径介导，不同信号通路介导的VSMC凋亡均能有效延缓血管术后RS的发生，尤其重要的是I型跨膜蛋白Fas与线粒体这两条信号途径。

2.1 Fas途径介导的VSMC凋亡可延缓RS

当死亡信息传递到细胞膜表面的时候，配体会与细胞膜表面凋亡信息受体结合，然后以这个死亡受体作为起始点，介导诱发一连串反应的途径，称为死亡受体启动途径，又称Fas途径。一般来讲，Fas凋亡途径作用比较短暂、直接、迅速[9]。Knapp等[10]研究发现：正常情况下VSMC 对Fas 和细胞因子诱导的凋亡有一定抵抗能力，但在动脉硬化中，Fas 广泛表达于VSMC，并促进细胞凋亡。有研究表明玉米苞叶可能通过上调Fas，Fas的配体(Fas-L)和半胱氨酸天冬氨酸蛋白酶3 (caspase-3)基因表达，启动凋亡途径的级联反应，促进过度增殖的VSMC 凋亡，从而有效延缓RS。实验[11]证实：大鼠行球囊扩张手术后，在颈总动脉通过腺病毒载体局部过表达Fas-L后，会导致VSMC凋亡增多，VSMC增殖减少，从而抑制内膜增厚。

2.2 线粒体信号途径介导的VSMC可改善术后RS

VSMC凋亡由细胞内部的粒线体所发动，有别于依赖细胞外的受体信息传递模式，称线粒体途径。一旦线粒体接收到死亡讯息的时候，其膜的通透性会上升，释放出诸多物质可直接或间接地诱发细胞凋亡。损伤后的血管也可以通过内因式线粒体凋亡途径引起VSMC凋亡[12]。有报道[13-14]称层流剪切力可通过磷酸化Akt [又称蛋白激酶B(protein kinase B，PKB)]，继而经线粒体途径诱导VSMC凋亡，改善术后新生内膜增生。另外，NO亦可以通过线粒体途径促进VSMC凋亡，延缓RS的发生[15]。

2.3 MAPK途径介导的VSMC凋亡可抑制RS发生

丝裂原活化蛋白激酶(mitogen activated protein kinase pathway，MAPK)信息转导路径也参与VSMC凋亡。 MAPK路径转导区分为三条：1) 细胞外信号调节激酶(extracellular signald regulated kinase，ERK)通路，此路径主要是负责细胞生长与分化；2) p38MAPK通路和ERK5/大丝裂素活化蛋白激酶1 (big MAP kinase1，BMK1)通路；3)c-Jun氨基末端激酶(c-Jun N-terminal kinase，JNK)/应激活化蛋白激酶(stress-activated protein kinase，SAPK)通路，后面两条路径则和VSMC凋亡有较大的关联性。VSMC凋亡还可以由环境压力介导的 JNK 及 p38 MAPK 增多而触发，然而它们的酶抑制剂能够抑制压力所致的VSMC凋亡[16]。许多研究[17]表明，JNK/p38途径在促VSMC 凋亡过程中具有重要作用。Sotoudeh等[18]报道：予以循环中机械牵拉刺激，同时持续激活JNK和p38，可导致猪的VSMC凋亡增强。体外实验[19]表明：机械牵拉刺激能够激活ras/rac/p38 信号途径和p38 磷酸化途径，这也是机械应力导致凋亡的主要原因。 生物学应力研究[20]证实：P38/JNK的活化可增加大鼠静脉移植物术后VSMC凋亡，有效抑制术后RS。Han等[21]发现：血管受损伤后，腺病毒E1A基因刺激的细胞抑制基因(cAMP-response element binding protein，CREG)可通过p38/JNK 信号途径调节VSMC凋亡。无独有偶，α-硫辛酸亦可通过p38MAPK途径促进VSMC凋亡，抑制内膜增生[22]。

2.4 MiRNA促进VSMC凋亡可减轻RS

已知人类有1 500 不同 miRNAs，调节着30%的基因[23]。近来研究热点集中在miRNAs参与VSMC的增殖、分化及凋亡的作用。大部分miRNA

在内膜形成过程中促进VSMC分化及凋亡，在动脉硬化及RS中，这些miRNA的过表达可导致VSMC凋亡[24]。研究[25]证实：过表达miR145及miR143能够充分促进VSMC的分化及凋亡，抑制其增殖；相反，缺乏miR145或miR143会减轻凋亡；Ji等[26]在颈动脉球囊损伤的大鼠和体外培养的去分化的VSMC中均发现miR21水平明显升高，而miR21反义寡核苷酸可明显降低VSMC的增殖，促进其凋亡，减轻血管损伤后的RS程度。进一步的研究[27]发现，这种作用与类脂磷酸酶PTEN(phosphatas andtensinhomolog deleted onchromosome ten)表达水平增加和Bcl2表达水平减弱有关；球囊损伤后，在血管平滑肌中过表达的miR-195可通过抑制Cdc42(cell division cycle 42)、周期素D1(cyclin D1)和成纤维细胞生长因子-1的表达，进而促进其凋亡，最终有效限制内膜形成。

3 VSMC凋亡与RS的治疗

随着对VSMC凋亡在RS中的重要作用的认识及研究，一些治疗方法现正在广泛应用于临床或临床前期，包括药物治疗、基因治疗、药物洗脱支架治疗。

3.1 药物治疗

目前已经发现有多种西药可通过调节VSMC凋亡途径，进而改善血管新生内膜增生。如糖尿病大鼠的颈动脉球囊扩张实验表明：曲美他嗪治疗组能够减少活性氧(reactive oxygen species，ROS)产物生成，促进VSMC凋亡，缓解内膜增生[28]。还有实验发现：旋覆花内酯能够抑制ERK1/2的磷酸化，使细胞周期停留在G_1期，加快细胞凋亡。给予大鼠血管球囊扩张后，发现术后14 d旋覆花内酯处理组颈动脉VSMC凋亡明显增加，内膜增生较手术组明显减轻[29]。另外，有研究表明匹伐他汀的浓缩物在氧化应激所致人VSMC的凋亡中起着重要作用，其通过持续激活JNK和p38 MAPK来增强H_2O_2所致VSMC凋亡，延缓RS[30]。此外，近年来随着对中药研究的深入，一些具有促VSMC凋亡的中药逐渐被人们发现，如姜黄素类合成物HO-3867[(3E，5E)-3, 5-bis[(4-fluorophenyl)methylidene]-1-[(1-hydroxy-2, 2, 5, 5-tetramethyl-2, 5-dihydro-1H-pyrrol-3-yl)methyl] piperidin-4-one)]可通过上调PTEN表达，抑制ERK1/2和MMPs(matrix-metallo preoteinases)的表达，促进VSMC凋亡，抑制VSMC生长，在颈动脉球囊损伤后其能够有效减轻术后RS问题[31]。在大黄素[32]、厚朴[33]经血管内注入球囊扩张手术后的大鼠颈动脉中也发现，VSMC凋亡增加，能够明显减轻RS。有趣的是，另有报道[34]称激素亦可治疗RS：脱氢表雄酮作为一种甾体类激素，不仅能够减少细胞增殖，并且能够促使增殖细胞凋亡，在颈动脉球囊损伤后，其能够抑制Akt轴的活化，通过促进VSMC的凋亡减轻球囊损伤后新生内膜增生。血管紧张素1~7亦能够明显减轻球囊损伤后的RS，其作用与血浆sFas峰浓度提前，抑制VSMC过度增殖和促进过度增殖的凋亡有关，并且不依赖血浆中血管紧张素2的浓度[35]。

3.2 基因治疗

运用转基因技术，通过载体高表达促VSMC凋亡蛋白，能明显减少内膜增生。基因治疗的关键是选择合适载体及特异的靶基因[36]。目前腺病毒[27]、反转录病毒、脂质体等载体在体内及体外实验中广泛应用于基因的转移[37]。慢病毒作为反转录病毒的亚类，具有优于其它载体之处：它能够易感于分化及未分化细胞，并能够维持基因稳定运用及长久表达，且无细胞毒性及免疫反应；因而可以运用于心血管中[38]。而在靶基因方面，特异性强且在体内试验已证实能通过增加凋亡抑制血管损伤后内膜增厚的靶基因有氧化还原因子1[39](redox factor-1，Ref-1)，NOS[40]，p53[41]，组织因子途径抑制基因[7](tissue factor pathway inhibitor gene，TFPIG)，环腺苷酸反应部位结合蛋白[42](cAMP-response element binding protein binding protein，CBP)等。其中CBP是一种转录因子，不同于NOS和p53，尽管它们都在球囊损伤后的RS中起作用，但后两者只能调节血管球囊损伤后某一个因素，前者确能够影响多种信号转导通路；血管损伤后基因靶向CBP-siRNA慢病毒表达的载体研究[42]发现：CBP能促进VSMC凋亡，明显减轻RS。靶向STAT4-siRNA (signal transducer and transcription-siRNA)[43]慢病毒表达载体也能有效促进血管球囊扩张术后大鼠VSMC凋亡，抑制新生内膜增生。

3.3 药物洗脱支架治疗

血管腔内支架可以有效地治疗血管狭窄及RS，目前已广泛使用于临床中。使用药物涂层支架的病例，其RS的发生率明显低于使用裸支架

的病例[44]。最常见的涂层的药物是紫杉醇及雷帕霉素，雷帕霉素与紫杉醇都能够通过影响p27及p53，使VSMC停留在细胞周期某一期，促进损伤后VSMC凋亡，抑制内膜增生；另外作为涂层药物它们具有亲脂性，能够较易穿过细胞膜从而被细胞快速吸收[45]。在活体动物中已证实，与手术组相比较，使用雷帕霉素支架组50%RS可得到改善[46]。

4 展 望

VSMC凋亡不仅是动脉硬化的重要病理过程，更是腔内血管治疗术后RS不可忽视的一个因素。血管损伤后，尤其是球囊扩张后，VSMC凋亡贯穿整个血管修复过程，且在术后RS中占有重要地位，因此充分了解促进VSMC凋亡的因素及作用机制，可以寻找有效的作用靶点以促进VSMC凋亡，可以有效改善术后患者远期通畅率及提高生活质量。尽管现在有许多关于促进VSMC凋亡靶点的药物治疗、基因治疗应用于临床前期和临床上，但是寻找更加安全、有效、特异性强的药物仍显得格外重要。

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