综　述

颅内动脉瘤发生发展中的炎症反应及信号通路研究进展

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[摘要]　颅内动脉瘤(IA)是一种常见的血管异常，其特点为颅内动脉血管膨胀，常导致脑血管破裂，引起蛛网膜下腔出血(SAH)，造成严重的后果。研究发现，除遗传因素外，由血流动力学改变诱发的炎症反应在IA的形成和破裂过程中也起着关键作用。血管炎症可引发一系列生化反应，涉及多种细胞，包括血管平滑肌细胞、巨噬细胞、淋巴细胞、肥大细胞和中性粒细胞，并涉及多种信号传导途径，包括PGE2-EP2-NF-κB、JAK/STAT3/NF-κB、PI3K/Akt(PKB)及AMPK/ACC信号传导途径。目前IA的具体发病机制尚不明确，且针对IA发病机制的免疫疗法仍处于基础研究阶段，临床并未广泛应用。本文综述了IA发生发展过程中涉及的细胞、细胞因子及信号通路，旨在探讨IA发生发展的病理及病理生理学机制，为IA免疫治疗药物的开发提供参考。

[关键词]　颅内动脉瘤；炎症反应；细胞凋亡；病理学；病理生理学

Research advances in the inflammatory responses and signaling pathways in the development and progression of intracranial aneurysms

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[**Abstract**]　Intracranial aneurysm (IA), characterized by distended blood vessels within the arteries, is a common vascular anomaly that frequently leads to cerebral blood vessel rupture, causing subarachnoid hemorrhage (SAH) with serious consequences. It has been found that, in addition to genetic factors, inflammatory responses induced by altered hemodynamics play a key role in the formation and rupture of IA. Subsequently, vascular inflammation can trigger a series of biochemical responses involving a variety of cells, including vascular smooth muscle cells, macrophages, lymphocytes, mast cells, and neutrophils, and involving several signaling pathways, including the PGE2-EP2-NF-κB signaling pathway, the JAK/STAT3/NF-κB signaling pathway, PI3K/Akt (PKB) signaling pathway, and AMPK/ACC signaling pathway. However, no clear conclusions have been made regarding the specific pathogenesis of IA, and immunotherapies targeting the pathogenesis of IA are still under basic research and not widely used in clinical practice. This review describes the cells, cytokines, and signaling pathways involved in the development of IA, in the hope that it will contribute to the understanding of the pathogenesis of IA and inspire the development and use of immunological drugs.

[**Key words**]　intracranial aneurysm; inflammatory response; apoptosis; pathology; pathophysiology

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颅内动脉瘤(IA)的形成涉及复杂的病理生理学过程，除遗传因素(如Ehlers-Danlos综合征、Loeys-Dietz综合征、马方综合征、神经纤维瘤病1型)外[1]，其与血流动力学改变引发的内皮炎症反应也明显相关[2]，脑动脉血流动力学的变化可触发血管壁的长期过度炎症反应，从而导致IA的形成、生长及破裂[3]。这种慢性炎症涉及单核/巨噬细胞的浸润，炎性因子和相关蛋白酶如基质金属蛋白酶(MMP)的释放，从而诱导血管壁细胞死亡及细胞外基质(ECM)破坏[4]。伴随着IA的生长，动脉瘤壁内巨噬细胞数量增加，而广泛的巨噬细胞浸润可使ECM降解增强，最终增加IA破裂的风险。T细胞、肥大细胞和体液反应同样参与了IA的形成[3]。Santarosa等[5]使用高分辨率血管壁磁共振成像(VW-MRI)观察到了IA血管壁中的炎性细胞浸润，证实炎症参与了IA的形成。随着炎性细胞浸润及内皮功能障碍的加重，核因子κB(NF-κB)激活，白细胞介素-1β(IL-1β)表达增加，肿瘤坏死因子-α(TNF-α)水平升高[6]，随后，NF-κB介导产生的一氧化氮(NO)与促炎介质、活性氧(ROS)、细胞因子及细胞黏附分子(CAM)攻击内皮细胞、ECM和血管平滑肌细胞(VSMC)，进一步引起内皮损伤、VSMC表型转换、ECM重塑，以及Fas介导的细胞凋亡，增加了动脉瘤破裂的可能性。本文主要阐述了IA发生发展过程中涉及的细胞、细胞因子及信号通路，旨在探讨IA发生发展的病理及病理生理学机制，为IA免疫治疗药物的开发提供参考。

1 正常颅内动脉

颅内动脉由内膜、中膜和外膜三层组成。内膜为面向血管腔并与血流直接接触的最内层，由单层内皮细胞和内皮下ECM组成；糖蛋白、蛋白多糖和弹性蛋白沉积到ECM中，形成将内膜与中膜分开的内弹性层。中膜主要由平滑肌细胞组成，其ECM主要包含Ⅲ型胶原蛋白。外膜为最外层，由Ⅰ型胶原纤维、弹性蛋白、神经纤维和成纤维细胞构成。值得注意的是，颅内动脉中不存在将动脉中膜与外膜分开的外弹性层(EEL)，这可能使颅内动脉更容易受到血流动力学压力的影响[7]。VSMC是血管中膜中的一种重要细胞类型，在维持脑血管系统的完整性方面发挥着重要作用。与颅外动脉相比，颅内动脉的中膜是构成动脉壁的最主要部分，而外膜弹性纤维较为稀疏，因而更易发生动脉瘤[8]。颅内动脉壁对机械拉伸的抵抗几乎完全由内弹性层与胶原纤维承担[9]。内弹性层在血压升高时可发生扩张，而胶原纤维几乎无延展性，仅靠曲张程度维持血管张力[10]，当动脉瘤发生时，内弹性层丧失，外膜胶原纤维则承担了主要的血流压力，并致使胶原纤维曲张程度降低，血管弹性降低，从而容易发生破裂[11]。

2 血流动力学改变

血流壁剪切应力(WSS)可引起内皮细胞破坏及功能障碍，随后，血管炎症可引发一系列生化反应，导致VSMC凋亡和迁移，使脑血管壁弹性进一步减弱，从而更加无法适应血流动力改变[12]。动脉瘤壁上的胶原纤维重塑是根据血流和内皮细胞层感受到的WSS而定向发生的。异常的WSS可致内皮细胞损伤，并通过单核细胞趋化蛋白-1(MCP-1)将巨噬细胞募集至高WSS部位。巨噬细胞浸润可使MMP-2、MMP-9表达升高，破坏内弹性层，并促进胶原蛋白重塑和VSMC增殖[13]，而对IA的生长来说，胶原蛋白重塑和VSMC增殖是必不可少的。一旦失去弹性层，这种胶原蛋白的重塑决定了动脉瘤壁的强度，也决定了动脉瘤破裂的可能性。随着炎性细胞浸润、多种细胞因子和炎性因子释放，血管壁逐渐退化，最终使IA进展并破裂。

3 细胞学改变

3.1 内皮细胞 内皮细胞可通过血管壁和血流之间的屏障功能防止管腔血栓形成。IA的一个早期特征是内皮细胞的功能障碍和退化[14]。血管壁损伤会刺激内皮祖细胞(EPC)[15]的释放。与健康对照组相比，有血管疾病风险的患者其循环EPC减少，内皮细胞衰老增加，血管壁的修复能力降低[16]。Wang等[17]发现，内皮细胞出现大量凋亡时，内皮型一氧化氮合酶(eNOS)的表达可减少或缺失，进而降低一氧化氮(NO)的生物利用度，而NO是维持血管张力、调节血压稳定的重要物质。然而，此时VSMC产生大量诱导型一氧化氮合酶(iNOS)，生成大量的NO自由基，进一步损伤血管壁。有动物实验证实，iNOS基因敲除小鼠的VSMC凋亡减少，IA的发生率降低，提示iNOS是动脉瘤的重要保护因素[18]。内皮细胞分泌的MCP-1是动脉瘤形成的另一个重要影响因素。NF-κB可通过与MCP-1基因上的两个位点结合，上调内皮细胞中MCP-1的表达，后者表达升高可致血管壁的巨噬细胞和单核细胞浸润，而浸润的巨噬细胞可进一步分泌MCP-1，使其产生自我放大回路，进一步导致VSMC和ECM的降解，促进动脉瘤的发展[19]。在MCP-1基因敲除小鼠中，MMP的表达水平及动脉瘤形成的发生率明显降低[20]。有研究发现，IA样本和IA患者血液中的肝细胞生长因子(HGF)浓度较高，而HGF可降低内皮细胞中血管细胞黏附分子-1(VCAM-1)和E-选择素的表达水平，产生防止血管炎症发生的效应[21]。Kim

等[22]发现，Yes相关蛋白(YAP)可通过调节肌动蛋白及内皮细胞的代谢活性而在血管生成中发挥重要作用，若内皮特异性缺失YAP/盘状同源区域结合基序(Taz)将导致内皮屏障完整性降低。

3.2 VSMC VSMC主要集中在血管壁中层，产生血管壁的主要成分ECM。VSMC存在几种不同的表型，最常见的是收缩型，这是一种高度特化的收缩细胞，其主要功能是维持正常血管形态。在动脉瘤形成过程中，TNF-α在VSMC的表型调节中起关键作用。TNF-α可抑制VSMC的收缩表型，诱导促炎基因及基质重塑基因(如MMP、VCAM-1、MCP-1和IL-1β)的表达增加[23]。TNF-α对VSMC表型的调节与Kruppel样因子4(KLF4)的表达增加有关，抑制KLF4可减少炎症基因的表达[24]。一系列研究表明，过氧化物酶体增殖物激活受体(PPAR)家族成员PPARγ及PPARβ/δ主要调节血管细胞增殖和血管炎症[25-27]。Shimada等[25]发现，VSMC中PPARγ的功能受到抑制后，TNF-α、MCP-1、趋化因子C-X-C配体1(chemokine C-X-C ligand 1，CXCL1)、MMP-3和MMP-9的基因表达增强，可使IA的发生率和破裂率增高。在病理状态下，受炎症反应因子(如NF-κB、TNF-α、IL-1β和氧自由基)的影响，VSMC可分泌MMP来参与ECM的重塑；而在生理状态下，MMP的表达有限，并以无活性的酶原形式存在。总体来说，VSMC的表型调控与动脉瘤壁的重塑及动脉瘤破裂的机制密切相关。

有研究证实，在IA的形成过程中存在VSMC的凋亡[28]。VSMC凋亡的两个主要原因是血流动力学改变和炎症刺激。体外实验结果表明，机械应力增加可诱导培养基内VSMC的凋亡[29]。循环张力增加可上调p53蛋白的表达并增强其转录活性，从而导致VSMC凋亡增加。同时，机械应力也会增加钙蛋白酶的活性，进而降解p53来抵消过度的VSMC凋亡，而抑制钙蛋白酶的活性后，p53的表达增强，则可导致VSMC的凋亡率进一步增高[29]。炎性细胞因子如IL-1β、IFN-γ和iNOS也有助于VSMC的凋亡。Moriwaki等[30]发现，在IA形成的早期阶段，动物模型的血管介质中即可检测到IL-1β。与野生型小鼠相比，IL-1β$^{-/-}$小鼠的凋亡细胞数量明显减少，caspase-1表达增加。同样，Sadamasa等[18]发现，与iNOS$^{-/-}$组相比，iNOS$^{+/+}$组中VSMC的凋亡数量增多，IA也明显增大。也有研究认为，导致VSMC凋亡的炎症反应也可通过氧化应激启动[31]。

3.3 巨噬细胞 巨噬细胞介导的免疫反应可促进IA的发展。循环单核细胞在炎症期间可浸润血管，并发展为巨噬细胞，从而调节免疫反应[32]。巨噬细胞通常极化为M1或M2表型，M1和M2型细胞的功能不同，其中M1型为促炎细胞，而M2型则参与炎症消退和组织修复[33]。M1型巨噬细胞通过释放MMP尤其是MMP-2和MMP-9，在血管重塑中发挥关键作用[34]。由于血流量增大，对内皮的机械应力增加，导致内皮细胞紧密连接减弱，M1型巨噬细胞在MCP-1的作用下可迁移至血管壁[35]。浸润的M1型巨噬细胞可释放促炎细胞因子如TNF-α、IL-1和IL-6以进一步募集巨噬细胞，放大炎症反应[36]。除细胞因子外，M1型巨噬细胞还可释放MMP、降解ECM，并可一定程度上重塑血管[37]。在脑动脉平滑肌细胞PPARγ(-/-)小鼠中观察到单核/巨噬细胞标志物CD68表达水平升高，同时CXCL1、MCP-1、TNF-α表达上调，使小鼠动脉瘤形成和破裂的发生率明显增高[38]。抑制巨噬细胞在IA血管壁中的募集和积累，可明显降低动物模型中IA的发生率和大小[39]。有研究发现，在MCP-1敲除小鼠中巨噬细胞募集减少，炎症反应明显减轻，且MMP-2和MMP-9的表达水平也明显降低[37]。以上研究均证实，巨噬细胞在IA的发生发展中发挥了重要作用。

3.4 淋巴细胞 已有研究发现，在IA患者的瘤壁和外周血管中存在淋巴细胞，提示此类型的细胞可能参与了IA的发生机制，但目前尚不清楚淋巴细胞是否直接参与了IA的进展及破裂。为此，Sawyer等[40]研究了淋巴细胞缺失型小鼠与野生型小鼠IA模型，结果显示淋巴细胞缺失组小鼠中IA的形成、破裂较野生型小鼠明显减少，且IL-6、MMP-2、MMP-9和平滑肌肌球蛋白重链(SM-MHC)水平较野生型小鼠明显降低，但两组巨噬细胞的浸润无明显差异，推测淋巴细胞可通过降解ECM和重塑血管而参与动脉瘤的形成。此外，对IA患者外周血的研究发现，其$CD4^+$ T细胞的比例异常，并伴有不平衡特征，如Th-1、Th-17表达增强，Th-2、Treg表达降低，而$CD4^+$ T细胞亚群的不平衡可能通过正反馈环路加重IA的炎症状态[41]。但Miyata等[42]发现，虽然在IA血管壁上可检测到T细胞存在，但其并未影响动脉壁的退行性改变、巨噬细胞浸润及IA的形成和进展。

目前，人类T细胞是否参与IA的形成仍未得到具体验证，有研究在破裂的IA中发现存在TNF-α而缺乏IL-10，提示Th-1细胞或细胞毒性T细胞(Tc)反应占主要地位[43]。由Th-1、Tc和活化的巨噬细胞产生的γ干扰素(IFN-γ)可抑制SMC增殖和胶原蛋白重塑，并与IL-1β和TNF-α共同诱导几种白细胞黏附分子的表达[44]。同时，Jayaraman等[45]发现了无活性且被抑制的Th-2。Th-1产生的细胞因子可抑制Th-2，反之，Th-2也可抑制Th-1；Th-1与Th-2之间的平衡状态可影响IA的进展或破裂[46]。此外，在

IA患者中可检测到自然杀伤细胞(NK)，NK产生的IL-4和IFN-γ可介导$CD4^+$ T细胞反应，使其向Th-1或Th-2方向发展[47]。关于不同类型T细胞在IA进展、破裂过程中所起的作用，目前仍在进一步研究中。

3.5 肥大细胞 肥大细胞是重要的促炎细胞，通过释放前列腺素(PGs)和白三烯参与各种血管疾病。Ollikainen等[48]研究了36个动脉瘤标本，所有动脉瘤均表现为管腔内皮受损，并在其中9个标本中发现了肥大细胞。肥大细胞的存在与较多的$CD3^+$ T淋巴细胞和$CD68^+$巨噬细胞浸润有关。因此，肥大细胞可能与其他炎性细胞共同参与了IA血管壁的炎症反应调节，且肥大细胞数量在破裂的动脉瘤中较未破裂的动脉瘤中更多[33]。Furukawa等[49]在缺乏成熟肥大细胞的小鼠体内使用肥大细胞的激活剂和稳定剂，结果显示，肥大细胞可促进动脉瘤破裂，但在动脉瘤的形成过程中未发挥任何重要作用。同样，Ishibashi等[50]在手术诱导的大鼠IA模型中发现，在手术当天，肥大细胞可使大脑动脉内的巨噬细胞浸润减少、炎症减轻，但并不影响动脉瘤的形成，与Furukawa等[49]的发现一致，即肥大细胞对动脉瘤的形成无明显影响。

肥大细胞在活化和脱颗粒后可释放多种细胞因子和趋化因子，包括TNF-α、IL-1、IL-3、IL-4、IL-6、IL-8、IL-13和TGF-β[51]；据报道，这些细胞因子与IA的破裂有关[6]，如由肥大细胞释放的TNF-α和HGF已被证实在促进动脉瘤破裂中起关键作用[21]。动脉瘤壁中肥大细胞产生的糜酶可将血管紧张素Ⅰ(AngⅠ)转化为AngⅡ，激活肾素-血管紧张素系统，并促进动脉瘤破裂[25]。有研究发现，肥大细胞的存在与动脉瘤壁的变性和微出血有关[52]。此外，肥大细胞还可促进动脉瘤壁上新生血管的形成。还有研究发现，在含有肥大细胞和新生血管的动脉瘤壁上发现了铁质沉积物，提示内皮细胞同时存在新生与破坏，这也是IA血管壁退化的证据[52]。Furukawa等[49]发现，应用色甘酸处理肥大细胞后可降低类胰蛋白酶的表达，这可能为肥大细胞稳定剂的保护作用提供了直接证据。

3.6 中性粒细胞 有研究发现，未破裂的IA更多地与重塑过程相关，而破裂的IA则与炎症和免疫反应关系更加密切[53]。中性粒细胞在炎症反应的维持和加剧中起关键作用，可促进IA血管壁的退行性改变。体外实验发现，中性粒细胞可产生大量的促炎因子如TNF-α和PGE_2，以此提供炎症微环境，而中性粒细胞产生的趋化因子CXCL-1可继续招募炎性细胞，形成正反馈通路，进一步加剧炎症反应[54]。Kushamae等[55]通过IA动物模型发现中性粒细胞对IA的破裂具有重要作用。在炎症微环境中聚集的中性粒细胞可产生破坏性蛋白酶如MMP-9，直接加速血管壁的退行性改变，促进病变部位的破裂。此外，对临床患者的长期观察研究发现，炎症反应参与了IA的形成、破裂过程，而使用具有抗炎作用的药物(如他汀类和非甾体抗炎药)可减少因IA破裂导致的蛛网膜下腔出血(SAH)的风险[56]。

4 相关信号通路

4.1 前列腺素E_2(PGE_2)-前列腺素E_2受体2亚型(EP2)-NF-κB信号通路 PGE_2-EP2-NF-κB信号通路是IA形成和发展过程中最重要的信号通路。内皮损伤后，花生四烯酸(AA)通过胞质磷脂酶A_2α($CPLA_2$α)自核膜内的磷脂中释放出来；环氧合酶(COX)-1和(或)COX-2将AA氧化成前列腺素，然后酶促还原为前列腺素H_2(PGH_2)[57]。PGH_2相对不稳定，因此再由微粒体前列腺素E合酶-1(mPGES-1)或胞质前列腺素E合酶(cPGES)通过PGH_2异构化合成PGE_2[58]，随后PGE_2通过自由扩散，或通过多耐药相关蛋白4(MRP4)从细胞内转运至细胞膜，与EP2结合，并与巨噬细胞释放的TNF-α共同激活NF-κB。NF-κB激活后，可上调MCP-1的表达，并参与VSMC的细胞凋亡过程[59]。TNF-α激活NF-κB时也会激活丝裂原活化蛋白激酶(MAPK)，后者可使细胞外信号调节激酶(ERK)磷酸化并转移至细胞核。NF-κB及ERK可增加各种促炎基因如COX-2、CC趋化因子配体2(CCL-2)、MMP、iNOS的转录[60]。其中，COX-2的表达增加可使AA转变为PGE_2增多，并在PGE_2-EP2-NF-κB-COX-2之间形成正反馈回路；CCL-2可刺激CC类趋化因子受体2(CCR-2)的表达并与其结合，随后募集白细胞，并实现自我放大效应；iNOS则被L精氨酸转化为ROS，继而发生氧化应激，损伤血管内皮。有研究发现，当巨噬细胞特异性缺失或在NF-κB抑制蛋白(IκBα)突变体作用下，巨噬细胞浸润、NF-κB活化均减少，最终可导致小鼠IA发生率明显降低[61]。

4.2 JAK/STAT3/NF-κB信号通路 促炎因子尤其是IL-6可激活信号转导和转录激活因子3(STAT3)[62]，后者在炎症反应过程中发挥了关键作用[63]。STAT3失调可导致急慢性炎症和肿瘤的发生，并与哮喘、炎症性肠病、纤维化和恶病质有关[63]。研究发现，STAT3可通过诱导CCL-5表达上调促进VSMC的表型转化，而当抑制半乳糖凝集素-3(gal-3)从而降低CCL-5的表达、减少巨噬细胞浸润后，腹主动脉瘤的发生率也随之降低[64]。此外，STAT3可诱导VSMC中的长链非编码RNA核富集丰度转录物1(NEAT1)表达上调，从而促进腹主动脉瘤的形

成[65]。Jiang等[66]发现，在IA组织中，STAT3和炎性因子(包括IL-1β、IL-6、TNF-α和MCP-1)的表达均上调，且STAT3与这些炎性因子表达水平呈正相关，且上述所有因子在破裂的颅内动脉瘤(RIA)组织中的表达水平均高于未破裂颅内动脉瘤(UIA)和正常组织。该研究还发现，过表达STAT3的VSMC中MMP-2和MMP-9的mRNA水平升高，而MMP-2、MMP-9可降解血管内皮ECM，破坏血管内皮[66]。然而，另有研究认为，STAT3可抑制抗原呈递细胞如树突细胞(DC)，当利用IL-10激活STAT3时，后者可抑制DC介导的炎性因子(如IL-6、TNF-α)的产生，从而抑制依赖DC的免疫及炎症反应[67]，这可能是细胞类型不同所致。Zhang等[68]的进一步研究表明，除介导炎症反应外，过表达STAT3的VSMC中SM-MHC和平滑肌α肌动蛋白(SM-α-actin)的水平下降，可抑制VSMC的收缩能力，并促使VSMC向合成型发展。

4.3 磷脂酰肌醇3激酶(PI3K)/蛋白激酶B(Akt/PKB)信号通路　在细胞生理活动中，PI3K/Akt(PKB)信号通路的主要功能为调节细胞的增殖、凋亡及迁移过程[69]。有研究发现，血管紧张素转化酶Ⅱ(ACEⅡ)代谢物apelin-13可通过PI3K/Akt信号轴使VSMC异常增殖[70]，而阻断PI3K/Akt信号传导后，VSMC的增殖明显减弱[71]。PI3K/Akt信号通路的失调与多种疾病(如肿瘤[72]、2型糖尿病[73])有关。有研究发现，PI3K/Akt信号通路的激活促进了VSMC的增殖，与主动脉瘤的形成有关[74]，而抑制miR-195介导的VEGF/PI3K/Akt信号通路可抑制腹主动脉瘤的形成[75]。PI3K/Akt通过调节VSMC的增殖、凋亡和迁移，可影响IA的形成及生长[76]。PI3K/Akt通路下游转录因子FoxO1与周期蛋白D1(CCND1)启动子区结合，该过程可调节VSMC的增殖及血管重塑[77]。Akt的另一个下游分子丝氨酸/精氨酸蛋白激酶1(SRPK1)可诱导SR蛋白磷酸化，调节RNA转录后的多种修饰，包括RNA稳定性、选择性剪接和翻译，进而调节细胞增殖或凋亡[78]。Li等[79]发现，与正常脑血管壁相比，IA大鼠模型中的PI3K/Akt信号通路被激活，SRPK1在IA动脉瘤壁中的表达水平升高，而应用SRPK1抑制剂(si-SRPK1)处理的IA模型组大鼠血管完整性明显优于单纯IA模型组。除参与VSMC的调控外，PI3K/Akt还可通过控制NF-κB的激活，参与调节炎症反应[80]，而失调的炎症反应可加重IA的发展。此外，Sun等[81]发现，骨髓间充质干细胞分泌的外泌体可抑制PI3K/Akt/NF-κB信号通路以维持Th17/Treg平衡，调节炎症反应，并可抑制IA的发展。

4.4 AMP蛋白激酶(AMPK)/乙酰辅酶A羧化酶(ACC)信号通路　最近的研究发现，AMPK/ACC信号通路具有血管保护作用[82]。AMPK是一种高度保守的蛋白激酶，而ACC作为AMPK的下游效应器，二者共同在细胞和器官代谢中发挥关键作用，并可能参与血管疾病的调控[83]。在内皮损伤的情况下，VSMC可由收缩型转变为合成型，随着炎症介质和MMP的产生，VSMC的分化潜能和合成能力逐渐增强[84]。调节VSMC这种反应的信号通路包括丝裂原活化蛋白激酶(MAPK)通路[85]、PI3K/Akt通路[86]、Rho激酶(ROCK)通路[87]和哺乳动物雷帕霉素靶蛋白(mTOR)[88-89]通路。有研究认为，AMPK激活后，可通过抑制mTOR信号通路使细胞周期停滞在G_0/G_1期，从而抑制VSMC的增殖[90]。Li等[91]使用血小板衍生生长因子B(PDGF-B)诱导VSMC增殖并模拟IA期间血管壁中VSMC的病理生理环境，发现使用二甲双胍可通过激活AMPK/ACC通路抑制VSMC的增殖，而使用ND-646处理VSMC后，ACC磷酸化水平降低，VSMC向合成型转化，从而使SM-MHC和SM-α-actin表达下调，而IL-1β、IL-6、MMP-3、MMP-9、iNOS和TNF-α表达水平升高，进而使IA进展、破裂率增高。二甲双胍可通过激活AMPK/ACC信号通路，抑制IA血管壁中VSMC的表型转换，从而降低大鼠模型中IA的发生率和破裂率，这种作用在人类IA和颞浅动脉标本中也得到了证实[91]。Mao等[92]同样证实，西多龙二醇介导的AMPK/ACC磷酸化对PDGF-B诱导的VSMC增殖具有抑制作用，因而认为增加AMPK/ACC的磷酸化可能会成为治疗脑血管疾病的靶点。

5 总结与展望

IA的发生发展涉及众多复杂的细胞及信号通路，而人们的认识主要来源于手术标本及动物实验。由于IA介入治疗的开展，开颅手术量逐渐减少，且IA的病理生理学变化易受临床治疗及破裂状态的影响，与IA相关的大部分研究进展主要来自动物实验，但将动物实验结果推断到人体时应慎重。目前，大部分免疫治疗方案，如阿司匹林[93]、ASP4058[94]、BP-1-102[95]、间充质干细胞[96]仍处于动物实验阶段，尚未进入临床阶段。一般而言，成功的药物治疗可抑制炎症信号及炎性细胞浸润，然而，单一的免疫疗法可能无法完全有效地阻止IA的发生发展。因而，未来可通过有针对性地调节IA形成过程中涉及的多条病理生理变化途径(如抑制促炎介质、中性粒细胞，调节巨噬细胞M2型极化及维持Th17/Treg平衡)来减轻炎症反应，延缓IA的发展，而这可能成为治疗IA的新兴研究方向。

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