中医药调控动脉粥样硬化相关信号通路的研究进展

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［摘要］ 动脉粥样硬化性心血管疾病是全世界发病和死亡的常见原因。动脉粥样硬化的形成是冠心病等缺血性心血管疾病形成的重要病理基础，与炎症、氧化应激、细胞凋亡、血管内皮损伤、泡沫细胞的形成、血小板活化等多个方面有关，涉及丝裂原活化蛋白激酶（MAPK）、磷脂酰肌醇3-激酶/蛋白激酶B（PI3K/Akt）、环磷酸腺苷/蛋白激酶A（cAMP/PKA）、Ras同源基因家族蛋白A/Rho相关卷曲螺旋蛋白激酶（RhoA/ROCK）及核转录因子-κB（NF-κB）等多条信号通路。在过去的几十年中，动脉粥样硬化的治疗策略主要集中在使用高强度他汀类药物降低血脂水平，药物通常会引起明显的不良反应。因此开发更安全、有效的药物和治疗模式是现阶段研究的重点方向。近年来中医药在我国心血管疾病的防治中发挥着日益重要的作用，探索中医药预防和治疗动脉粥样硬化的机制研究较多，并发现多种单味中药可以通过靶向信号分子调控动脉粥样硬化的形成过程。本文通过对参与动脉粥样硬化病理形成过程的相关信号转导通路及中医药防治的作用机制等研究成果进行综述，旨在为临床方面治疗心血管类疾病提供参考依据。

［关键词］ 动脉粥样硬化；中医药；信号通路；病理机制；研究进展
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Chinese Medicine Regulates Atherosclerosis-related Signaling Pathway: A Review

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［**Abstract**］ Atherosclerotic cardiovascular disease is a common disease with high incidence rate and mortality worldwide. Atherosclerosis is an important pathological basis for the formation of ischemic cardiovascular diseases such as cardiovascular disease, which is related to inflammation, oxidative stress, apoptosis, vascular endothelial damage, foam cell formation, platelet activation, and so on, involving mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), cyclic adenosine monophosphate/protein kinase A (cAMP/PKA), Ras homolog gene family member A (RhoA)/Rho-associated coiled-coil containing protein kinase (ROCK), nuclear factor-kappa B (NF-κB), and other signaling pathways. In the past few decades, high-intensity statins were mainly used to treat atherosclerosis by reducing blood lipid levels, which usually caused obvious side effects. Therefore, the development of safer and more effective drugs and treatment modes is the focus of research at this stage. In recent years, Chinese medicine has been playing an increasingly important role in the prevention and treatment of cardiovascular diseases in China. There are many

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studies on the mechanism of Chinese medicine in the prevention and treatment of atherosclerosis, and it is found that a variety of single Chinese medicine regulate the formation process of atherosclerosis by regulating targeted signal molecules. This paper reviewed the research results of related signaling pathways involved in the pathological formation of atherosclerosis and the mechanism of Chinese medicine in the prevention and treatment of cardiovascular diseases, thereby providing references for the clinical treatment of cardiovascular diseases.

［**Keywords**］ atherosclerosis; Chinese medicine; signaling pathway; pathological mechanism; research progress

动脉粥样硬化(AS)是冠心病等缺血性心血管疾病的重要病理基础,是动脉壁内斑块发展贯穿始终的过程,涉及几个并存的事件,包括炎症、氧化应激、细胞凋亡、血管内皮损伤、泡沫细胞的形成、血小板活化等多个方面[1]。血管内皮损伤作为AS形成的关键过程,是一个可以将其他病理机制联系起来的宏观概念。氧化应激水平和炎症反应的升高是介导血管内皮损伤的重要机制,而血管内皮细胞凋亡是心血管疾病进展过程中的特征性病理改变[1]。内皮受损处招募单核细胞分化为巨噬细胞,并吸收氧化型低密度脂蛋白(ox-LDL)慢慢转变为泡沫细胞,这是AS斑块形成早期的标志[2]。泡沫细胞产生后进一步传播并放大炎症反应,刺激血小板到达并黏附到受损区域。血小板的活化是一个复杂的过程,包括血小板与受损内皮的黏附及血小板间的聚集,这进一步促进了AS斑块的形成。目前用于治疗AS的合成药物的不良反应及其高昂的成本促使人们开始将目光投向不良反应较小的中医药。中医药作为我国的传统医学,理论体系成熟,一直以来在我国心血管疾病的防治中发挥着重要的作用。由于中药复方多靶点的作用,使得中药发挥作用的机制仍然很难完全阐释清楚,因此针对单味中药的有效成分研究便成为了揭示中药作用机制的良好切入点[3]。在此基础上,国内外诸多科研工作者以体内实验、体外实验为研究载体,开展了诸多单味中药有效成分的机制研究[4]。本文主要对参与AS病理形成过程的相关信号转导通路及中医药防治的作用机制等研究成果进行综述。

1 不同信号通路在AS病变中的作用机制

AS形成过程的潜在机制具有复杂的交集和相互作用的特点,涉及炎症、氧化应激、细胞凋亡、血管内皮损伤、泡沫细胞的形成、血小板活化等多个方面[1]。丝裂原活化蛋白激酶(MAPK)、磷脂酰肌醇3-激酶/蛋白激酶B(PI3K/Akt)、环磷酸腺苷/蛋白激酶A(cAMP/PKA)、Ras同源基因家族蛋白A/Rho相关卷曲螺旋蛋白激酶(RhoA/ROCK)及核转录因子-κB(NF-κB)等多个信号通路已被证实参与了AS发生发展的过程。

1.1 PI3K/Akt信号通路 PI3K/Akt信号通路可以调节巨噬细胞的极化,影响血管内炎症因子的表达[5]。LI等[6]以人脐静脉内皮细胞(HUVECs)和载脂蛋白E(ApoE)$^{-/-}$雌性小鼠为模型,研究发现PI3K/Akt/哺乳动物雷帕霉素靶蛋白(mTOR)通路作用于NF-κB的上游,激活PI3K/Akt/mTOR/NF-κB信号通路会导致血管细胞黏附分子-1(VCAM-1)表达升高,单核细胞黏附增加。YU等[7]在研究中却发现低浓度的ox-LDL可上调PI3K、Akt和内皮型一氧化氮合酶(eNOS)的磷酸化。XING等[8]也认为在内皮细胞中,PI3K激活Akt可直接磷酸化eNOS产生NO,介导内皮细胞存活。此外,PI等[9]发现,抑制PI3K/Akt通路可以减少血管平滑肌细胞(VSMCs)中的脂质沉积,增加脂质外流,降低总胆固醇水平。自噬调节也会影响巨噬细胞中胆固醇的外流,选择性抑制PI3K/Akt/mTOR信号通路已被证明可以调节巨噬细胞的自噬,改善血脂代谢紊乱,降低斑块形成的概率[9]。此外,PI3K/Akt通路的激活还能抑制VSMCs迁移,减少血小板黏附,被认为是一个有价值的抗血栓治疗靶点[5]。PI3K及其下游效应因子Akt调节许多重要的血小板反应,如血小板形状改变、整合素$\alpha_{\mathrm{IIb}}\beta_3$激活和不可逆的血小板聚集,血栓体积的增加等[10-11]。

1.2 MAPK信号通路 p38 MAPK也是一个活跃的炎症驱动过程,位于NF-κB信号通路的上游。体外实验研究显示,间歇性缺氧/复氧(IHR)的刺激可激活牛动脉内皮细胞的p38 MAPK/NF-κB通路,诱导促炎细胞因子的表达[12]。相反,使用p38 MAPK的特异性抑制剂可导致IHR诱导的NF-κB活性显著降低,促炎因子的表达减少。炎症反应的增加只能部分解释AS形成的机制,氧化应激也是引发血管内皮损伤和AS形成的关键因素[13]。活性氧(ROS)作为信号分子之一调节一些信号转导通路进而发挥作用,MAPK属于ROS的作用靶标[1]。

GONG等[14]研究结果表明，ox-LDL可诱导HUVECs中p38 MAPK磷酸化，并产生大量的ROS，阻断ROS/p38 MAPK信号通路是减轻ox-LDL介导的内皮功能障碍的机制之一，同时也能阻止泡沫细胞的形成[15]。此外，细胞外信号调节激酶(ERK)还可以作为促进VSMCs增殖的重要信号通路介导AS的发生[16]。MAPK信号通路作为调节血小板活化和凋亡的分子开关，在血栓形成过程中发挥着关键的作用[17]。整合素$\alpha_{\text{Ⅱb}}\beta_3$的激活、血栓烷$A_2$($TXA_2$)的产生和颗粒的分泌均依赖于MAPK通路，其功能障碍会影响整合素$\alpha_{\text{Ⅱb}}\beta_3$活化，造成血栓形成受损[18]。

1.3 cAMP/PKA信号通路　cAMP/PKA信号通路介导VSMCs的增殖和迁移，激活状态的cAMP/PKA信号通路可抑制血管损伤诱导的VSMCs增殖[19]。cAMP/PKA信号通路是氧化应激下稳定内皮屏障的有效保护途径，同时也是RhoA/ROCK的重要负调控因子[20]。内皮cAMP的增加是稳定内皮屏障抵御几乎任何障碍刺激的最有效的触发因素之一[21]。LIAO等[22]在RAW264.7和THP-1细胞实验中证实cAMP/PKA/ATP结合盒转运体A1(ABCA1)通路是促进胆固醇外流，改善泡沫细胞形成以治疗AS的新机制。据报道，cAMP是PKA的激活剂，PKA参与刺激胆固醇外流。阻断PKA对ABCA1磷酸化和胆固醇外流有抑制作用[23]。一些研究表明，自噬是巨噬细胞炎症的负调节因子[24-25]。内皮细胞内cAMP/PKA信号通路的激活参与了自噬的诱导，其主要作用机制是通过位于PKA信号通路下游的腺苷酸活化蛋白激酶(AMPK)调节沉默信息调节因子1(SIRT1)，SIRT1使得几个与自噬相关的基因发生去乙酰化，从而诱导自噬减轻了内皮的炎症反应[26]。cAMP是血小板活性的重要调节因子，对多种激动剂诱导的血小板聚集有抑制作用，参与血小板黏附、钙动员和肌动蛋白重排等功能调节[27-29]。cAMP已被证明通过血管扩张刺激磷蛋白(VASP)Ser157的磷酸化增加其细胞内产量并在整合素$\alpha_{\text{Ⅱb}}\beta_3$失活后抑制血小板的聚集[30-31]。因此，提高cAMP生成、增加VASP活性将有助于预防血小板聚集相关的AS性疾病。

1.4 RhoA/ROCK信号通路　内皮屏障是维持血管内稳态的关键，RhoA及其下游的ROCK在氧化应激和内皮屏障功能中发挥重要作用[32]。IH诱导的ROS过度产生可能激活RhoA/ROCK通路，RhoA/ROCK通路又在IH环境中诱导ROS产生过多，促使内皮屏障功能障碍，从而形成ROS增加和内皮屏障破坏的恶性循环[33]。以前的研究表明RhoA/ROCK可以通过影响VSMCs增殖和迁移，参与血管再狭窄的发生及在动脉血管重构中刺激新生内膜形成[34]。最新的一份研究报道显示RhoA/ROCK通路还能调控AS过程中的炎症反应，介导内皮祖细胞迁移，激活巨噬细胞促炎表型，诱导巨噬细胞源性泡沫细胞的形成[35]。血栓损伤部位骨骼重排增加黏附的血小板与受损部位的接触被认为是止血和血栓形成的关键步骤[36]。ROCK在调节血凝块收缩中被发现通过肌球蛋白轻链磷酸化介导RhoA刺激的肌动蛋白细胞骨架改变，具有促进血凝块回缩的作用[37]。

1.5 NF-κB信号通路　NF-κB是目前研究最广泛的多种炎症反应的关键调节因子。NF-κB的上调可直接由细胞内ROS介导，NF-κB抑制蛋白(IκB)被磷酸化后，激活的NF-κB进入细胞核，启动各种炎症反应，从而引起血管内皮细胞的炎症和促凋亡反应[1,38]。在AS部位和斑块中可以发现活化的NF-κB，而在正常血管中，几乎没有检测到NF-κB的表达[39]。有研究对NF-κB p50基因敲除后的C57BL/6小鼠进行高脂饮食、慢性间歇性缺氧(CIH)干预，结果发现在p50基因敲除的小鼠中，NF-κB的激活及由CIH和高脂饮食引发的AS斑块的形成均受到明显的抑制[40]。另一项使用IHR诱导的人脐静脉杂交瘤细胞EA.hy926的研究发现，抑制NF-κB可显著改善IHR介导的以白细胞介素(IL)-6和IL-8为代表的炎症因子的上调[41]。AN等[42]报道了NF-κB通路参与活化的中性粒细胞胞外陷阱(NETs)诱导巨噬细胞产生IL-8，从而加剧AS的发展。见图1。

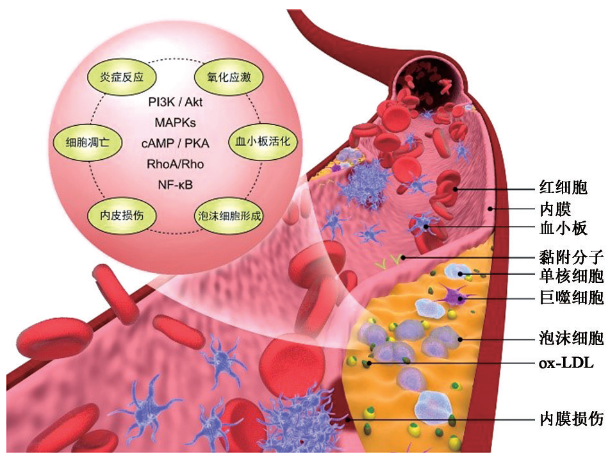

图1　AS形成机制

Fig. 1　Mechanism of Atherosclerosis

2 中药调控相关信号通路治疗AS

2.1 减轻炎症反应 丹参酮Ⅱ$_A$(TS Ⅱ$_A$)属于丹参的主要脂溶性活性成分,而黄芪甲苷Ⅳ(AS Ⅳ)是从黄芪中分离得到的环阿糖烷型三萜苷[5]。WANG等[43]发现TS Ⅱ$_A$和AS Ⅳ通过抑制NF-κB从胞浆到胞核的转运来减轻炎症反应,蛋白免疫印迹法(Western blot)检测结果进一步显示IL-6、肿瘤坏死因子-α(TNF-α)等炎症介质的表达水平在体内和体外实验中均受到了明显的抑制。WU等[44]的研究证实黄芩苷是治疗AS的良好选择。黄芩苷以剂量依赖关系抑制NF-κB和p38 MAPK信号通路,减弱AS诱导的c-Jun氨基末端激酶(JNK)和ERK1/2的高磷酸化水平,从而实现其抗氧化和抗炎作用。在WANG等[35]研究中,红景天苷(SAL)则是通过抑制VSMCs中的RhoA/ROCK通路降低促炎因子的表达,增加抗炎因子的血清水平来减弱炎症反应。黄连碱(Coptisine)被认为是一种新型的抗炎降脂药物。FENG等[45]认为黄连碱对AS的保护作用是通过MAPK/NF-κB依赖的机制实现的。黄连碱抑制IκB的激活阻止NF-κB的核转位,进而减少黄连碱组大鼠主动脉NF-κB/p65蛋白表达,此外抑制p38、JNK的磷酸化能够有效阻止AS小鼠促炎因子TNF-α、IL-1β和IL-6的释放。淫羊藿苷是从淫羊藿中分离得到的一种黄酮类化合物,已有报道具有抗炎和抗氧化作用[46]。淫羊藿苷不仅能改善高胆固醇饮食诱导的AS,而且还能激活p38 MAPK通路,下调AS大鼠组织中明显升高的磷酸化(p)-p38 MAPK蛋白表达水平,减少TNF-α、IL-6等炎症介质的释放[47]。

2.2 减少泡沫细胞形成 人参皂苷化合物K(CK)是从人参中提取的代谢物,具有抗炎[48]、诱导自噬[49]的作用。LU等[50]对ox-LDL处理过的RAW264.7细胞选用CK进行干预治疗,通过油红O染色、Western blot和实时荧光定量聚合酶链式反应(Real-time PCR)检测发现,CK能增加自噬小体数量,上调微管相关蛋白1轻链3(LC3)Ⅱ/LC3Ⅰ和自噬相关蛋白5(Atg5)、自噬关键分子酵母Atg6同系物(Beclin-1)的表达诱导自噬,同时又能调节NF-κB、p38 MAPK和JNK信号通路,刺激巨噬细胞转化为抗炎的M2表型,从而减轻巨噬细胞炎症;有研究证实了激活后的p38 MAPK及JNK通过抑制自噬促进血管内胆固醇酯累积[51]。CK处理后,ox-LDL诱导的巨噬细胞p38和JNK磷酸化水平显著降低,CK通过下调胆固醇摄取和上调胆固醇流出而有效地减少巨噬细胞向泡沫细胞转化[50]。在栀子苷(Geniposide)处理的脂质负载的Raw264.7巨噬细胞中,磷酸化的p38 MAPK和Akt通路的表达水平降低,ABCA1的表达水平显著增加,这些改变使得脂质负载的Raw264.7巨噬细胞的胆固醇流出增加,抑制了泡沫细胞的形成[52]。WANG等[43]采用动物模型(高脂饮食喂养ApoE$^{-/-}$小鼠)和细胞模型(用ox-LDL处理RAW264.7细胞)发现,TS Ⅱ$_A$和AS Ⅳ联用通过影响PI3K/Akt信号通路转导降低体内、外炎症反应和基质金属蛋白酶-9(MMP-9)的表达,阻止ox-LDL诱导的巨噬细胞源泡沫细胞的形成,显著增强AS斑块的稳定性。

2.3 抑制内皮凋亡 丹酚酸B(SAB)是丹参根中的主要生物活性成分,可明显改善内皮功能,通过显著上调B细胞淋巴瘤-2(Bcl-2)蛋白表达,下调Bcl-2相关X蛋白(Bax)表达,有效减少血管内皮细胞凋亡[53]。SAL是从药用植物红景天中分离得到的一种苯丙酸苷。LI等[32]首次证明了SAL激活cAMP/PKA后作用于RhoA/ROCK的上游,发挥对内皮屏障功能的保护作用。另有研究发现,SAL通过PI3K/Akt通路诱导eNOS磷酸化后,提高了NO的生物利用度,改善了血管的内皮功能[8]。NO生物利用度降低会引起血管内皮细胞的凋亡[38]。在LIAO等[54]实验研究中发现,益母草碱(LEO)可通过激活PI3K/Akt-eNOS信号通路有效刺激eNOS活化和内皮NO产生,改善过氧化氢(H_2O_2)诱导的HUVECs氧化应激损伤和血管内皮凋亡。柴胡皂苷(Saikosaponin)通过抑制JNK和p38 MAPK磷酸化水平,上调Bcl-2的表达,下调胱天蛋白酶-3(Caspase-3)和Bax的表达,在一定程度上降低了ox-LDL诱导的HUVECs凋亡[55]。灯盏乙素被证实在体外和体内实验中均通过上调PI3K/Akt的表达而发挥抗凋亡作用。激活Akt可以抑制通路下游的效应因子叉头框蛋白O3a(FoxO3a)核转录,促进其在细胞质中的滞留,产生抗凋亡的效应[56]。

2.4 抗血小板 三七皂苷R_1在大鼠血栓形成模型中可增加血小板内cAMP水平并抑制Ca^{2+}释放,cAMP水平升高会导致$\alpha_{\text{Ⅱb}}\beta_3$活化下调,这是血小板抑制的关键机制之一[57]。在三七的不同部位中,花中皂苷(PNF)的含量最高[58]。在ZUO等[59]进行的研究中,PNF衍生的G-Rb2和G-Rd2通过上调cAMP/PKA/VASP信号和下调PI3K/Akt/ERK1/2信号,有效地抑制了ADP诱导的血小板整合素$\alpha_{\text{Ⅱb}}\beta_3$活化,阻止了血小板聚集和血栓的形成。G-RP3属

于人参皂苷Re的衍生物,是从人参中分离得到的一种天然成分[60]。细胞内cAMP水平显著升高导致PKA依赖的VASP磷酸化,VASP在Ser157处的磷酸化与整合素$\alpha_{\text{Ⅱb}}\beta_3$活性降低和血小板聚集抑制相关[61]。NAM等[62]实验研究结果支持牛蒡子苷元(ATG)通过抑制血小板活化和血小板凝块形成来减轻血栓事件。ATG抑制PI3K/Akt/mTOR和MAPK信号通路,提高细胞内cAMP水平及VASP Ser157的磷酸化,对激动剂诱导的人血浆血小板聚集、颗粒分泌、TXA_2生成、整合素$\alpha_{\text{Ⅱb}}\beta_3$活化和血栓凝块收缩均有明显的抑制作用。西洋参总皂苷(PQS)是从西洋参茎叶中提取的活性成分,作为双重抗血小板药物(DA)的补充剂广泛应用于冠心病的治疗已有20多年之久[63]。一项ox-LDL损伤的HUVECs体外培养研究发现,与单用DA治疗相比,PQS联合DA可减少HUVECs凋亡,并上调HUVECs中的Akt磷酸化水平,其机制可能与PI3K/Akt通路有关。见表1。

表1 单味中药有效成分调控相关信号通路治疗AS的研究

Table 1 Study on treatment of AS by regulating related signal pathways with effective components of single traditional Chinese medicine

中药	中药单体	治疗效应	功效	作用机制
丹参	TS Ⅱ$_A$;丹酚酸B	减轻炎症反应;抑制内皮凋亡	活血化瘀,通经止痛	作用于NF-κB通路,抑制IL-6、TNF-α的表达;上调Bcl-2蛋白表达,下调Bax蛋白表达
黄芩	黄芩苷	减轻炎症反应	清热燥湿,泻火解毒	作用于NF-κB、p38 MAPK通路,抑制JNK和ERK1/2的磷酸化
红景天	SAL	减轻炎症反应;抑制内皮凋亡	益气活血,通脉平喘	作用于RhoA/ROCK通路,抑制促炎因子的表达;作用于cAMP/PKA/RhoA/ROCK/PI3K/Akt通路
黄连	黄连碱	减轻炎症反应	清热燥湿,泻火解毒	作用于MAPK/NF-κB通路,阻止TNF-α、IL-1β和IL-6的释放,抑制p38、JNK的磷酸化
淫羊藿	淫羊藿苷	减轻炎症反应	补肾壮阳、祛风除湿	作用于p38 MAPK通路,减少TNF-α、IL-6释放
人参	人参皂苷化合物K;G-RP3	减少泡沫细胞形成;抗血小板治疗	大补元气,补脾益肺	作用于NF-κB、p38 MAPK和JNK通路,诱导自噬因子的表达,降低p38和JNK磷酸化水平;作用于cAMP/PKA通路,促使VASP磷酸化,降低$\alpha_{\text{Ⅱb}}\beta_3$活性
栀子	栀子苷	减少泡沫细胞形成	清热利湿,凉血解毒	作用于p38 MAPK和Akt通路,降低ABCA1的表达
黄芪	AS	减少泡沫细胞形成	补益脾肺,益气固表	作用于PI3K/Akt通路,降低炎症因子和MMP-9的表达
益母草	LEO	抑制内皮凋亡	活血调经,利尿消肿	作用于PI3K/Akt-eNOS信号通路
柴胡	柴胡皂苷	抑制内皮凋亡	解表退热、疏肝解郁	作用于MAPK通路,上调Bcl-2的表达,下调Caspase3和Bax的表达
灯盏细辛	灯盏乙素	抑制内皮凋亡	活血通络,祛风散寒	作用于PI3K/Akt通路,抑制FoxO3a核转录
三七	三七皂苷R_1;PNF	抗血小板治疗	活血化瘀、止痛止痛	作用于cAMP/PKA/VASP、PI3K/Akt/ERK1/2,下调$\alpha_{\text{Ⅱb}}\beta_3$活性
牛蒡子	ATG	抗血小板治疗	疏风散热、解毒利咽	PI3K/Akt/mTOR、MAPK、cAMP/PKA通路,促使VASP磷酸化,降低$\alpha_{\text{Ⅱb}}\beta_3$活性
西洋参	PQS	抗血小板治疗	补气养阴,清热生津	作用于PI3K/Akt通路,促使Akt磷酸化

3 小结与展望

综上可知,单味中药有效成分通过相关信号通路干预AS形成过程的相关机制研究越来越多。基于信号通路分子的研究可能更加有助于未来进行精确靶点治疗药物的研发,以实现特定的抗AS的疗效。PI3K/Akt、MAPK、RhoA/ROCK及NF-κB通路在AS形成过程中具有放大信号传递的作用,降低这些通路分子的磷酸化将有助于改善AS的发生。而机体内的cAMP/PKA信号通路赋予了某些中药成分,如SAL、PNF,G-RP3减轻内皮屏障功能损伤及阻止血栓形成的功能,细胞内cAMP水平的升高可以抑制介导AS形成的病理因素的产生。这种"一正一反"的调节机制与中医理论中"扶正祛邪""平衡阴阳"的理念相近[64]。随着国内外学者们开展大量研究,大批中药有效成分被逐渐开发,中医药以其不良反应少、多途径、多靶点等优点得到广泛认可。其中尤以益气活血类药物居多,这正好契合了中医学中关于冠心病"日久营血瘀滞,沉积血府"的病机描述。目前已经取得了丰硕的研究成果,但对于抗AS治疗严格意义上的临床随机对照试验偏少,转化为广泛适用于临床患者的药物还有一定距离。建议今后应当更加积极借助组学等新技术、新方法,充分挖掘中医药大宝库,重视大样本、多中心的随机对照,寻找以AS为病理基础的心

血管疾病治疗的临床新策略。

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