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Hans汉斯

# 平滑肌细胞与腹主动脉瘤发病机制的研究概述

张　霞，郭　莹*，陈雪英

济宁医学院临床医学院，山东　济宁

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## 摘　要

**腹主动脉瘤(AAA)是一种致命的血管退行性病变，其发病机制十分复杂，根据2022版腹主动脉瘤诊断治疗专家共识，AAA特征是腹主动脉的永久性局部扩张(气球样膨胀)超过正常直径50%以上，破裂和相关的灾难性生理损伤的总死亡率超过80%。病理特征是以中膜缺陷为主的主动脉壁结构破坏。AAA的发生涉及多种病理过程，包括细胞外基质降解、炎症、氧化应激、平滑肌衰老、凋亡及表型转化。目前关于AAA的治疗，手术仍是唯一的治疗手段，现仍未有高级别证据支持药物可以有效缓解甚至逆转AAA的发展，所以需要进一步了解AAA病理生理机制。平滑肌细胞(VSMC)是动脉壁中膜最主要的细胞类型，平滑肌细胞的衰老、凋亡、炎症反应以及与平滑肌细胞有关的细胞外基质的降解共同导致血管壁受损，促进AAA的形成。本文以平滑肌为中心，表述平滑肌与腹主动脉瘤之间的关系，这可能为AAA的治疗及预防提供新的思路。**

## 关键词

**腹主动脉瘤，平滑肌细胞，平滑肌表型转化**

# Overview of Studies on Smooth Muscle Cells and the Pathogenesis of Abdominal Aortic Aneurysms

**Xia Zhang, Ying Guo*, Xueying Chen**

School of Clinical Medicine, Jining Medical College, Jining Shandong

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## Abstract

**Abdominal aortic aneurysm (AAA) is a fatal vascular degenerative diseases, its pathogenesis is**

*通讯作者。

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**complex, according to the 2022 edition of expert consensus, diagnosis and treatment for abdominal aortic aneurysm AAA is characterized by the permanent local expansion of abdominal aorta (ballooning inflation) than normal diameter by more than 50%, rupture and the associated total mortality of more than 80% of catastrophic physical damage. The pathological feature is the destruction of aortic wall structure mainly due to media defect. The occurrence of AAA involves various pathological processes, including extracellular matrix degradation, inflammation, oxidative stress, smooth muscle aging, apoptosis and phenotypic transformation. At present, surgery is still the only treatment for AAA, and there is still no high-level evidence to support that drugs can effectively alleviate or even reverse the development of AAA. Therefore, it is necessary to further understand the pathophysiology of AAA. Smooth muscle cells (VSMCS) are the most important cell type in the media of arterial wall. Aging, apoptosis, inflammation and degradation of extracellular matrix related to smooth muscle cells jointly lead to the damage of vascular wall and promote the formation of AAA. This paper focuses on smooth muscle and describes the relationship between smooth muscle and abdominal aortic aneurysm, which may provide new ideas for the treatment and prevention of AAA.**

## Keywords

**Abdominal Aortic Aneurysms, Smooth Muscle Cells, Smooth Muscle Phenotype Transformation**



## 1. 引言

在过去的研究中，性别、年龄、吸烟、血脂水平等各种因素均与 AAA 的形成发展有关[1]，随着全球人口老龄化的发展，AAA 的发病呈逐年上升的趋势，是造成 65 岁以上老年人死亡的主要原因[2]。根据各种筛查研究发现，AAA 的患者男女比例在 3.5~6.1 之间，且常见于老年男性[3]。

AAA 的病理学特征主要是炎症、ECM 的降解、EC 的功能障碍、VSMC 的表型转化以及，导致局部永久不可逆扩张，最终破裂[4]。AAA 的基本特征是主动脉壁的炎症伴随炎性细胞的浸润，在临床和实验性 AAA 中，均可见许多促炎因子的升高，如单核细胞趋化蛋白 1 (MCP-1)、白细胞介素-1$\beta$ (IL-1$\beta$)、IL-6 和肿瘤坏死因子-$\alpha$ (TNF-$\alpha$)。这些炎性介质与炎性细胞相互作用，促进了后续的炎症反应以及 EC 及 VSMC 功能障碍、ECM 降解，最终导致 AAA [5]。VSMC 是中膜最主要的细胞类型，现已有很多研究表明 VSMC 在 AAA 的形成发展中起到至关重要的作用。现尚无特效药物预防甚至逆转 AAA 进展。

## 2. 平滑肌细胞的凋亡

VSMC 的凋亡被认为是 AAA 进展中的关键病理改变，主动脉壁 VSMC 数量的减少使得产生弹性蛋白、胶原蛋白等细胞外基质的能力下降，动脉管壁的韧性和强度减低，从而导致 AAA 的形成[6] [7]。细胞凋亡产生凋亡小体，凋亡小体若没有被及时清除，可以促进钙沉积在管壁，使血管硬化，从而促进 AAA 的进展[8]。导致 VSMC 的凋亡的因素很多，包括炎症因子、缺氧、PDGF 等生长因子、缺氧以及 DNA 损伤等[9] [10]。另外，细胞的老化最终也会走向死亡，在死亡介导因子 Fas/FasL 信号被激活之后，激活 caspase 级联(Caspase-3 和-7)，诱导染色体 DNA 降解和细胞凋亡[11]。此前已有研究报道了在 AAAs 中 Fas/FasL 在 VSMC 中被激活[12]。现又越来越多的证据表明 ER 应激、氧化应激和弹性蛋白酶均可诱导

VSMC 凋亡，其中 Serpin 蛋白酶抑制剂 B9 (SerpinB9)可以抑制弹性蛋白酶诱导的细胞凋亡[13]。自噬有关的凋亡也与 AAA 的发展密切相关，转录因子 EB(TFEB)作为 MITF/TFE 家族的一个成员，作为自噬和溶酶体生物发生的主调控因子，在内皮细胞、巨噬细胞及平滑肌细胞中均有表达，其中在内皮细胞中 TFEB 具有减少动脉粥样硬化并促进缺血后血管形成的作用[14]。TFEB 可以通过调节凋亡信号通路特别是上调 BCL2 来抑制 VSMCs 的凋亡，此研究还证明了 2-羟丙基-$\beta$-环糊精(HP$\beta$CD)，可以激活 TFEB 并通过 VSMC 依赖的方式抑制小鼠 AAA 的形成和发展[15]，在不同的 AAA 临床前模型中，VSMC 特异性敲除 TFEB 增强 VSMC 凋亡并促进 AAA 形成[15]。自噬的关键调节因子 ATG7 的敲除也会加重血管紧张素 II 相关的主动脉重塑[16]。

越来越多的研究证明非编码 RNA 在调节 VSMC 的凋亡中的重要作用。许多研究报道，miR-21 是几种心血管疾病中最常见和最显著的解除调控的 miRNA [17]，也是唯一被证明通过调节 SMC 增殖和凋亡在 AAA 形成中发挥核心作用的 miRNA [18]。miR-21 的过度表达，可以使得磷酸酶和张力蛋白同源物(PTEN)表达降低，导致 Akt 磷酸化和活化，从而抑制 VSMC 凋亡[18]。有研究表明，在 AAA 组织中表达明显升高的长非编码 RNA GAS5，直接靶点作用于 Y-box-binding 蛋白 1 (YBX1)，与 GAS5 形成正反馈环，调节下游靶点 P21，抑制 VSMC 的增值并诱导其凋亡，从而促进 AAA 的形成。另有研究报道 GAS5 作为 miR-21 海绵释放 PTEN，阻断 Akt 的活化和磷酸化，从而抑制 SMCs 增殖，促进凋亡。因此有研究提出，GAS5 通过同时调节蛋白和 miR-21 来刺激 SMC 的凋亡和增殖，最终参与 AAA 的形成[19]。最近有研究证明，GAS5 还可能通过与 EZH2 结合激活 RIG-I 信号通路，导致 SMCs 凋亡[20]。GAS5 还可以通过激活血管重塑中的 p53 信号通路，抑制血管平滑肌细胞增殖，促进细胞凋亡[21]。另有 miR-26a 也可以通过抑制 VSMC 凋亡来抑制 AAA 的形成[22]，通过抗 MIR 转染抑制 miR-26a 促进 $H_2O_2$ 诱导的人主动脉 SMCs 凋亡[16]。另有长链非编码 RNA H19 可以通过 HIF-1$\alpha$ 诱导平滑肌细胞凋亡，H19 可以通过结合细胞质 HIF-1$\alpha$，HIF-1$\alpha$ 直接与 MDM2 相互作用，阻止 MDM2 介导的 p53 (主抑癌基因)降低，诱导 SMC 的凋亡[23]。最近有实验证明，针对长链非编码 RNAH19 干扰可以阻止 AAA 的进展，并且能抑制 HIF1$\alpha$ 信号及其在动脉瘤发展过程中对 VSMCs 的凋亡作用[24]。在 Ang II 诱导的小鼠 AAA 模型中，LncRNA pVT1 的过度表达可诱导 VSMC 凋亡，使 MMP-2 和 MMP-9 升高，TIMP-1 降低。相反，阻断 PVT1 在体外和体内均可以逆转这些作用[25]。以上发现均说明了非编码 RNA 在 VSMCs 凋亡中至关重要的作用。

赖氨酰羟化酶 1 (LH1)的缺失可引起 VSMC 的凋亡。研究表明，LH1 缺失引起的胶原蛋白交联受损可能引发异常的机械感知，从而引起血栓软骨素-1 (Thbs1 编码)的表达上调，导致基质金属蛋白酶(MMP)活性增加以及 VSMC 大量凋亡[26]。其中，MMP 不仅可以降解 ECM，还可以调节 VSMC 的增殖、迁移和凋亡，但 MMPs 介导 VSMC 凋亡的直接证据仍有待于进一步研究[6]。

## 3. 平滑肌细胞与细胞外基质的降解

AAA 的基本病理改变是细胞外基质(Extracellular matrix, ECM)过度降解和重塑，对主动脉的扩张甚至最终的破裂至关重要。弹性蛋白和胶原蛋白是主动脉血管壁 ECM 的主要成分，它们决定了管壁的弹性和韧性，共同维持主动脉机械强度，抵抗血管的扩张和破裂[6]。基质金属蛋白酶(MMPs)对血管胶原和弹性蛋白等细胞外基质的降解是 AAA 形成的关键[27]。平滑肌细胞(Smooth Muscle Cells, SMC)的是动脉管壁中膜中最主要的细胞类型，在健康的脉管系统中，ECM 为管壁细胞提供稳固的物理支架，一方面，VSMC 可以产生弹性蛋白和胶原蛋白修复 ECM，另一方面，VSMC 通过 MMPs 和组织金属蛋白酶抑制剂(TIMPs)的降解 ECM，维持血管的稳态[6] [7]。

在 AAA 病变处，基质金属蛋白酶-2 (Matrix metalloproteinase-2, MMP-2)和基质金属蛋白酶-9 (Matrix metalloproteinase-9, MMP-9)在 VSMC 中显示出明显的上调[28]，MMPs 抑制剂中 TIMP-1 和 TIMP-2 缺乏

增加，提示一种不平衡的蛋白水解状态[29] [30]。传统认为，SMC 主要表达 MMP-2 参与到 ECM 降解[27]。有研究报道，SMC 特异性肝激酶 B1 (LKB1)表达缺失会加剧血管紧张素 II 诱导小鼠的 AAA 形成，并伴有 AAA 发生率增加和主动脉扩张。LKB1 是一种肿瘤抑制因子，是细胞极性和能量平衡的中枢调节因子。机制上，LKB1 可与 MMP-2 转录因子特异性蛋白 1 (SP1)结合，从而降低 SP1 与 MMP-2 启动子的结合，从而抑制 MMP-2 的表达，提示 LKB1 可能通过抑制 MMP-2 的表达在 AAA 的形成中起保护作用，可作为 AAA 疾病的潜在治疗靶点[31]。

有实验通过在标记的不溶性弹性蛋白和小鼠主动脉切片上孵育 VSMC，证实 AAA 来源的 VSMCs 比非扩张的肾下主动脉或颈动脉斑块来源的细胞能够降解更多的不溶性弹性蛋白调，AAA 中的 VSMC 可以通过 MMP 溶解弹性蛋白参与 ECM 的降解。实验表明，在激活的巨噬细胞环境中，动脉瘤来源的 VSMC 协同大量生产弹性蛋白酶，特别是 MMP-9 显著增加[28]，具体分子机制仍需进一步探究。巨噬细胞不仅可以与 VSMC 协同产生大量 MMP9 参与基质的降解，还可以表达 netrin-1，它一方面可以诱导白细胞迁移，另一方面可以通过结合其受体 neogenin-1 诱导 VSMCs 内钙离子的内流，对基质金属蛋白酶-3 (MMP3)进行转录调控和持续催化活化，促进 AAA 中 ECM 的局灶性降解。此外，netrin-1 还可以通过结合激活其受体 neogenin-1，活化 T 细胞的转录因子核因子细胞质 3(NFATC3)的核易位，从而增强基质金属蛋白酶 3 (MMP3)的催化活性。在动脉瘤组织中，微钙化丰富的区域显示出广泛的弹性蛋白断裂，Netrin-1 可能可以同步细胞内钙池，而钙池可能在广谱范围内协调 VSMCs 的功能[32]。钙是维持血管壁细胞稳态的关键辅助因子，钙库的异常调节现被认为是包括动脉粥样硬化和马凡综合征等动脉疾病的原因[33]。

## 4. 平滑肌细胞的表型转化

动脉壁分为内膜、中膜和外膜，腹主动脉属于弹性动脉，中层厚，VSMC 及 ECM 是中膜最主要的组成部分。VSMC 具有高度可塑性，可在两种表型之间发生转化，收缩表型和增殖/合成的表型。在健康的血管壁中，VSMC 主要是以收缩型为主，通过其收缩和舒张维持血管张力[34] [35]，保持血压稳定。分化的 VSMC 呈纺锤形，表达高水平的收缩蛋白，如 $\alpha$-平滑肌肌动蛋白($\alpha$-SMA)、SM 肌球蛋白重链(SMMHC)、平滑肌 22$\alpha$ (SM22$\alpha$)、SM-calponin (CNN)和 smoothelin-B [36]。在病理条件下，VSMCs 可被转化生长因子-$\beta$ (TGF-$\beta$)、PDGF-BB、Ang II 等诱导，去分化转变为增殖/合成表型[35] [37] [38] [39]。VSMCs 收缩功能的丧失可能降低血管张力，管壁从而促进动脉瘤的形成[38] [40]。一些早期的研究已经揭示，促进 SMC 分化能够抑制实验性 AAA 形成[41] [42]。在人 AAA 活检中，TGF-$\beta$ 受体 2 (TGFBR2)显著下调[43]，最近有一项使用 SMC 特异性缺失 TGFBR2 的谱系追踪研究，在 ApoE-/-背景下，那些 SMC 中缺乏 TGF-$\beta$ 信号的小鼠在高胆固醇高脂肪饮食 4 个月后发生了 AAAS，而野生型小鼠没有[44]。另有与 TGF-$\beta$ 相互负调节彼此转录的 VEPH1，一个与肝细胞肝癌发生发展相关的重要抑癌基因，在 Ang II 诱导的主动脉中膜中表达[45]，当在其过表达时能够加剧 Ang II 诱导 AAA，并抑制重组 TGF-$\beta$1 诱导的 MYH11 和 $\alpha$-SMA 的增加，抑制 Smad3 的磷酸化和核积累，促进 SMCs 的合成表型转换[46]。Veph1 对 SMCs 中 TGF-$\beta$/Smad3 通路的负调控作用还得到了 Shathasivam 小组在癌细胞中报道的早期发现的支持[47] [48] [49]。以上充分说明 TGF-$\beta$ 信号转导对维持 SMCs 的结构完整性和防止 AAA 时主动脉扩张是必要的。

小型非编码 RNA microRNA (miRNA)也可以调控 VSMC 的表型转换，miRNA 可以通过降解信使 RNAs 或模拟小干扰 RNAs 抑制基因翻译来抑制基因表达。有研究已证实，在细胞中存在一个 21-nt 具有高度序列保守性的 microRNA——microRNA-126A-5P (miR-126A-5P)，负责调节 SMC 功能。miR-126-5P 的异位过表达可以恢复 SMC 的分化——收缩型/分化型 SMC 标志物平滑肌肌球蛋白重链(MYH11)和 $\alpha$-平滑肌肌动蛋白($\alpha$-SMA)的表达增加，而合成型/去分化型 SMC 标志物增殖细胞核抗原(PCNA)和波形蛋

白的表达减少[50]。它还可以通过下调 ADAM 金属肽酶与血小板反应蛋白 1 型基序 4 (ADAMTS-4)起到抗 AAA 的作用，ADAMTS-4 是一种调节基质降解的分泌型蛋白酶[51]，作为血管平滑肌细胞分化的负调节因子，与 miR-126-5P 在小鼠腹主动脉中的表达呈负相关[50]。另有 miR-143/145 簇在血管平滑肌细胞中高表达，在心脏和主动脉中表达最为丰富，血清反应因子(SRF)、肌红蛋白和 NKX2.5 可诱导 SMCs 中 miR-143/145 的表达[52] [53]。miR-145 的过度表达提高了 SMC 收缩蛋白的水平，包括 $\alpha$-SMA、SMMHC 和 CNN。miR-145 增强平滑肌细胞收缩能力的作用主要是通过抑制 Kruppel 样转录因子 4 (KLF4)和 KLF5 抑制肌红蛋白下调 VSMC 分化标志基因[53]。

此外，有研究表明，FoxO3A 通过 P62/LC3BII 自噬信号通路促进 VSMC 表型转换以加速 AAA 的形成[54]。在 AAA 中，维持 VSMCs 的收缩表型的 PI3K/Akt 信号通路[55] [56] [57]，可以通过抑制 Foxo 转录因子(尤其是 FoxO3A 和 FoxO4) [57] [58]活性，抑制 AAA 的形成；VEPH1 对此通路亦有调控作用。最近的一项研究表明，XBP1U-FOXO4-Myocardin 轴通过维持 VSMCs 的收缩表型，在预防主动脉瘤形成中起着关键作用，这进一步表明了 FOXO 转录因子在血管疾病中的新作用[59]。FOXO3A 还在抑制 VSMC 增殖和促进 VSMC 凋亡方面发挥重要作用，表明 FOXO3A 可能在 AAA 从发病到整个疾病进展的发病机制中发挥核心作用[54]。先前的一项研究表明，抑制自噬可以阻止 PDGF 诱导的表型转换，表明自噬在 VSMC 表型转换中起重要作用。FoxO3A 已被证明在各种细胞的自噬中起关键作用[60] [61] [62]。

在微环境改变的情况下，VSMCs 部分由收缩型转化为其他表型，采用巨噬细胞样分泌杂交作用；也可以继承增强的收缩电位[63]。SMC 表型与 ECM 组成和组织之间存在双向的关系，SMC 表型改变可能影响 ECM 的降解和合成，这与 SMC 表达蛋白酶及其抑制剂的制衡有关，而 ECM 也被证明影响 SMC 表型和 SMC 对机械刺激的反应[64]。众所周知，当收缩刺激时，形成 ECM 粘附复合物的蛋白质在细胞膜上组装，并触发肌动蛋白丝的聚合，从而增强细胞膜[65]，这种现象在富含肌动蛋白的细胞中更加明显。这有助于将由细胞内肌球蛋白重链精心策划的收缩机制所产生的力传递给 ECM，从而使细胞适应其环境中的机械应力[66]。在 AAA 微环境中的巨噬细胞也对 SMC 的表型产生影响，在 AAA 中 VSMCs 有一个独特的前弹性溶解表型，它可以通过 MMP-9 合成控制的转录后失败导致弹性溶解性 MMP 的产生和激活增加而发生的。在激活的巨噬细胞的环境下，这种表型会增强，但具体细胞内及细胞间的机制需要进一步研究[28]。

在血管壁中还存在一系列多能祖细胞，具有高度增殖及分化成包括平滑肌及内皮细胞等细胞后代的潜力。这些细胞可能从出生一直持续存在，并影响出生后的生长、衰老和疾病。谱系追踪研究表明，在病变血管壁中，SMC 经历了多种表型转变，其特征在于表达替代细胞类型的标志物，并通过有限数量的内侧 SMC 的寡克隆扩增来填充受伤或患病的血管[67]。在血管壁中存在一种由骨髓间充质干细胞衍生的平滑肌细胞(BM-SMCs)，它可以在 PDGF (血小板衍生生长因子)和 TGF-$\beta$1 (转化生长因子-$\beta$1)存在下在 2D 纤连蛋白底物上分化 BM-MSCs 产生一种更加稳定的 BMSMC 表型(cBM-SMC)，其 MYH11 和 $\alpha$-SMA 表达相对增加[68]，还分泌具有促弹性和抗蛋白酶水解的生物因子作用于血管的 SMC [66]，从而起到一定抵抗 AAA 形成发展的作用。在此理论研究基础上，可进一步探索是否可以通过细胞疗法达到延缓甚至逆转 AAA 发展的作用。另有研究发现，SMC 的分化不仅可以在收缩表型(表达 MYH11、ACTA2 和 TAGLN)和去分化的合成表型(表达 COL1A1、MGP 和 COL3A1)之间转变[69]，还可以转化为其他类型的细胞，如软骨细胞样细胞(SOX9+、Runx2/Cbfa1+)、泡沫细胞和巨噬细胞样细胞(Oil Red O+、LGALS3+和 Mac3+)、间充质干细胞样细胞(Sca1+)、肌成纤维细胞(PDGF$\beta$R+)或米色脂肪细胞样细胞(UCP1+) [67]。

## 5. 平滑肌细胞的衰老

AAA 的患病风险随着年龄而增加[70]，据资料查证动脉瘤的 SMC 是衰老的[71]，衰老的细胞通过分

泌相关介质，典型的如 IL-1、IL-6、IL-8 和单核细胞趋化蛋白-1 等[72]，这些因子可以通过旁分泌/自分泌机制诱导邻近细胞的衰老[73]。有研究发现，Myocardinrelated 转录因子(MRTFs)家族成员之一，Myocardin 相关转录因子 A (MRTFA, MKL1)的缺乏能抑制血管衰老，并显著减少动脉瘤的发生率，减轻病理变化程度。相反，其活性增加是包括血管再狭窄、动脉粥样硬化及血管纤维化在内的多种血管并发症发生的基础[74]。MKL1 已被证明在损伤性狭窄、动脉粥样硬化和缺氧性肺紧张等几种血管疾病中起着重要的作用。野生型与 MKL1 敲基因小鼠的对比，野生小鼠 SA-$\beta$-gal 活性增加，p16、p21 和 p53 等衰老标志物表达增加，在细胞水平的实验中，MKL1 缺乏在 mRNA 和蛋白水平上都减轻了 Ang II 诱导的一种明确的衰老标志物 p16 (CDKN2A)的表达。并且还在 VSMCs 中找到了 p38MAPK 激活血管炎症和衰老的机制途径[75]，组成了关键的动脉瘤前通路。除文献记载的 p38MAPK 的促炎作用外，该途径已成为细胞衰老的一个关键激活因子，并有助于多种衰老相关疾病，如癌症和认知功能衰退[76] [77]。但 p38MAPK 调控血管炎症和衰老的详细分子机制仍有待进一步研究。

沉默信息调节因子 1 (sirtuin1, SIRT1)是哺乳动物最具特征性的 sirtuin，在血管中高表达，调节健康和疾病中心血管功能，SIRT1 对应激诱导的血管重塑、腹主动脉瘤、主动脉夹层和小鼠动脉粥样硬化有保护作用，在 ANG II 以及氯化钙($CaCl_2$)诱导的 AAA 模型中均证明了 SIRT1 对 AAA 形成的抑制作用。DNA 损伤驱动细胞老化[78]，细胞暂时退出细胞周期，进行 DNA 的修复，当损伤超过修复能力，发生细胞的衰老或凋亡。SIRT-1 通过 p53 依赖的机制，可以促进 DNA 修复和调节细胞周期，从而促进活力和寿命[79]。从机制上看，SIRT1 的减少可促进血管细胞衰老，上调 p21 的表达，增强血管炎症反应。此外，SIRT1 对 p21 依赖性血管细胞衰老的抑制阻断了 Ang II 诱导的 NF-$\kappa$B 与单核细胞趋化蛋白-1 (MCP-1/CCL2)启动子的结合，并抑制了其表达。总之，VSMCs 中 SIRT1 的年龄相关减少通过促进 p21 依赖性血管细胞衰老、炎性细胞募集分子分泌和血管炎症而使主动脉易发生 AAAS [80]。另外众所周知在过敏性哮喘的气道炎症和重塑中起关键作用的 IgE，可以通过激活 lincRNAp21-p21 途径诱导 SMC 衰老[81]从而促进 AAA 的形成。

## 6. 结语

AAA 是致死率极高的心血管系统疾病，主要见于老年人，对公众的生命健康造成威胁。目前对于 AAA 的治疗除手术外仍没有有效的药物治疗。本文关于平滑肌细胞在 AAA 形成发展中的作用作一综述，然而还有许多机制仍未被探究，分子机制尚不明确，这需要我们对 AAA 的病理机制作进一步的了解。

## 参考文献


[1] Altobelli, E., Rapacchietta, L., Profeta, V.F., *et al*. (2018) Risk Factors for Abdominal Aortic Aneurysm in Population-Based Studies: A Systematic Review and Meta-Analysis. *International Journal of Environmental Research and Public Health*, **15**, 2805. https://doi.org/10.3390/ijerph15122805

[2] Anderson, P.L., Arons, R.R., Moskowitz, A.J., *et al*. (2004) A Statewide Experience with Endovascular Abdominal Aortic Aneurysm Repair: Rapid Diffusion with Excellent Early Results. *Journal of Vascular Surgery*, **39**, 10-19. https://doi.org/10.1016/j.jvs.2003.07.020

[3] Kim, L.G., Thompson, S.G., Marteau, T.M., *et al*. (2004) Screening for Abdominal Aortic Aneurysms: The Effects of Age and Social Deprivation on Screening Uptake, Prevalence and Attendance at Follow-Up in the MASS Trial. *Journal of Medical Screening*, **11**, 50-53. https://doi.org/10.1177/096914130301100112

[4] Kuivaniemi, H., Ryer, E.J., Elmore, J.R., *et al*. (2015) Understanding the Pathogenesis of Abdominal Aortic Aneurysms. *Expert Review of Cardiovascular Therapy*, **13**, 975-987. https://doi.org/10.1586/14779072.2015.1074861

[5] Bown, M.J., Burton, P.R., Horsburgh, T., *et al*. (2003) The Role of Cytokine Gene Polymorphisms in the Pathogenesis of Abdominal Aortic Aneurysms: A Case-Control Study. *Journal of Vascular Surgery*, **37**, 999-1005. https://doi.org/10.1067/mva.2003.174

[6] Chen, Q., Jin, M., Yang, F., *et al*. (2013) Matrix Metalloproteinases: Inflammatory Regulators of Cell Behaviors in

Vascular Formation and Remodeling. *Mediators of Inflammation*, **2013**, Article ID: 928315. https://doi.org/10.1155/2013/928315

[7] Saatchi, S., Azuma, J., Wanchoo, N., *et al*. (2012) Three-Dimensional Microstructural Changes in Murine Abdominal Aortic Aneurysms Quantified Using Immunofluorescent Array Tomography. *Journal of Histochemistry & Cytochemistry*, **60**, 97-109. https://doi.org/10.1369/0022155411433066

[8] Yamanouchi, D., Morgan, S., Stair, C., *et al*. (2012) Accelerated Aneurysmal Dilation Associated with Apoptosis and Inflammation in a Newly Developed Calcium Phosphate Rodent Abdominal Aortic Aneurysm Model. *Journal of Vascular Surgery*, **56**, 455-461. https://doi.org/10.1016/j.jvs.2012.01.038

[9] Thompson, R.W., Liao, S. and Curci, J.A. (1997) Vascular Smooth Muscle Cell Apoptosis in Abdominal Aortic Aneurysms. *Coronary Artery Disease*, **8**, 623-631. https://doi.org/10.1097/00019501-199710000-00005

[10] Rajagopalan, S., Meng, X.P., Ramasamy, S., *et al*. (1996) Reactive Oxygen Species Produced by Macrophage-Derived Foam Cells Regulate the Activity of Vascular Matrix Metalloproteinases *in Vitro*. Implications for Atherosclerotic Plaque Stability. *Journal of Clinical Investigation*, **98**, 2572-2579. https://doi.org/10.1172/JCI119076

[11] Waring, P. and Müllbacher, A. (1999) Cell Death Induced by the Fas/Fas Ligand Pathway and Its Role in Pathology. *Immunology & Cell Biology*, **77**, 312-317. https://doi.org/10.1046/j.1440-1711.1999.00837.x

[12] Lee, T. and Chau, L. (2001) Fas/Fas Ligand-Mediated Death Pathway Is Involved in oxLDL-Induced Apoptosis in Vascular Smooth Muscle Cells. *The American Journal of Physiology-Cell Physiology*, **280**, C709-C718. https://doi.org/10.1152/ajpcell.2001.280.3.C709

[13] Kuiper, J., Quax, P.H. and Bot, I. (2013) Anti-Apoptotic Serpins as Therapeutics in Cardiovascular Diseases. *Cardiovascular & Hematological Disorders-Drug Targets*, **13**, 111-122. https://doi.org/10.2174/1871529X11313020004

[14] Lu, H., Fan, Y., Qiao, C., *et al*. (2017) TFEB Inhibits Endothelial Cell Inflammation and Reduces Atherosclerosis. *Science Signaling*, **10**, eaah4214. https://doi.org/10.1126/scisignal.aah4214

[15] Lu, H., Sun, J., Liang, W., *et al*. (2020) Cyclodextrin Prevents Abdominal Aortic Aneurysm via Activation of Vascular Smooth Muscle Cell Transcription Factor EB. *Circulation*, **142**, 483-498. https://doi.org/10.1161/CIRCULATIONAHA.119.044803

[16] Leeper, N.J., Raiesdana, A., Kojima, Y., *et al*. (2011) MicroRNA-26a Is a Novel Regulator of Vascular Smooth Muscle Cell Function. *Journal of Cellular Physiology*, **226**, 1035-1043. https://doi.org/10.1002/jcp.22422

[17] Kumarswamy, R., Volkmann, I. and Thum, T. (2011) Regulation and Function of miRNA-21 in Health and Disease. *RNA Biology*, **8**, 706-713. https://doi.org/10.4161/rna.8.5.16154

[18] Maegdefessel, L., Azuma, J., Toh, R., *et al*. (2012) MicroRNA-21 Blocks Abdominal Aortic Aneurysm Development and Nicotine-Augmented Expansion. *Science Translational Medicine*, **4**, 122ra22. https://doi.org/10.1126/scitranslmed.3003441

[19] He, X., Wang, S., Li, M., *et al*. (2019) Long Noncoding RNA GAS5 Induces Abdominal Aortic Aneurysm Formation by Promoting Smooth Muscle Apoptosis. *Theranostics*, **9**, 5558-5576. https://doi.org/10.7150/thno.34463

[20] Le, T., He, X., Huang, J., *et al*. (2021) Knockdown of Long Noncoding RNA GAS5 Reduces Vascular Smooth Muscle Cell Apoptosis by Inactivating EZH2-Mediated RIG-I Signaling Pathway in Abdominal Aortic Aneurysm. *Journal of Translational Medicine*, **19**, Article No. 466. https://doi.org/10.1186/s12967-021-03023-w

[21] Tang, R., Mei, X., Wang, Y.C., *et al*. (2019) LncRNA GAS5 Regulates Vascular Smooth Muscle Cell Cycle Arrest and Apoptosis via p53 Pathway. *Biochimica et Biophysica Acta*: *Molecular Basis of Disease*, **1865**, 2516-2525. https://doi.org/10.1016/j.bbadis.2019.05.022

[22] Boon, R.A. and Dimmeler, S. (2011) MicroRNAs and Aneurysm Formation. *Trends in Cardiovascular Medicine*, **21**, 172-177. https://doi.org/10.1016/j.tcm.2012.05.005

[23] Li, D.Y., Busch, A., Jin, H., *et al*. (2018) H19 Induces Abdominal Aortic Aneurysm Development and Progression. *Circulation*, **138**, 1551-1568. https://doi.org/10.1161/CIRCULATIONAHA.117.032184

[24] Busch, A., Pauli, J., Winski, G., *et al*. (2021) Lenvatinib Halts Aortic Aneurysm Growth by Restoring Smooth Muscle Cell Contractility. *JCI Insight*, **6**, e140364. https://doi.org/10.1172/jci.insight.140364

[25] Zhang, Z., Zou, G., Chen, X., *et al*. (2019) Knockdown of lncRNA PVT1 Inhibits Vascular Smooth Muscle Cell Apoptosis and Extracellular Matrix Disruption in a Murine Abdominal Aortic Aneurysm Model. *Molecules and Cells*, **42**, 218-227.

[26] Li, H., Xu, H., Wen, H., *et al*. (2021) Lysyl Hydroxylase 1 (LH1) Deficiency Promotes Angiotensin II (Ang II)-Induced Dissecting Abdominal Aortic Aneurysm. *Theranostics*, **11**, 9587-9604. https://doi.org/10.7150/thno.65277

[27] Prescott, M.F., Sawyer, W.K., Von Linden-Reed, J., *et al*. (1999) Effect of Matrix Metalloproteinase Inhibition on Progression of Atherosclerosis and Aneurysm in LDL Receptor-Deficient Mice Overexpressing MMP-3, MMP-12, and MMP-13 and on Restenosis in Rats after Balloon Injury. *Annals of the New York Academy of Sciences*, **878**, 179-190.

https://doi.org/10.1111/j.1749-6632.1999.tb07683.x

[28] Airhart, N., Brownstein, B.H., Cobb, J.P., *et al*. (2014) Smooth Muscle Cells from Abdominal Aortic Aneurysms Are Unique and Can Independently and Synergistically Degrade Insoluble Elastin. *Journal of Vascular Surgery*, **60**, 1033-1041. https://doi.org/10.1016/j.jvs.2013.07.097

[29] Howard, E.W., Bullen, E.C. and Banda, M.J. (1991) Preferential Inhibition of 72- and 92-kDa Gelatinases by Tissue Inhibitor of Metalloproteinases-2. *Journal of Biological Chemistry*, **266**, 13070-13075. https://doi.org/10.1016/S0021-9258(18)98804-6

[30] Tamarina, N.A., Mcmillan, W.D., Shively, V.P., *et al*. (1997) Expression of Matrix Metalloproteinases and Their Inhibitors in Aneurysms and Normal Aorta. *Surgery*, **122**, 264-271. https://doi.org/10.1016/S0039-6060(97)90017-9

[31] Nosoudi, N., Nahar-Gohad, P., Sinha, A., *et al*. (2015) Prevention of Abdominal Aortic Aneurysm Progression by Targeted Inhibition of Matrix Metalloproteinase Activity with Batimastat-Loaded Nanoparticles. *Circulation Research*, **117**, e80-e89. https://doi.org/10.1161/CIRCRESAHA.115.307207

[32] Wanga, S., Hibender, S., Ridwan, Y., *et al*. (2017) Aortic Microcalcification Is Associated with Elastin Fragmentation in Marfan Syndrome. *The Journal of Pathology*, **243**, 294-306. https://doi.org/10.1002/path.4949

[33] Handford, P., Downing, A.K., Rao, Z., *et al*. (1995) The Calcium Binding Properties and Molecular Organization of Epidermal Growth Factor-Like Domains in Human Fibrillin-1. *Journal of Biological Chemistry*, **270**, 6751-6756. https://doi.org/10.1074/jbc.270.12.6751

[34] Mazurek, R., Dave, J.M., Chandran, R.R., *et al*. (2017) Vascular Cells in Blood Vessel Wall Development and Disease. *Advances in Pharmacology*, **78**, 323-350. https://doi.org/10.1016/bs.apha.2016.08.001

[35] Owens, G.K., Kumar, M.S. and Wamhoff, B.R. (2004) Molecular Regulation of Vascular Smooth Muscle Cell Differentiation in Development and Disease. *Physiological Reviews*, **84**, 767-801. https://doi.org/10.1152/physrev.00041.2003

[36] Guo, X. and Chen, S.Y. (2012) Transforming Growth Factor-*β* and Smooth Muscle Differentiation. *World Journal of Biological Chemistry*, **3**, 41-52. https://doi.org/10.4331/wjbc.v3.i3.41

[37] Coll-Bonfill, N., De la Cruz-Thea, B., Pisano, M.V., *et al*. (2016) Noncoding RNAs in Smooth Muscle Cell Homeostasis: Implications in Phenotypic Switch and Vascular Disorders. *Pflügers Archiv*, **468**, 1071-1087. https://doi.org/10.1007/s00424-016-1821-x

[38] Ailawadi, G., Moehle, C.W., Pei, H., *et al*. (2009) Smooth Muscle Phenotypic Modulation Is an Early Event in Aortic Aneurysms. *The Journal of Thoracic and Cardiovascular Surgery*, **138**, 1392-1399. https://doi.org/10.1016/j.jtcvs.2009.07.075

[39] Yoshida, T., Kaestner, K.H. and Owens, G.K. (2008) Conditional Deletion of Krüppel-Like Factor 4 Delays Downregulation of Smooth Muscle Cell Differentiation Markers but Accelerates Neointimal Formation Following Vascular Injury. *Circulation Research*, **102**, 1548-1557. https://doi.org/10.1161/CIRCRESAHA.108.176974

[40] Crosas-Molist, E., Meirelles, T., López-Luque, J., *et al*. (2015) Vascular Smooth Muscle Cell Phenotypic Changes in Patients with Marfan Syndrome. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **35**, 960-972. https://doi.org/10.1161/ATVBAHA.114.304412

[41] Huang, X., Yue, Z., Wu, J., *et al*. (2018) MicroRNA-21 Knockout Exacerbates Angiotensin II-Induced Thoracic Aortic Aneurysm and Dissection in Mice with Abnormal Transforming Growth Factor-*β*-SMAD3 Signaling. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **38**, 1086-1101. https://doi.org/10.1161/ATVBAHA.117.310694

[42] Liang, E.S., Bai, W.W., Wang, H., *et al*. (2018) PARP-1 (Poly[ADP-Ribose] Polymerase 1) Inhibition Protects from Ang II (Angiotensin II)-Induced Abdominal Aortic Aneurysm in Mice. *Hypertension*, **72**, 1189-1199. https://doi.org/10.1161/HYPERTENSIONAHA.118.11184

[43] Biros, E., Walker, P.J., Nataatmadja, M., *et al*. (2012) Downregulation of Transforming Growth Factor, Beta Receptor 2 and Notch Signaling Pathway in Human Abdominal Aortic Aneurysm. *Atherosclerosis*, **221**, 383-386. https://doi.org/10.1016/j.atherosclerosis.2012.01.004

[44] Chen, P.Y., Qin, L., Li, G., *et al*. (2020) Smooth Muscle Cell Reprogramming in Aortic Aneurysms. *Cell Stem Cell*, **26**, 542-557.e11. https://doi.org/10.1016/j.stem.2020.02.013

[45] Cui, M., Cai, Z., Chu, S., *et al*. (2016) Orphan Nuclear Receptor Nur77 Inhibits Angiotensin II-Induced Vascular Remodeling via Downregulation of *β*-Catenin. *Hypertension*, **67**, 153-162. https://doi.org/10.1161/HYPERTENSIONAHA.115.06114

[46] Shi, X., Xu, C., Li, Y., *et al*. (2020) A Novel Role of VEPH1 in Regulating AoSMC Phenotypic Switching. *Journal of Cellular Physiology*, **235**, 9336-9346. https://doi.org/10.1002/jcp.29736

[47] Kollara, A., Shathasivam, P., Park, S., *et al*. (2020) Increased Androgen Receptor Levels and Signaling in Ovarian Cancer Cells by VEPH1 Associated with Suppression of SMAD3 and AKT Activation. *The Journal of Steroid Biochemi-*

*stry and Molecular Biology*, **196**, Article ID: 105498. https://doi.org/10.1016/j.jsbmb.2019.105498

[48] Shathasivam, P., Kollara, A., Ringuette, M.J., *et al*. (2015) Human Ortholog of Drosophila Melted Impedes SMAD2 Release from TGF-*β* Receptor I to Inhibit TGF-*β* Signaling. *Proceedings of the National Academy of Sciences of the United States of America*, **112**, E3000-E3009. https://doi.org/10.1073/pnas.1504671112

[49] Shathasivam, P., Kollara, A., Spybey, T., *et al*. (2017) VEPH1 Expression Decreases Vascularisation in Ovarian Cancer Xenografts and Inhibits VEGFA and IL8 Expression through Inhibition of AKT Activation. *British Journal of Cancer*, **116**, 1065-1076. https://doi.org/10.1038/bjc.2017.51

[50] Shi, X., Ma, W., Pan, Y., *et al*. (2020) MiR-126-5p Promotes Contractile Switching of Aortic Smooth Muscle Cells by Targeting VEPH1 and Alleviates Ang II-Induced Abdominal Aortic Aneurysm in Mice. *Laboratory Investigation*, **100**, 1564-1574. https://doi.org/10.1038/s41374-020-0454-z

[51] Li, L., Ma, W., Pan, S., *et al*. (2020) MiR-126a-5p Limits the Formation of Abdominal Aortic Aneurysm in Mice and Decreases ADAMTS-4 Expression. *Journal of Cellular and Molecular Medicine*, **24**, 7896-7906. https://doi.org/10.1111/jcmm.15422

[52] Rangrez, A.Y., Massy, Z.A., Metzinger-Le Meuth, V., *et al*. (2011) miR-143 and miR-145: Molecular Keys to Switch the Phenotype of Vascular Smooth Muscle Cells. *Circulation*: *Cardiovascular Genetics*, **4**, 197-205. https://doi.org/10.1161/CIRCGENETICS.110.958702

[53] Xin, M., Small, E.M., Sutherland, L.B., *et al*. (2009) MicroRNAs miR-143 and miR-145 Modulate Cytoskeletal Dynamics and Responsiveness of Smooth Muscle Cells to Injury. *Genes & Development*, **23**, 2166-2178. https://doi.org/10.1101/gad.1842409

[54] Lu, W., Zhou, Y., Zeng, S., *et al*. (2021) Loss of FoxO3a Prevents Aortic Aneurysm Formation through Maintenance of VSMC Homeostasis. *Cell Death & Disease*, **12**, 378. https://doi.org/10.1038/s41419-021-03659-y

[55] Hayashi, K., Saga, H., Chimori, Y., *et al*. (1998) Differentiated Phenotype of Smooth Muscle Cells Depends on Signaling Pathways through Insulin-Like Growth Factors and Phosphatidylinositol 3-Kinase. *Journal of Biological Chemistry*, **273**, 28860-28867. https://doi.org/10.1074/jbc.273.44.28860

[56] Hayashi, K., Takahashi, M., Kimura, K., *et al*. (1999) Changes in the Balance of Phosphoinositide 3-Kinase/Protein Kinase B (Akt) and the Mitogen-Activated Protein Kinases (ERK/p38MAPK) Determine a Phenotype of Visceral and Vascular Smooth Muscle Cells. *Journal of Cell Biology*, **145**, 727-740. https://doi.org/10.1083/jcb.145.4.727

[57] Liu, Z.P., Wang, Z., Yanagisawa, H., *et al*. (2005) Phenotypic Modulation of Smooth Muscle Cells through Interaction of Foxo4 and Myocardin. *Developmental Cell*, **9**, 261-270. https://doi.org/10.1016/j.devcel.2005.05.017

[58] Wang, C., Wen, J., Zhou, Y., *et al*. (2015) Apelin Induces Vascular Smooth Muscle Cells Migration via a PI3K/Akt/FoxO3a/MMP-2 Pathway. *The International Journal of Biochemistry & Cell Biology*, **69**, 173-182. https://doi.org/10.1016/j.biocel.2015.10.015

[59] Zhao, G., Fu, Y., Cai, Z., *et al*. (2017) Unspliced XBP1 Confers VSMC Homeostasis and Prevents Aortic Aneurysm Formation via FoxO4 Interaction. *Circulation Research*, **121**, 1331-1345. https://doi.org/10.1161/CIRCRESAHA.117.311450

[60] Murdoch, J.D., Rostosky, C.M., Gowrisankaran, S., *et al*. (2016) Endophilin-A Deficiency Induces the Foxo3a-Fbxo32 Network in the Brain and Causes Dysregulation of Autophagy and the Ubiquitin-Proteasome System. *Cell Reports*, **17**, 1071-1086. https://doi.org/10.1016/j.celrep.2016.09.058

[61] Fitzwalter, B.E., Towers, C.G., Sullivan, K.D., *et al*. (2018) Autophagy Inhibition Mediates Apoptosis Sensitization in Cancer Therapy by Relieving FOXO3a Turnover. *Developmental Cell*, **44**, 555-565.e3. https://doi.org/10.1016/j.devcel.2018.02.014

[62] Wang, C., Xu, W., Zhang, Y., *et al*. (2018) PARP1 Promote Autophagy in Cardiomyocytes via Modulating FoxO3a Transcription. *Cell Death & Disease*, **9**, 1047. https://doi.org/10.1038/s41419-018-1108-6

[63] Dale, M., Fitzgerald, M.P., Liu, Z., *et al*. (2017) Premature Aortic Smooth Muscle Cell Differentiation Contributes to Matrix Dysregulation in Marfan Syndrome. *PLOS ONE*, **12**, e0186603. https://doi.org/10.1371/journal.pone.0186603

[64] Rensen, S.S., Doevendans, P.A. and Van Eys, G.J. (2007) Regulation and Characteristics of Vascular Smooth Muscle Cell Phenotypic Diversity. *Netherlands Heart Journal*, **15**, 100-108. https://doi.org/10.1007/BF03085963

[65] Kim, H.R., Graceffa, P., Ferron, F., *et al*. (2010) Actin Polymerization in Differentiated Vascular Smooth Muscle Cells Requires Vasodilator-Stimulated Phosphoprotein. *The American Journal of Physiology-Cell Physiology*, **298**, C559-C571. https://doi.org/10.1152/ajpcell.00431.2009

[66] Dahal, S., Swaminathan, G., Carney, S., *et al*. (2020) Pro-Elastogenic Effects of Mesenchymal Stem Cell Derived Smooth Muscle Cells in a 3D Collagenous Milieu. *Acta Biomaterialia*, **105**, 180-190. https://doi.org/10.1016/j.actbio.2020.01.030

[67] Psaltis, P.J., Simari, R.D. (2015) Vascular Wall Progenitor Cells in Health and Disease. *Circulation Research*, **116**, 1392-

1412. https://doi.org/10.1161/CIRCRESAHA.116.305368

[68] Dahal, S., Broekelman, T., Mecham, R.P., *et al*. (2018) Maintaining Elastogenicity of Mesenchymal Stem Cell-Derived Smooth Muscle Cells in Two-Dimensional Culture. *Tissue Engineering Part A*, **24**, 979-989. https://doi.org/10.1089/ten.tea.2017.0237

[69] Liu, M. and Gomez, D. (2019) Smooth Muscle Cell Phenotypic Diversity. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **39**, 1715-1723. https://doi.org/10.1161/ATVBAHA.119.312131

[70] Erbel, R., Aboyans, V., Boileau, C., *et al*. (2014) 2014 ESC Guidelines on the Diagnosis and Treatment of Aortic Diseases: Document Covering Acute and Chronic Aortic Diseases of the Thoracic and Abdominal Aorta of the Adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *European Heart Journal*, **35**, 2873-2926. https://doi.org/10.1093/eurheartj/ehu281

[71] Riches, K., Angelini, T.G., Mudhar, G.S., *et al.* (2013) Exploring Smooth Muscle Phenotype and Function in a Bioreactor Model of Abdominal Aortic Aneurysm. *Journal of Translational Medicine*, **11**, 208. https://doi.org/10.1186/1479-5876-11-208

[72] Coppé, J.P., Desprez, P.Y., Krtolica, A., *et al*. (2010) The Senescence-Associated Secretory Phenotype: The Dark Side of Tumor Suppression. *Annual Review of Pathology*, **5**, 99-118. https://doi.org/10.1146/annurev-pathol-121808-102144

[73] Nelson, G., Wordsworth, J., Wang, C., *et al*. (2012) A Senescent Cell Bystander Effect: Senescence-Induced Senescence. *Aging Cell*, **11**, 345-349. https://doi.org/10.1111/j.1474-9726.2012.00795.x

[74] Minami, T., Kuwahara, K., Nakagawa, Y., *et al*. (2012) Reciprocal Expression of MRTF-A and Myocardin Is Crucial for Pathological Vascular Remodelling in Mice. *The EMBO Journal*, **31**, 4428-4440. https://doi.org/10.1038/emboj.2012.296

[75] Gao, P., Gao, P., Zhao, J., *et al*. (2021) MKL1 Cooperates with p38MAPK to Promote Vascular Senescence, Inflammation, and Abdominal Aortic Aneurysm. *Redox Biology*, **41**, Article ID: 101903. https://doi.org/10.1016/j.redox.2021.101903

[76] Brichkina, A., Bertero, T., Loh, H.M., *et al*. (2016) p38MAPK Builds a Hyaluronan Cancer Niche to Drive Lung Tumorigenesis. *Genes & Development*, **30**, 2623-2636. https://doi.org/10.1101/gad.290346.116

[77] Moreno-Cugnon, L., Revuelta, M., Arrizabalaga, O., *et al.* (2019) Neuronal p38$\alpha$ Mediates Age-Associated Neural Stem Cell Exhaustion and Cognitive Decline. *Aging Cell*, **18**, e13044. https://doi.org/10.1111/acel.13044

[78] Medema, R.H. and Macurek, L. (2011) Checkpoint Recovery in Cells: How a Molecular Understanding Can Help in the Fight against Cancer. *F*1000 *Biology Reports*, **3**, Article No. 10. https://doi.org/10.3410/B3-10

[79] Vaziri, H., Dessain, S.K., Ng Eaton, E., *et al*. (2001) hSIR2(SIRT1) Functions as an NAD-Dependent p53 Deacetylase. *Cell*, **107**, 149-159. https://doi.org/10.1016/S0092-8674(01)00527-X

[80] Chen, H.Z., Wang, F., Gao, P., *et al.* (2016) Age-Associated Sirtuin 1 Reduction in Vascular Smooth Muscle Links Vascular Senescence and Inflammation to Abdominal Aortic Aneurysm. *Circulation Research*, **119**, 1076-1088. https://doi.org/10.1161/CIRCRESAHA.116.308895

[81] Guo, W., Gao, R., Zhang, W., *et al*. (2019) IgE Aggravates the Senescence of Smooth Muscle Cells in Abdominal Aortic Aneurysm by Upregulating LincRNA-p21. *Aging and Disease*, **10**, 699-710. https://doi.org/10.14336/AD.2018.1128