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不同脂肪组织与动脉粥样硬化关系的研究进展

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摘　要：动脉粥样硬化是一种复杂的心血管疾病，由动脉内部脂质代谢紊乱和炎症引起，目前仍是全球死亡的主要原因之一。而肥胖引起的脂肪组织功能障碍能够诱发血脂异常、激活血管炎症，促进动脉粥样硬化的发生。脂肪组织包括白色脂肪组织(white adipose tissue, WAT)、棕色脂肪组织(brown adipose tissue, BAT)和血管周围脂肪组织(perivascular adipose tissue, PVAT)。不同类型的脂肪组织对于动脉粥样硬化的发生具有不同的调节作用。肥胖时，WAT释放脂肪酸增加，BAT和胸主动脉PVAT脂质燃烧减少，导致高脂血症，诱导动脉粥样硬化的发生；此外，肥胖时WAT和腹主动脉PVAT释放促炎因子，进一步促进动脉粥样硬化的发生。为了抵抗动脉粥样硬化的发展，减少WAT和腹主动脉PVAT中促炎因子、脂肪酸的释放，或通过激活BAT和胸主动脉PVAT促进WAT棕色化来增加脂肪酸燃烧的策略可能是最有效的。综上所述，在肥胖状态下，减少炎症和增加脂质燃烧的联合治疗可能是抑制动脉粥样硬化有效的方法。该文就不同脂肪组织在动脉粥样硬化发展中的独特作用，以及如何靶向这些脂肪组织以减少动脉粥样硬化的发生进行综述。

关键词：动脉粥样硬化；脂肪组织；脂质代谢；炎症反应；棕色化

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Research progress of different adipose tissues and atherosclerosis

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Abstract: Atherosclerosis is a chronic inflammatory disease characterized by lipid metabolism disorder. The related diseases can be considered as the most important cause of death in the world. The dysfunction of adipose tissue can induce dyslipidemia, activate vascular inflammation and promote the development of atherosclerosis. There are three kinds of adipose tissues including white adipose tissue (WAT), brown adipose tissue (BAT) and perivascular adipose tissue (PVAT), which have different effects on the development of atherosclerosis. In obesity, increased fatty acids release by WAT and decreased lipid combustion by BAT and thoracic PVAT both lead to hyperlipidemia and atherosclerosis. In addition, pro-inflammatory factors released by WAT and abdominal PVAT could further promote atherosclerosis. To resist atherosclerosis development, strategies that reduce the release of pro-inflammatory factors and fatty acids by WAT and abdominal PVAT, or increase combustion of fatty acids by activation of BAT and thoracic PVAT and browning of WAT are probably efficient. In conclusion, combination therapy of reducing inflammation and increasing lipid combustion is probably an effective way to defect atherosclerosis. In this paper, we will focus on the distinct role of different adipose tissues in the development of atherosclerosis, and the therapy to target these adipose tissues to inhibit atherosclerosis.

Key words: atherosclerosis; adipose tissue; lipid metabolism; inflammation; browning

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动脉粥样硬化是由血管壁中低密度脂蛋白(low-density lipoprotein, LDL)和极低密度脂蛋白(very-low-density lipoprotein, VLDL)残余颗粒的滞留增加、积聚引起的[1]。积聚的LDL随即被氧化或进行其他化学修饰，氧化修饰的LDL诱导血管发生炎症反应，招募巨噬细胞吞噬脂质，形成泡沫细胞，导致动脉粥样硬化的发展[2]。在高血压、高血脂等不稳定因素的作用下，动脉粥样硬化斑块脱落，形成血栓，导致严重心血管疾病的发生[3]。

哺乳动物的脂肪组织是机体储存多余热量的主要场所。根据存在的部位、形态以及功能的不同，可以将脂肪组织分类为白色脂肪组织(white adipose tissue, WAT)、棕色脂肪组织(brown adipose tissue, BAT)和血管周围脂肪组织(perivascular adipose tissue, PVAT)(表1)。脂肪组织作为一类具有分泌功能的器官，可以通过内分泌和旁分泌的作用，与包括血管系统在内的其他器官进行交流[4]。肥胖导致的脂肪组织代谢异常可能会促进脂肪细胞脂解，增加释放到循环中的游离脂肪酸 (fatty acids, FAs)[5]，引发高脂血症进而促进动脉粥样硬化的发生。在脂肪组织功能异常的情况下，其分泌的促炎因子增加，作用到血管后会加重血管对于炎症刺激的反应，加剧动脉粥样硬化的发展[6]。脂肪组织功能改善可减少小鼠动脉粥样硬化的发生，并且不同的脂肪组织类型对动脉粥样硬化的发展发挥不同的调节作用[7]，提示脂肪组织可以作为治疗动脉粥样硬化的靶组织。因此，全面了解脂肪组织类型和动脉粥样硬化之间的关系将为动脉粥样硬化高危人群提供新的预防治疗策略。

1　白色脂肪组织与动脉粥样硬化

根据存在部位和功能的不同，白色脂肪组织又可以分为皮下脂肪组织(subcutaneous adipose tissue, SCAT)和内脏脂肪组织(visceral adipose tissue, VAT)。在健康条件下，WAT通过储存脂质作为脂质库，防止脂质在循环中积累，具有抗动脉粥样硬化的作用。相反，在肥胖情况下，WAT扩张造成的脂肪组织功能异常，脂解增加，引起循环中脂质代谢紊乱进而诱发动脉粥样硬化。交感神经激活和激素刺激(如儿茶酚胺、去甲肾上腺素等)[8-9]能够诱导脂解发生，而胰岛素能抑制脂肪细胞的脂解活动。相较于SCAT，VAT对儿茶酚胺更敏感，更容易发生儿茶酚胺诱导的脂解，释放更多的FAs，诱导胰岛素抵抗[10]。这一研究结果提示，VAT积累引起的代谢功能障碍是心血管疾病发生的一个更为危险的因素。

WAT具有免疫调节的特性，其中已经发现存在包括B细胞、T细胞、巨噬细胞和中性粒细胞在内的大量免疫细胞[11]。脂肪细胞肥大会导致JNK (c-Jun N-terminal kinase, JNK)和NF-κB (nuclear factor kappa-B, NF-κB)信号通路的激活，发生氧化应激和内质网应激，释放促炎因子[12-13]。随后，免疫细胞浸润WAT，加剧局部炎症，最终导致系统炎症的发生，表现为激活循环中的免疫细胞，增加循环中的促炎因子和C-反应蛋白[14-15]。脂肪组织炎症会导致血管活性氧(reactive oxygen species, ROS)增加和一氧化氮(nitric oxide, NO)生物利用度下降，诱发血管内皮功能障碍[16]。由此看来，在疾病状态下，WAT的免疫细胞浸润和活化增加能诱导炎症发生以及随后的代谢紊乱，同时脂肪细胞分泌更多促炎因子。而这些变化会破坏血管稳态，导致血管炎症发生。

WAT释放的许多脂肪因子能够直接作用到血管壁。其中，瘦素(Leptin)被证明可以促进促炎因子肿瘤坏死因子α (tumor necrosis factor-α, TNF-α)、白细胞介素-6 (interleukin-6, IL-6)等的表达，诱导内皮ROS，增强巨噬细胞吞噬作用以及促进血管平滑肌细胞的迁移[17-18]。抵抗素(Resistin)会增加人肝脏中LDL的产生并降低LDL受体水平，阻断胆固醇的肝脏排除机制，导致更多LDL在动脉中聚集[19]。其他可能刺激动脉粥样硬化发生的促炎性脂肪因子包括内脂素(Visfatin)[20]和趋化素(Chemerin)[21]。而WAT

表1 不同脂肪组织特征的比较

特征	WAT	BAT	PVAT
脂滴	单个大脂滴	多个小脂滴	多个较小脂滴
线粒体数目	少	多	较多
功能	储存脂质、内分泌功能	产热	产热、调节血管稳态
位置	皮下或内脏	肩胛或锁骨等	血管周围
对动脉粥样硬化的作用	皮下WAT抑制、内脏WAT促进	抑制	胸主动脉PVAT抑制、腹主动脉PVAT促进

分泌的一些其他脂肪因子对动脉粥样硬化具有抵抗作用。脂联素(Adiponectin)能够改善内皮功能障碍[22]，直接抑制血小板来源的生长因子诱导的人平滑肌的增殖和迁移[23]，抑制单核细胞和内皮细胞的黏附[24]，降低巨噬细胞对LDL的摄入和向泡沫细胞的转化[25]。外源Adiponectin处理动脉粥样硬化小鼠，能够减轻小鼠病症[26]。网膜素-1 (Omentin-1)能够改善游离脂肪酸诱导的内皮细胞增殖、迁移和炎症[27]，抑制血管平滑肌细胞增殖和内膜新生[28]。FAM19A5，一种新型的脂肪因子，能够减轻损伤诱导的内膜新生，抑制平滑肌增殖和迁移，进而抵抗心血管疾病的发生[29]。此外，内脏脂肪来源丝氨酸蛋白酶抑制剂(visceral adipose tissue-derived serine protease inhibitor, Vaspin)和爱帕琳肽(Apelin)分别通过抑制ROS生成和促进胆固醇流出，发挥抗动脉粥样硬化的作用[30-31]。

除了分泌因子外，脂肪细胞还会分泌各种类型的胞外囊泡(extracellular vesicles, EVs)[32-33]，包括外泌体和微囊泡。EVs通过蛋白质、脂质和核酸(包括microRNA)的选择性包装，在细胞间通讯中发挥重要作用[34-35]。2018年，研究表明，脂肪细胞与内皮细胞[36]/巨噬细胞[37]之间存在EVs介导的信息交流和物质交换。此外，肥胖动物的VAT来源的外泌体可以通过促进泡沫细胞的形成和巨噬细胞促炎极化来加剧动脉粥样硬化的发展[38]。肥胖动物的脂肪细胞分泌含有miR-221-3p的EVs，miR-221-3p被带入血管平滑肌细胞，促进平滑肌细胞的增殖和迁移[39]。总而言之，WAT通过多种途径实现与血管的交流，在不同情况下，对动脉粥样硬化发展发挥不同的调节作用。

2 棕色脂肪组织与动脉粥样硬化

与WAT储存能量不同，BAT能够燃烧FAs产生热量以维持体温，是机体发生适应性产热的主要场所。近些年的研究表明，除了经典棕色脂肪细胞，啮齿类动物和人类体内还存在另一类产热脂肪细胞，即米色脂肪细胞。米色脂肪细胞存在于SCAT中，其在某些特定的环境信号(如慢性冷暴露)的作用下，被显著诱导，高表达解偶联蛋白1 (uncoupling protein 1, UCP1)，并表现出UCP1依赖的产热能力[40]。棕色和米色脂肪细胞有许多共同的生化特征，包括丰富的线粒体、多腔小脂滴和产热作用。

当细胞内的脂质储存被消耗殆尽时，BAT会从血液中摄取葡萄糖和甘油三酯(triglycerides, TGs)源性的FAs，而这些FAs来自于循环中富含甘油三酯的脂蛋白(triglycerides-rich lipoproteins, TRLs)[41]。与BAT的激活类似，在白色脂肪组织米色化的过程中，葡萄糖和甘油三酯的吸收和代谢增加，增强系统代谢，发挥抵抗包括动脉粥样硬化在内的多种疾病的作用[42]。因此，产热细胞被认为是减缓动脉粥样硬化发展的潜在靶点。

2011年，Bartelt等[43]首先报道了冷暴露激活BAT时，BAT通过增加TRLs的摄入显著降低了高脂血症Apoa5$^{-/-}$小鼠循环中的TGs水平，这一过程依赖于脂蛋白脂肪酶(lipoprotein lipase, LPL)的活性和跨膜受体CD36。随后，众多实验证明，激活BAT能够降低血浆TGs水平，进而缓解高甘油三酯血症[44-45]。然而，增加血浆TRLs中甘油三酯的清除自然也会加速促进动脉粥样硬化的富含胆固醇的脂蛋白残体的形成，这些残体随后通过载脂蛋白E (apolipoprotein E, ApoE)和肝脏低密度脂蛋白受体(LDL receptor, LDLR)从血浆中清除。因此，完整的ApoE-LDLR清除途径对于降低血浆胆固醇水平至关重要。两种经典动脉粥样硬化模型ApoE$^{-/-}$和LDLR$^{-/-}$小鼠，虽然能够诱导动脉粥样硬化的发生，但是，由于这一清除途径受损，冷暴露或者药物激活它们的BAT，会加重小鼠的高脂血症和动脉粥样硬化发展[46-47]。APOE*3-Leiden.CETP小鼠模型能够表达人的ApoE3突变体，减慢了富含胆固醇残体的清除速率，但是保留了肝脏的清除途径[48]。在这种小鼠模型的基础上，研究者们发现激活BAT不仅能够降低血浆中TGs，还能降低胆固醇水平，进而改善动脉粥样硬化[49-50]。2017年的研究显示，产热脂肪细胞还可以通过促进高密度脂蛋白(high-density-lipoprotein, HDL)的周转和肝脏胆固醇的清除，改善动脉粥样硬化[51]。反之，ApoE$^{-/-}$小鼠敲除BAT胰岛素受体可导致BAT萎缩，血脂升高，脂肪组织中促炎标记物的表达增高，并伴随着主动脉根部巨噬细胞的浸润增加，动脉粥样硬化加剧[52]。肥胖诱导的BAT功能失调表现为棕色脂肪细胞的白色化转变和线粒体的功能异常，会导致脂质积累，促进动脉粥样硬化的发生[53]。

BAT的激活除了通过提高脂蛋白清除来降低血脂外，还可以改变不同类型脂肪组织之间的脂质分布，白色脂肪细胞的脂质分解产生的FAs可以被转运到棕色脂肪细胞作为产生热量的底物。脂质以FAs或者TRLs的形式运输到BAT[43]。冷刺激诱导的BAT和WAT之间FAs分布的改变依赖于血管生成素

样蛋白4 (Angptl4)对LPL活性的调节[54-55]。虽然大多数关于BAT通过改善血脂抵抗动脉粥样硬化的数据都是在啮齿类动物中获得的，但也有一些证据表明，BAT激活对人类也有类似的有益影响。例如，每天暴露在寒冷中20 min，持续90 d，可以降低高胆固醇血症患者的总胆固醇和低密度脂蛋白胆固醇[56]，BAT激活的受试者血浆TGs较低，富含胆固醇的高密度脂蛋白(high-density-lipoprotein-cholesterol, HDL-C)水平较高[57]。使用FAs示踪剂[18F]FTHA与[18F]FDG的研究表明，急性冷刺激后BAT对FAs的摄入增加[58]。

WAT能够分泌大量的分泌因子，BAT同样具有分泌功能。棕色和米色脂肪细胞分泌几种特定的脂肪因子，包括神经调节素4 (neuregulin 4, Nrg4)、胰岛素样生长因子1 (insulin-like growth factor 1, IGF-1)、成纤维细胞生长因子21 (fibroblast growth factor 21, FGF21)和IL-6。研究显示，循环中Nrg4与肥胖人群的动脉粥样硬化呈负相关[59]。IGF-1可降低炎症反应，抑制氧化应激及病变中巨噬细胞和泡沫细胞的积累，减轻ApoE$^{-/-}$小鼠的动脉粥样硬化进展[60-61]。FGF21通过维持线粒体动力学和功能，抑制线粒体分裂，减少ROS产生，抑制内质网应激及NOD样受体3 (NOD-like receptors, NLRP3)炎性体介导的血管内皮细胞焦亡，从而减轻动脉粥样硬化[62]。尽管BAT中促炎因子的转录水平低于WAT，但在肥胖者的BAT中促炎细胞因子的表达增强。这些促炎因子能够减弱BAT的功能[63]，从而降低BAT对血脂的燃烧，促进动脉粥样硬化的发展。此外，促炎因子的释放导致全身炎症，从而刺激动脉粥样硬化的形成。将肥胖小鼠置于使BAT失去活性的热中性环境中，会导致性腺WAT、BAT和血管系统炎症增加，并促进动脉粥样硬化的发展[64]，但BAT的激活是否也通过减少炎症来抵抗动脉粥样硬化还有待研究。

3　血管周围脂肪组织与动脉粥样硬化

PVAT是一类与大多数大动脉的外膜并列，对血管具有支撑和保护作用的脂肪组织。PVAT与血管外膜直接接触，对于血管的紧张度、代谢稳态及动脉粥样硬化都有直接的调控作用[65-66]。相较于WAT或BAT这两种远距离脂肪组织对血管的内分泌调节，PVAT的旁分泌作用更加引起人们的重视。

PVAT分泌的活性物质主要包括气体分子(NO和H_2S)和分泌蛋白。动脉粥样硬化与内皮功能障碍密切相关，而内皮发挥正常的功能依赖于NO。NO是由内皮一氧化氮合酶(endothelial nitric oxide synthase, eNOS)产生的，具有抑制血管平滑肌增殖、血小板聚集、白细胞黏附和血管炎症等多种抗动脉粥样硬化特性[67]。健康个体去除PVAT后，小动脉基础NO的生成减少，提示PVAT参与了血管NO的生成[68]。PVAT来源的H_2S可以通过激活平滑肌细胞中的钾通道来降低血管张力，发挥舒张血管作用[69]。PVAT可以分泌Adiponectin，通过增加eNOS磷酸化改善内皮功能异常[70]。PVAT来源的补体3(C3)可以通过激活JNK信号通路，刺激外膜成纤维细胞的迁移和分化，并参与促进高血压模型小鼠的外膜重塑中[71]。PVAT还可以通过分泌血管内皮生长因子(vascular endothelial growth factor, VEGF)和内脂素(Visfatin)促进血管平滑肌细胞的增殖，参与血管功能的调节[72-73]。

B-1细胞来源的免疫球蛋白M (immunoglobulin M, IgM)可以减弱M1巨噬细胞产生促炎性细胞因子。Srikakulapu等[74]研究表明，在年轻的ApoE$^{-/-}$小鼠中，与主动脉相比，PVAT中含有大量分泌IgM的B-1细胞，提示PVAT具有抗炎作用。在疾病状态下，PVAT发生功能异常，表现为免疫细胞（单核细胞、淋巴细胞和粒细胞）的浸润以及促炎脂肪因子、细胞因子和趋化因子的产生。PVAT的炎症可能会传递到血管壁，引起局部平滑肌细胞和内皮功能障碍[75]。Konaniah等[76]发现，LRP1 (low-density lipoprotein receptor-related protein-1)缺失的PVAT表现为促炎表型，Resistin表达升高。此外，LRP1缺失的PVAT移植到小鼠颈动脉后诱导的动脉粥样硬化病变面积是对照小鼠的3倍[76]。临床观察表明，冠状动脉PVAT炎症状态与冠状动脉斑块大小和心血管疾病死亡风险呈正相关[77]。研究证明，功能失调的PVAT与血管的功能异常以及血压失常的发生有关。脂周蛋白Perilipin$^{-/-}$小鼠与肥胖小鼠的状态相似，但PVAT的质量减少，其PVAT的功能失调伴随着主动脉/肠系膜动脉的不良收缩，以及内皮细胞和平滑肌细胞的结构损伤[78]。PVAT中敲低时钟基因Baml1的小鼠表现出血压昼夜节律的失调[79]。Gálvez等[80]关于自发性高血压大鼠的研究结果显示，PVAT的质量和功能的差异与肠系膜动脉抗收缩能力有关。

PVAT中同时包含BAT和WAT，根据解剖位置的不同表现出不同的BAT/WAT比率。啮齿类动物胸主动脉周围的PVAT主要呈棕色表型，而腹主动脉

周围的PVAT呈白色和棕色的混合表型[81]。研究显示，腹主动脉PVAT中的炎症基因和免疫细胞浸润标志物(即巨噬细胞和T细胞)的表达高于胸主动脉PVAT[82]。在大型动物和人类中，腹主动脉比胸主动脉更容易发生动脉粥样硬化[83]，那么是否由于PVAT的不同而导致动脉粥样硬化斑块在整个主动脉分布不均一，需要进一步的研究。虽然不同部位的PVAT可能表现出不同的形态和功能，但人们普遍认为PVAT通过其产热和清除脂肪酸在生理条件下抑制动脉粥样硬化。冷暴露可激活PVAT，并伴随着ApoE$^{-/-}$小鼠动脉粥样硬化斑块的减少，而在PVAT缺失的小鼠中，这种保护作用消失了，提示PVAT的产热特性具有抗动脉粥样硬化的作用[84-85]。

在生理条件下，PVAT可以通过分泌多种生物活性因子，诱导非颤抖性产热和脂肪酸代谢，发挥抵抗动脉粥样硬化的作用。而在病理状态下，PVAT功能失调，产热能力降低，分泌促炎因子，诱导内皮功能障碍和炎性细胞浸润，促进动脉粥样硬化的发展。

4 预防和治疗策略

4.1 促进WAT的脂质贮存

以WAT为靶点降低血浆甘油三酯水平的一种方法是刺激脂质储存，减少脂肪酸向循环中的释放。噻唑烷二酮类(TZDs)和二甲双胍(Metformin)是目前已经得到认可的，能够促进健康脂质储存和提高胰岛素敏感性的药物。LYSO-7作为新型TZDs，能够通过调节脂质代谢和改善炎症，抵抗动脉粥样硬化[86]。在人体中，TZD药物吡格列酮可降低甘油三酯、颈动脉内膜中膜厚度[87]和冠状动脉粥样硬化斑块体积[88]。二甲双胍通过激活5'腺苷单磷酸活化蛋白激酶(adenosine monophosphate activated protein kinase, AMPK)增强胰岛素敏感性，广泛应用于2型糖尿病的降糖治疗。值得注意的是，二甲双胍也能够降低血浆中的甘油三酯和胆固醇，并且可以通过血液AMPK直接抑制血糖正常小鼠的动脉粥样硬化[89]。纤维酸盐(Fibrates)通过激活细胞内受体过氧化物酶体增殖活化受体α (peroxisome proliferator-activated receptor alpha, PPAR-α)上调HDL，增加LPL介导的脂解，并促进胆固醇从泡沫细胞逆向转运至HDL[90]。但储存白色脂肪细胞的脂质增加可能会导致WAT肥大、胰岛素抵抗和炎症发生。因此，应该在保持胰岛素敏感性的同时，促进白色脂肪细胞的健康扩张。

4.2 促进白色脂肪棕色化或激活BAT

与经典的棕色脂肪细胞相似，米色脂肪细胞也可以利用甘油三酯进行非颤抖产热。冷刺激和儿茶酚胺刺激是公认的诱导WAT棕色化的方法[91-92]。另外，还有多种促进WAT棕色化的方法被报道，包括β3-肾上腺素能受体激动剂[93]、激活β2-肾上腺素能受体[94]、激活AMPK[95]、乳酸盐[96]、肠道菌群[97]、甲状腺素[98]、 FGF21[99]和骨形成蛋白(BMP4[100]和BMP7[101])。β3-肾上腺素能受体的激动剂CL-316243可以有效促进BAT对于脂质的摄入[50]。他汀类药物治疗可加速肝脏吸收BAT活化产生的脂质残体，增强BAT活化的降脂和抗动脉粥样硬化作用[102]。在人体中，寒冷和甲状腺激素已经被证明能够有效激活BAT。在临床前的研究中，许多化合物被证实可以激活BAT，其中利莫那班[103]、二甲双胍[104] 和水杨酰水杨酸[44]可以降低血浆中甘油三酯水平。免疫系统的各种成分，包括巨噬细胞[105]、嗜酸粒细胞[106]、第二组先天性淋巴样细胞(ILC2)[107]也能够促进WAT棕色化。

此外，近期的研究显示，脂肪细胞缺氧诱导因子2α (hypoxia-inducible factor-2α, HIF-2α)可以通过激活神经酰胺分解，增加肝脏胆固醇的清除和脂肪组织的产热，进而发挥抵抗动脉粥样硬化的作用，并且国内批准用于贫血治疗的缺氧诱导因子脯氨酰羟化酶抑制剂(hypoxia-inducible factor prolyl hydroxylase inhibitor) FG-4592能够激活脂肪细胞HIF-2α，对小鼠动脉粥样硬化具有预防作用[108]。因此，诱导WAT的棕色化和激活BAT都是有效降低血浆甘油三酯水平和预防动脉粥样硬化的策略。

4.3 抑制PVAT的肾素-醛固酮系统和促进PVAT棕色化

肾素-血管紧张素醛固酮系统(renin angiotensin aldosterone system, RAAS)参与全身血压调节和肾脏电解质稳态。除了肾素，RAAS系统的所有成分都在脂肪组织中表达[109]。已有文献报道PVAT中能检测到RAAS成分的活性[110]，血管紧张素II (AngII)是RAAS的主要成分，具有收缩血管、刺激肾上腺醛固酮释放、保障钠水重吸收等多种生理作用。AngII通过两种主要的膜受体发挥作用：血管紧张素1型受体(angiotensin type l receptor, AT1R)和血管紧张素2型受体(AT2R)。Sakaue等[111]研究表明，PVAT中的AT1R促进血管炎症和动脉瘤的形成。血管紧张素受体阻滞剂(angiotensin receptor blockers, ARBs)和血管紧张素转换酶抑制剂(angiotensin converting

enzyme inhibitor, ACEI)都能够减少PVAT炎症，改善动脉粥样硬化[112]。2016年，研究人员利用脂肪组织特异性过表达盐皮质激素受体的小鼠，发现了醛固酮对脂肪组织的直接作用，并与代谢综合征、胰岛素抵抗以及脂肪组织促炎表型相关[113]。因此，RAAS抑制剂，如ACEI、ARBs和醛固酮抑制剂可能通过作用于脂肪组织，进而对代谢和心血管系统发挥有益作用。

PVAT的产热能够调节血管温度，清除血脂，改善动脉粥样硬化[84]。PVAT中过表达CISD1蛋白(CDGSH iron sulfur domain 1 protein)能够激活PVAT产热，进而减少PVAT炎症，阻止动脉粥样硬化的发展[114]。本课题组的前期实验也证明线粒体基因RPS3a能够激活心外膜脂肪细胞产热，改善血管内皮细胞炎症，预防心血管疾病的发生[115]。因此，激活PVAT的产热能力，对其发挥改善动脉粥样硬化病变的作用具有重要意义。

4.4　抵抗炎症策略

经常用于治疗心血管疾病的PPARα受体激动剂和他汀类药物，都被证明可以通过增强Adiponectin的作用和抑制炎症信号通路激活，降低脂肪组织炎症[116-117]。水杨酸盐能促进巨噬细胞M2型极化[44]，并通过抑制NF-κB增加动脉粥样硬化斑块的稳定性[118]。此外，膳食类黄酮和雌激素也被认为可以缓解脂肪组织的炎症[119-120]。近期的研究显示，间充质干细胞来源的体液因子能够通过抑制内皮细胞表达细胞黏附分子和巨噬细胞在血管壁的聚集，改善动脉粥样硬化[121]。虽然在BAT和PVAT中对免疫细胞的研究很少，但所有的WAT中都有大量的免疫细胞和细胞因子，它们与肥胖相关的疾病有关，包括动脉粥样硬化。肥胖时，脂肪组织释放的炎性细胞因子可导致肥胖相关的全身炎症，但其在肥胖相关炎症性动脉粥样硬化中的确切作用机制尚不清楚。

5　总结

综上所述，脂肪组织与动脉粥样硬化的发展存在密切的联系，WAT、BAT和PVAT在调节血管稳态和抑制动脉粥样硬化发展中都发挥着重要作用。在健康人体内，WAT起着脂质储存的作用，以保持血管的清洁。BAT燃烧脂肪产生热量，进而从血液中摄取甘油三酯衍生的脂肪酸，导致富含胆固醇的残体被肝脏清除。PVAT具有BAT和WAT的特性，因为它能够储存和燃烧脂肪。肥胖时，WAT的脂解增加会导致高甘油三酯血症，BAT活性降低，PVAT功能失调，这些都会导致动脉粥样硬化的发生。最重要的是，WAT和PVAT释放的细胞因子和脂肪因子的平衡会由于肥胖中脂质溢出而向促炎方向转移。这些促炎因子的免疫调节特性进一步促进了动脉粥样硬化的发展(图1)。因此，针对脂肪细胞功能障碍的研究可能成为未来预防或治疗肥胖相关心血

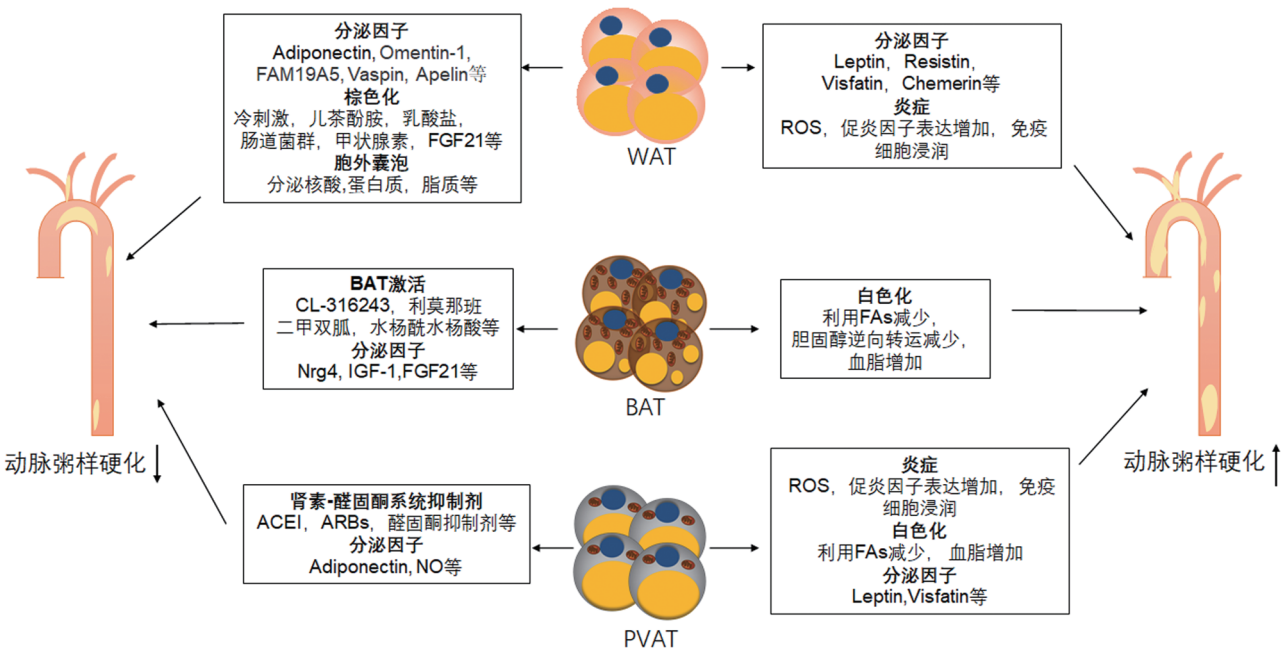

图1　脂肪组织在动脉粥样硬化发展中的作用

管疾病的有效方法，并且治疗时应关注WAT、BAT和PVAT的独特特性，以降低血浆甘油三酯水平和全身炎症。

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