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脂肪因子网膜素与动脉粥样硬化的关系

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[关键词]　脂肪因子；　网膜素；　动脉粥样硬化

[摘　要]　网膜素是由内脏脂肪组织分泌的一种细胞因子，能够增强胰岛素敏感性，与代谢综合征、炎症性疾病等多种疾病密切相关。循环网膜素水平是颈动脉粥样斑块的独立预测因素，表明网膜素可能参与了动脉粥样硬化发生发展的调控。网膜素可能通过内皮细胞保护作用、抑制巨噬细胞源性泡沫细胞形成、抑制血管平滑肌细胞的增殖、迁移、分泌以及抗炎作用发挥着抗动脉粥样硬化作用。文章将对网膜素的生物学特性、生理病理作用以及网膜素与动脉粥样硬化关系的研究进展作一综述。

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The adipocytokine omentin and its relationship with atherosclerosis

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[**KEY WORDS**]　Adipocytokine;　Omentin;　Atherosclerosis

[**ABSTRACT**]　The newly found adipocytokine omentin, secreted from visceral fat tissue, is reported to have close revelation with metabolic syndrome and inflammatory diseases with the ability of improving insulin sensitivity.　As an independent indicator of the existence of carotid atherosclerosis plaque, omentin might regulate the incidence and development of atherosclerosis.　Omentin may play an anti-atherosclerosis role by protecting endothelia cells from injuries, inhibiting the formation of macrophage-derived foam cells, suppressing the proliferation, migration and the secreting of smooth muscle cells, as well as its anti-inflammatory effects.　This review mainly goes through the papers in terms of omentin and its relationship with atherosclerosis, which may provide a valuable view of atherosclerosis.

心脑血管疾病仍为我国居民头号杀手，而肥胖相关的心血管事件逐年上升[1]。肥胖是动脉粥样硬化的重要危险因素，动脉粥样硬化是心脑血管事件的基础病理变化[2-3]。因此研究肥胖导致的动脉粥样硬化有利于控制动脉粥样硬化相关的心脑血管事件发生。脂肪组织不仅是能量储存器官，还是重要的内分泌器官，其分泌的细胞因子称为脂肪因子[4]。脂肪因子可作用于血管内皮细胞、血管平滑肌细胞以及巨噬细胞影响血管壁状态，进而参与动脉粥样硬化病变的调控。近年发现，脂肪因子网膜素(omentin)的外周血浓度在动脉粥样硬化及缺血性心脏病患者中明显降低[5-7]，并且可作为颈动脉粥样斑块的独立预测因素[8-9]，提示网膜素可能是动脉粥样硬化的保护因素。本文拟对网膜素与动脉粥样硬化的研究进行综述。

1　网膜素的生物学特性和生理病理作用

网膜素由 Yang Rong-Ze 等在 2003 年从 cDNA 文库发现，其基因位于与糖尿病相关的染色体区段 1q21.3，包含 8 个外显子、7 个内含子[10]。是由网膜脂肪组织主要表达的一种脂肪因子，由脂肪组织间

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质血管分泌,并且在内皮细胞、肺、小肠、结肠、卵巢以及胎盘组织中也有表达[11-12]。网膜素的蛋白质空间结构包含两个高度扭转的β-折叠及其周围7个短α-螺旋和随机卷曲结构[13]。网膜素有两种同源异构体,分别命名为网膜素1(omentin-1)和网膜素2(omentin-2)。这两者的氨基酸序列有83%的同源性,但是参与血液循环的主要是网膜素1[14]。因此网膜素1是目前的主要研究对象。

Moreno-Navarrete 等[15]在比较248位糖耐量正常及糖耐量受损受试者发现,循环网膜素水平越高,胰岛素敏感性越高。Mazakitovi 等[16]比较妊娠妇女宫外组织、胎儿组织及新生儿组织网膜素的表达水平发现胎儿及新生儿组织表达水平较高,推测其在生理状态下可能通过胰岛素增敏作用发挥着促进生长的作用。

在病理状况下,网膜素与机体异常代谢相关。肥胖患者血浆网膜素1浓度较正常人降低[17],但其减重后,可逆转这一现象[18]。在糖耐量受损、2型糖尿病患者以及伴有超重、胰岛素抵抗的多囊卵巢综合征患者中也发现网膜素1浓度降低[19-20]。网膜素1血浆浓度还与腰围、血脂等多种代谢性的危险因素呈负相关[21]。Bremer 等[22]发现在代谢综合征患者中,血浆与皮下脂肪组织中的网膜素1水平均下降。

网膜素还可能参与了炎症反应。伴发超重、胰岛素抵抗的多囊卵巢综合征患者在经过二甲双胍治疗后,炎症指标血浆C反应蛋白(C-reactive protein,CRP)的变化可预测网膜素1的变化[23],提示网膜素1可能参与了炎症反应。克罗恩病患者的网膜脂肪组织中网膜素mRNA表达水平不一,这可能与慢性炎症性肠病的肠道透壁炎症相关[12]。而类风湿性关节炎患者关节滑液网膜素水平高于骨关节炎患者[24],表明网膜素可能参与了局部炎症反应。

2 网膜素与动脉粥样硬化的关系

动脉粥样硬化的基本病理变化是动脉内膜脂质沉积、内膜灶状纤维化、粥样斑块形成。动脉粥样硬化主要累及大中动脉,可导致心脏、脑及四肢动脉的缺血甚至梗死[25-26]。颈部动脉超声可检测颈动脉内膜中膜厚度、颈动脉斑块,反应周围动脉粥样硬化程度。而肱踝脉搏波传导速度(brachial ankle pulse wave velocity,BaPWV)则提示动脉粥样硬化所致的动脉中层退行性改变。Kadoglou 等[27]将入组受试者分为重度动脉粥样硬化、轻度动脉粥样硬化及无动脉粥样硬化后发现,重度动脉粥样硬化和轻度动脉粥样硬化组血清网膜素1浓度低于无动脉粥样硬化组。Shibata 等[8]对日本健康男性的观察发现,独立于年龄因素,网膜素1与早期动脉粥样硬化的指标——颈动脉内膜中膜厚度呈负相关。Yoo 等[9]在对韩国2型糖尿病人群的研究中发现,血浆网膜素1是预测2型糖尿病患者是否存在颈动脉粥样斑块的可靠因素,较高水平的网膜素提示颈动脉粥样斑块发生的可能性低;此外血浆网膜素1是2型糖尿病患者BaPWV的独立负相关影响因素,并且在校正年龄、性别、体质指数后这种相关性仍然存在。这两项临床观察提示网膜素1与动脉粥样硬化呈负相关,可能发挥着抗动脉粥样硬化作用。

2.1 网膜素与血管内皮细胞

血管内皮细胞对损伤的反应是动脉粥样硬化的始动环节[25-26]。网膜素1的抗动脉粥样硬化作用可能与其内皮细胞保护作用相关。网膜素1能够抑制机械性损伤引起的血管内膜增生和细胞增殖[28]。在校准年龄、体质指数、CRP等因素后,网膜素1仍然能影响一氧化氮(nitric oxide,NO)引起的血管舒张[15],而内皮NO的缺乏会促进动脉粥样病变的发生[29]。动物实验进一步证明网膜素1的内皮保护作用通过调节NO实现的。并且对大鼠血管给予重组人网膜素蛋白后也可通过内皮型一氧化氮合酶(endothelial nitric oxide synthase,eNOS)通路对血管产生舒张作用[30]。腺病毒网膜素载体系统作用于小鼠后,伴随着eNOS的增加,网膜素促进了缺血肢体血流量的恢复,增加毛细血管密度[31]。此外,对人类脐静脉内皮细胞给予重组人网膜素处理后发现,网膜素能促进内皮细胞向血管样结构分化,并且能抑制内皮细胞的凋亡[31]。

2.2 网膜素与血管巨噬细胞、平滑肌细胞

在动脉粥样硬化的早期病变中,损伤的血管内皮细胞分泌细胞间黏附分子1(intercellular adhesion molecule-1,ICAM-1)、血管细胞黏附分子1(vascular cell adhesion molecule-1,VCAM-1)、环氧合酶2(cyclooxygenase-2,COX-2)及血小板源生长因子(platelet-derived growth factor,PDGF)等引起单核细胞黏附并迁移入损伤的内皮中,继而诱导巨噬细胞源性泡沫细胞聚集在内皮下形成动脉粥样硬化的早期病变——脂纹[32]。在巨噬细胞源性泡沫细胞形成过程中,网膜素1通过下调巨噬细胞CD36、清道夫受体A、乙酰辅酶A及上调中性胆固醇酯酶水

解酶抑制氧化型低密度脂蛋白引起的泡沫细胞形成[23]。巨噬细胞给予网膜素后,可降低胞内脂滴及胆固醇酯合成酶的表达[33],进而抑制巨噬细胞向泡沫细胞的转化。

ICAM-1、VCAM-1、COX-2、PDGF 等生长因子还可以引起血管平滑肌细胞的激活,而激活的血管平滑肌细胞可迁入血管内膜并且增殖、转化为泡沫细胞、合成包含胶原纤维与弹力蛋白等成分的细胞基质。平滑肌细胞的迁移增殖、泡沫细胞的形成促使动脉粥样硬化病变进一步发展,动脉管壁增厚,粥样斑块形成,血流动力学发生改变,继而引起心脑血管病变[25]。然而,网膜素 1 能够抑制 PDGF 与内皮生长因子(endothelia growth factor, EGF)引起的平滑肌细胞增殖与迁移[28]。这种作用可能是通过激活 p38 和 c-Jun 氨基端激酶(c-Jun N-terminal kinase,JNK)通路,抑制下游平滑肌细胞肿瘤坏死因子 α(tumor necrosis factor-α,TNF-α)介导的 VCAM-1 的表达[34]和一磷酸腺苷活化蛋白激酶(adenosine monophosphate-activated protein kinase,AMPK)磷酸化而实现的[28,35-36]。网膜素 1 还能抑制细胞基质的重要组成部分Ⅰ型胶原和Ⅲ型胶原蛋白的分泌[23]。

因此,网膜素可能通过巨噬细胞源性泡沫细胞的形成、血管平滑肌细胞的增殖、迁移、分泌抑制动脉粥样硬化的发生发展。

2.3 网膜素与血管炎症反应

Ross[25]认为,炎症反应是动脉粥样硬化发生发展中的核心因素。网膜素在血管炎症反应中发挥着抗炎作用。Moreno-Navarrete 等[15]在白种人群中观察到网膜素与炎症因子 CRP、白细胞介素 6(interleukin 6,IL-6)呈负相关。体外实验进一步表明网膜素 1 抑制 CRP、血管内皮生长因子(vascular endothelial growth factor,VEGF)引起的血管内皮迁移和血管生成,以及 CRP、TNF-α 引起的核因子 κB(nuclear factor kappa B, NF-κB)活化[15]。网膜素 1 还能够通过 AMPK 抑制 JNK 活化从而降低 COX-2 表达,发挥抗血管炎症作用[37]。人类脐静脉内皮细胞中,网膜素 1 抑制 TNF-α 介导的 THP-1 单核细胞黏附。内皮细胞中,网膜素 1 通过 NF-κB 抑制 TNF-α 介导的 ICAM-1 和 VCAM-1 的表达[38]。网膜素 1 还可抑制 TNF-α 介导的平滑肌细胞 ICAM-1 和 VCAM-1 的表达及单核细胞对平滑肌细胞的黏附作用[34]。在巨噬细胞中,网膜素 1 促进抗炎表型 M2 的上调、促炎表型 M1 的下调及降低 TNF-α、IL-16 的表达水平[23,28]。动脉粥样硬化模型小鼠给予网膜素 1 可降低小鼠血浆中胆固醇浓度,缩小主动脉动脉粥样硬化病理损伤,抑制粥样斑块中单核/巨噬细胞的渗出、平滑肌细胞的增殖及胶原蛋白的分泌[23]。载脂蛋白 E 基因缺乏小鼠和表达人类网膜素 1 小鼠杂交后,其后代小鼠主动脉粥样斑块面积较基因缺陷小鼠减小;并且在其主动脉中,巨噬细胞来源的 TNF-α、IL-6、单核细胞趋化蛋白 1 等促炎因子表达减少[33]。网膜素可能通过抑制炎症因子的效应或者直接抑制炎症因子分泌发挥血管抗炎作用。

综上所述,网膜素通过内皮保护作用、平滑肌细胞增殖、迁移和巨噬细胞源性泡沫细胞形成的抑制作用以及抗血管炎症作用,从而对动脉粥样硬化导致的心脑血管疾病产生保护作用。网膜素 1 能够促进蛋白激酶 B(protein kinase B, PKB)磷酸化,进而激活 eNOS 通路;在 TNF-α 介导下,网膜素 1 能够抑制 JNK 及细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)通路发挥下游效应[28,31,33,36-37]。但是网膜素 1 相互作用的受体仍未知晓,其下游信号分子及相互作用效应也不甚明了。并且在不同人群中的观察中,网膜素对动脉粥样硬化心脑血管并发症的影响不尽相同。在对日本男性的观察中发现,冠状动脉粥样硬化型心脏病患者血浆网膜素 1 水平较健康男性更低[39],提示网膜素对冠心病有保护作用。而在针对白种人的临床观察中发现,网膜素可能与卒中存在相关性[40],但是与冠心病却没有相关性[40-41]。由此可见,网膜素 1 对动脉粥样硬化及其并发症的作用效应仍有待进一步研究。

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