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评 述 血管稳态与重构的调控机制专辑

基质微环境和血管稳态

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摘要 心血管疾病是中国及全球人口死亡的主要原因, 且患病率持续上升. 心血管疾病的发生发展与血管稳态失衡和病理性血管重塑密切相关. 近年来的研究发现, 细胞外基质与血管壁细胞的交互作用参与血管稳态的调控, 深入了解基质微环境对血管稳态及血管重构的调控机制, 发掘血管重构相关的心血管疾病的治疗药物有重要意义. 本课题组及合作者在国家自然科学基金"血管稳态与重构的调控机制"重大研究计划的资助下开展了一系列研究工作, 对在生理和病理条件下基质蛋白对血管结构和功能的调控作用进行了深入探索. 本文围绕基质微环境对血管稳态与重构的作用, 重点对细胞外基质蛋白调控血管稳态的机制进行综述, 以期为高血压、动脉粥样硬化、血管再狭窄、血管钙化和动脉瘤等心血管疾病的防治提供新的思路和理论指导.

关键词 血管稳态, 基质微环境, 细胞外基质蛋白, 心血管疾病

我国心血管病人数为2.9亿, 占总死亡原因的首位(41%)[1]. 心血管病与动脉粥样硬化及其相关的血管再狭窄、钙化、主动脉瘤等血管病变密切相关, 多呈慢性进行性发展. 动脉粥样硬化所引起的脑卒中和心肌梗塞等病变危害最大, 致残率和致死率最高; 心梗后支架或搭桥术后的再狭窄是目前尚未完全解决的临床问题; 冠脉钙化是急性心血管事件的独立预测因子, 任何部位的钙化均增加3~4倍心血管事件的发生率; 主动脉瘤破裂是极其凶险的危重病, 目前无药可治, 发病机制亟待深入研究.

血管稳态是血管正常发挥功能的重要基石, 血管自稳态失衡及不良重构促进多种心血管疾病的发生发展. 在各种内外环境损伤因素的刺激下, 血管可以通过多种精细的调控机制, 维持血管自稳态. 其中, 血管内皮细胞作为首要防线, 通过合成和分泌多种血管活性物质如一氧化氮等, 调控血管张力、凝血及炎症过程. 血管平滑肌细胞通过收缩和舒张活动维持血管壁的张力、血压和血流分布. 近年来, 人们还注意到血管外膜的成纤维细胞和管周脂肪细胞等通过自分泌或旁分泌作用, 共同调节血管功能. 相比之下, 血管中占半数以上组成的基质蛋白在血管稳态调控中的作用, 则长期被忽视. 因此, 阐明基质微环境对血管稳态的调控机制, 对探索心血管疾病新的防治方法具有重要意义.

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1 基质微环境概述

细胞外基质蛋白由一系列生物大分子组成, 包括胶原蛋白、弹性蛋白及一些非结构蛋白, 如多种蛋白多糖和糖蛋白. 广义的细胞外基质, 还包括充斥于胞外基质的各种细胞因子、生长因子、基质蛋白酶和各种具有生物学功能的基质成分降解产物等. 它们通过复杂的蛋白-蛋白相互结合, 构成基质蛋白网络, 不仅为组织细胞提供支持和保护, 还可调节多种生长因子活性, 与细胞膜上重要的信号转导受体如整合素结合, 调控细胞识别、分化、黏附、增殖、迁移、衰老、凋亡等诸多生物学行为[2]. 胞外基质蛋白呈动态变化, 在疾病的不同时段表现为网络调控的异常, 影响到基质的支撑、巢穴、屏障、信息汇聚和传递功能, 进而引起细胞表型和组织结构的变化, 最后产生病理形态和组织器官的损伤. 基质蛋白网络的生物学功能及其重构在肿瘤、关节炎等疾病发生发展中的作用正受到越来越多的关注和重视, 而关于血管细胞外基质的认识才刚刚起步.

2 血管基质蛋白的组成

细胞外基质蛋白是血管壁的主要非细胞组分, 其成分的识别对于揭示生理和病理条件下血管动态结构和功能特征至关重要. 基质组学是一种蛋白质组学方法, 通过将组织去细胞化, 细胞外基质蛋白溶解和去糖基化, 进行液相色谱串联质谱分析, 可以获得细胞外基质蛋白的种类和数量的全面信息[3~5]. Mayr课题组[5]利用基质组学方法在人主动脉中鉴定了103种不同的细胞外基质蛋白, 其中包括弹性蛋白、胶原蛋白、糖蛋白和蛋白多糖, 以及蛋白酶及其抑制剂, 在支架成形术后猪的血管也发现了150多种基质蛋白.

细胞外基质蛋白组成在血管壁的不同层中有所不同[6]. 在血管内膜, Ⅳ型胶原和XV型胶原、XVIII型胶原、laminin、nidogen、perlecan、agrin、纤连蛋白等一起构成薄层网状基底膜, 为内皮细胞提供锚定支持[7]. 内弹力板主要由弹性蛋白构成, 将血管内膜与中膜分开. 在中膜层, 弹性蛋白沉积于由fibrilin、微原纤维相关糖蛋白(microfibrillar-associated glycoproteins, MAGP)、微原纤维相关蛋白(microfibrillar-associated proteins, MFAP)和fibulin构成的微纤维骨架上, 赖氨酰氧化酶(lysyl oxidase, LOX)交联弹性蛋白形成三维层状网络; 平滑肌细胞和弹力板成同心圆排列, 构成血管壁的收缩功能单元, 在心动周期中调节血管壁的收缩和扩张[8,9]; 弹力板间还分布着Ⅰ、Ⅲ、Ⅴ和Ⅵ型胶原、纤连蛋白、laminin、蛋白聚糖和糖蛋白[10]. 外膜中的主要细胞外基质成分是Ⅰ型和Ⅲ型胶原、硫酸软骨素和硫酸皮肤素蛋白多糖、纤连蛋白及由外膜成纤维细胞分泌的其他基质蛋白[10]. 分泌到中膜和外膜中的原胶原纤维通过LOX交联, 增加血管壁强度, 限制血管过度舒张. 血管细胞外基质还含有多种非结构性基质蛋白, 包括血小板反应蛋白(thrombospondins, TSPs)、tenascin C、骨桥蛋白(osteopontin, OPN)、酸性和富含半胱氨酸的分泌蛋白(secreted protein acidic and rich in cysteine, SPARC)等, 调节细胞黏附、增殖、迁移和细胞因子相关反应. 另外, 血管壁还含有丰富的细胞因子和各类生长因子, 如转化生长因子(transforming growth factor beta, TGFβ)、血小板衍生生长因子(platelet-derived growth factor, PDGF)、血管内皮生长因子(vascular endothelial growth factor, VEGF)等.

3 血管基质蛋白的动态调控

血管壁中的大多数细胞外基质成分是高度动态的, 不断合成、降解和交互作用以维持血管动态平衡. 水解细胞外基质的蛋白酶包括基质金属蛋白酶(matrix metalloproteinases, MMPs)、去整合素和金属蛋白酶(A disintegrin and metalloproteinase, ADAM)的成员以及具有血小板反应蛋白基序的去整合素和金属蛋白酶(A disintegrin and metalloproteinase with thrombospondin motifs, ADAMTS)家族、丝氨酸蛋白酶(如纤溶酶、中性粒细胞弹性蛋白酶和组织蛋白酶G)、半胱氨酸蛋白酶(如组织蛋白酶B, L和S)和天冬氨酰蛋白酶(如组织蛋白酶D)[11]. 其中, 对MMPs的研究最为广泛. 在血管组织中, 弹力纤维可被MMP-2, MMP-7, MMP-9, MMP-12降解, 胶原蛋白主要被MMP-1, MMP-8, MMP-13, MMP-18降解[12,13]. MMPs的活性受到内源性组织金属蛋白酶抑制剂(tissue inhibitors of metalloproteinases, TIMPs)的调控. 血管细胞外基质的代谢受到如MMP和TIMP平衡调节, MMP/TIMP比例失调将导致细胞外基质稳态受损. ADAMs是一类锚定于细胞

膜的脱落酶, 选择性剪切膜蛋白, 如CD23, CD30, L-selectin, E-cadherin和Notch等分子, 调节膜结合蛋白、生长因子、细胞因子、配体和受体的脱落[14]. 此外, ADAM10, ADAM12和ADAM15可切割细胞外基质蛋白Ⅳ型胶原和fibronectin, ADAM9, ADAM10和ADAM17可剪切XVII型胶原和laminin. ADAMTS家族有19个成员, 除ADAMTS-13分泌于血浆中外, 其余ADAMTSs主要在细胞外基质发挥作用. ADAMTS-1, ADAMTS-4, ADAMTS-5, ADAMTS-8和ADAMTS-15可降解蛋白聚糖, 又称蛋白聚糖酶[15]; ADAMTS-2是一种前胶原N-末端前肽酶, 可切割Ⅰ、Ⅱ和Ⅲ型胶原的N-末端前肽[16]; ADAMTS-3和ADAMTS-4可离体剪切前胶原蛋白[17]; ADAMTS-6, ADAMTS-10和ADAMTS-17调节fibrillin微纤维形成[18,19]; ADAMTS-13特异切割vWF, 缺乏可致血栓性血小板减少性紫癜. 丝氨酸蛋白酶家族是蛋白酶中最大的一类, 中性粒细胞弹性蛋白酶和组织蛋白酶G可以降解弹性蛋白、胶原(Ⅰ、Ⅱ、Ⅲ、Ⅳ、Ⅵ型)、fibronectin、laminin和aggrecan等基质蛋白, 还可通过激活基质金属蛋白酶酶原和灭活其抑制物, 间接参与细胞外基质的分解[20~23]. 组织蛋白酶B, L和S能有效分解弹性蛋白和胶原[24], 组蛋白酶D在酸性环境下降解aggrecan和胶原[25]. 血管中的新基质成分和蛋白酶数以百计, 然而, 其相互作用蛋白及网络调控体系尚未建立, 其降解酶在生理与病生理状态下的变化规律和作用机制远未阐明. 降解组学是揭示蛋白酶及其抑制剂、底物和相互作用物的组学方法, 利用高通量技术、底物氨基末端同位素标记(terminal amine isotopic labeling of substrates, TAILS)和液相色谱, 可以对蛋白酶和其底物水解片段进行鉴定和定量分析[26,27]. 目前的研究用降解组学鉴定了人类血管系统中MMP-3, MMP-9, MMP-12, MMP-14和ADAMTS-7的底物[28~30], 但其他蛋白酶底物谱和降解特点尚不清楚, 利用降解组学等方法进行深入分析, 将促进对血管基质蛋白代谢和稳态调控的全面了解.

血管基质蛋白在生理和病理刺激下, 其拓扑结构会相应发生改变, 以适应机体需求. 弹性蛋白和胶原纤维构成的复杂网络结构是血管壁的主要承压成分, Chow等人[31]通过多光子成像等方法观察了在机械负荷下弹性蛋白和胶原纤维的组织、重排和募集的变化. 中膜胶原纤维在静息状态下呈波浪状, 而在牵张过程中呈现接合和圆周分布; 外膜胶原蛋白初始以较大的波浪状纤维束存在, 在>20%的牵张时开始接合; 中膜和外膜胶原纤维在双轴负荷不等时, 将沿主要负荷方向重新排列; 中膜弹性纤维在负荷增加时开始变直, 在>20%牵张时达到极限. 另一项研究也报道了加压过程中胸主动脉弹性蛋白和胶原纤维长度和结构的变化, 小鼠主动脉腔内压力增加会导致胶原纤维的波纹减少. 另外, 平滑肌层中的胶原纤维比弹力板中胶原纤维的强度更大[32]. 因此, 由于不同血管层的异质性以及胶原蛋白和弹性蛋白的不同机械性能, 压力等引起的基质蛋白拓扑结构改变是多样的.

在衰老和其他病理状态下, 血管发生细胞外基质重塑, 血管硬度增加, 与高血压和心肌梗死等心血管病风险正相关[33]. 大动脉的硬度主要取决于胶原蛋白和弹性蛋白. 研究报道, 反映动脉硬度的脉搏波速度(pulse wave velocity, PWV)与血管壁胶原蛋白的相对含量呈正相关, 与弹性蛋白的相对含量呈负相关[34~36]. Martínez-Revelles等人[37]指出, 在平滑肌过表达LOX的小鼠中弹性蛋白交联紊乱, 动脉硬度增加. 另外, 纤连蛋白、fibulin、糖胺聚糖和蛋白聚糖的沉积也会影响动脉壁的机械特性[38]. 在醛固酮盐诱导的高血压大鼠中, 血管壁胶原蛋白和弹性蛋白的含量无明显变化, 但纤连蛋白累积, 颈动脉僵硬度增加[39]. 透明质酸转基因小鼠的主动脉硬度和强度增强, 透明质酸在中膜的过度积累和交联导致平滑肌细胞表型转化、增殖和骨保护素生成增加[40]. 最近的一项研究报道, 在年轻健康成人中聚集蛋白聚糖(aggrecan, ACAN)和fibulin-1基因多态性与主动脉PWV关联, 高动脉硬度和高收缩压供体的主动脉中聚集蛋白聚糖和fibulin-1均下调, 它们的表达减少和促进与年龄相关的主动脉硬化相关[41].

4　基质微环境与血管稳态维持

细胞外基质蛋白交织成网, 构成一个动态的细胞外基质微环境, 调节血管的稳态维持. 大量研究证实, 基底膜蛋白Ⅳ型胶原、laminin和perlecan可抑制平滑肌细胞增殖和炎症基因的表达, 促进平滑肌收缩表型, 抑制新生内膜形成和基质钙化[42~44]. Ⅳ型胶原、XV型胶原和XVIII型胶原的非胶原域降解片段具有抗血管新生活性, 可抑制新生血管形成[7,45,46]. 聚合的Ⅰ型胶

原和蛋白多糖有抑制平滑肌细胞增殖和促进平滑肌细胞收缩表型的作用[47,48]. 弹力蛋白不仅是可以储存反冲能量的动脉壁结构蛋白, 还可通过与平滑肌细胞膜上受体结合调节细胞迁移、趋化、增殖和发挥抗炎作用[49~52].

在国家自然科学基金委员会医学科学部于2013年启动的"血管稳态与重构的调控机制"重大研究计划的资助下, 本课题组针对血管基质微环境对血管稳态的调控做了系列探索, 发现基质蛋白COMP(cartilage oligomeric matrix protein)的存在对于维持血管平滑肌收缩表型及血管稳态至关重要(图1). COMP是分子量为524 kD的五聚体基质非胶原糖蛋白, 属于TSP家族的一员, 也称为TSP-5[53]. 本课题发现COMP在血管壁中表达丰富, 且主要由血管平滑肌细胞产生. 它通过不同功能结构域, 可以在细胞外结合平滑肌或心肌细胞膜表面integrinβ1/3, 防止其泛素化降解; 可在线粒体结合prohibitin2, 调控平滑肌细胞氧化磷酸化, 共同维持血管平滑肌的正常表型; 结合胚胎干细胞膜表面的NOTCH1, 诱导向血管平滑肌细胞分化; 亦可结合骨发生蛋白BMP-2, 是内源性血管中膜钙化抑制因子[54~60]. 巨噬细胞缺陷COMP会发生促炎和促成骨样转化, 通过旁分泌作用于平滑肌细胞, 从而促进斑块内微钙化及不稳定斑块的发生[27,61]. COMP还是天然的凝血酶抑制物, 可以在血管损伤后释放的促凝因素的刺激下, 由血小板产生, 负调控凝血酶引起的血小板聚集和血栓形成[62,63]. COMP虽然不表达在内皮, 但对于血流紊乱造成的内皮细胞炎性激活具有重要的保护作用[64]. 来自其他课题组的研究成果也表明, COMP的降解与人颈动脉硬化的进展相关, 新的COMP抗原表位形成是不稳定性动脉粥样硬化斑块的生物标志[65]. 此外, 本课题组[66]还发现, COMP是内源性血管紧张素Ⅱ受体AT1的偏好性抑制剂, 它通过EGF结构域与AT1的胞外N端直接结合, 选择性抑制AT1-β-arrestin-2信号及其相关的AT1受体构像变化, 在抑制腹主动脉瘤中发挥关键作用. 该研究首次发现和报道了GPCR的内源性偏好性拮抗剂, 具有重要的理论意义. 人类编码800多个GPCR, 其他GPCR是否也存在类似的内源性拮抗剂, 以维持组织稳态, 非常值得继续研究.

Nidogen是一种大分子细胞基底膜蛋白, 分为nidogen-1和nidogen-2, 可与其他基底膜成分, 如laminin、Ⅳ型胶原蛋白和perlecan等构成蛋白网络, 在发育和更新旺盛的阶段促进基底膜组装和稳定. Nidogen在血管分化和功能中报道很少, 已有的研究提示nidogen-2敲除小鼠醋酸脱氧皮质醇诱导的血压升高[67]. 本课题组[68]利用蛋白质相互作用(protein-prote ininteraction, PPI)、Gene Ontology、HPRD(http://www.hprd.org/)和PubMed等数据信息, 预测巢蛋白nidogen在平滑肌表型转化中可能发挥重要作用. 动物和细胞实验结果证明, nidogen-2维持血管平滑肌收缩表型, 它可以和Jagged-1和Notch3特异结合, 通过放大激活Jagged1-Notch3信号, 促进平滑肌细胞的分化, 抑制血管损伤

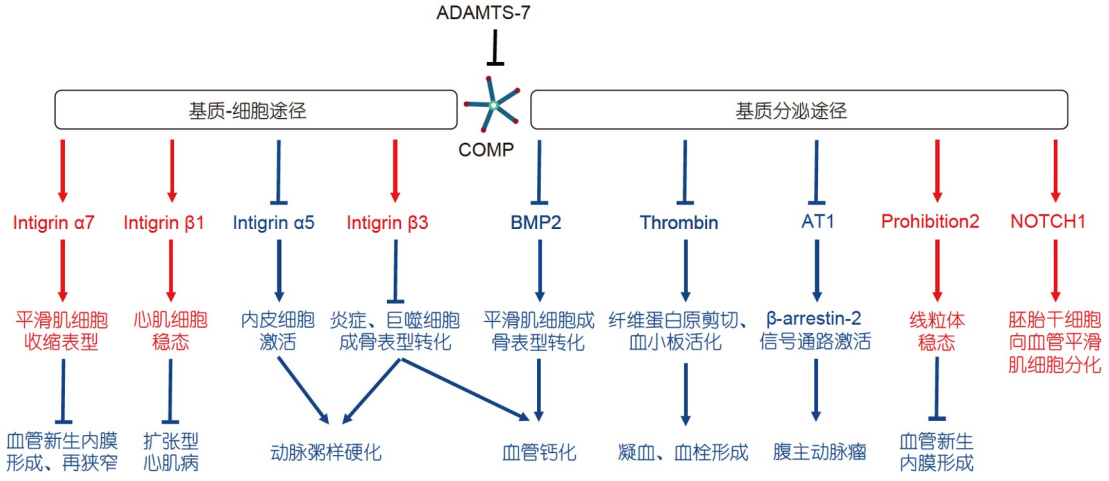

图 1 COMP对心血管的保护作用及相关调控机制(修改自文献[56])(网络版彩图)

Figure 1 A diagram of the effects and mechanisims of COMP in cardiovascular diseases (modified from ref. [56]) (color online)

后的血管新生内膜形成.

5　基质微环境与心血管疾病

血管内外环境变化引起基质蛋白生成、降解和组装的异常, 是多种心血管疾病发生发展的病理基础. 在高血压病时, 血管壁重塑, 血管顺应性发生改变. 受MMPs、丝氨酸蛋白酶和半胱氨酸蛋白酶作用, 主要维持血管壁机械特性的弹力蛋白含量减少、降解片段增多[69,70]; 相反, 具有限制血管舒张作用的胶原沉积增多, 在原发性高血压病人和高血压小鼠模型的弹性动脉和小动脉血管壁中发现有过多的Ⅰ、Ⅲ、Ⅳ型胶原沉积[71,72]. 此外, 蛋白多糖、糖胺聚糖、基质细胞蛋白等非结构蛋白也参与高血压血管重构, fibronectin和其选择性剪切物、osteopontin、biglycan、decorin、tenascin C、硫酸软骨素蛋白聚糖和硫酸肝素蛋白聚糖在自发性高血压大鼠和脱氧胆酸盐诱导的高血压小鼠的血管壁表达上调[73~76].

动脉粥样硬化是一种以广泛的动脉壁基质重塑为特征的炎症性疾病. 在动脉粥样硬化病变过程中, 血管壁MMP(-1, -2, -3, -7, -9, 10), ADAM(-9, -15, -17, -33), ADAMTS(-1, -4, -5, -8), 中性粒细胞弹性蛋白酶和组织蛋白酶(K, S和V)等基质蛋白酶的表达和活性增加[77~82], 细胞外基质蛋白降解片段增多, 促进血管壁炎症细胞浸润、平滑肌细胞的增殖和迁移、血管细胞的凋亡、新生内膜形成和最终血管壁的破裂. 人颈动脉粥样硬化斑块形成早期, 斑块内弹力蛋白表达增加, 但随着脂质沉积增多及炎症细胞释放弹性蛋白酶, 弹力蛋白降解增多、含量减少. 胶原是斑块内的主要细胞外基质蛋白成分, 其含量影响纤维帽的机械特性[83]. 在人颈动脉斑块中Ⅰ型和Ⅲ型胶原表达量及降解产物均增加, Ⅰ型胶原的降解片段可促进平滑肌细胞从中膜迁移至内膜. 另外, 平滑肌异常表达的Ⅷ型胶原可促进MMP-2和MMP-9分泌, 介导平滑肌细胞迁移[84]; 硫酸软骨素/皮质素蛋白多糖可加速LDL氧化、巨噬细胞募集和吞噬、免疫系统激活及平滑肌细胞增殖, 促进动脉粥样硬化的发生发展[85].

细胞外基质降解是主动脉瘤和主动脉夹层发病的重要病理基础. 病理情况下, 血管平滑肌细胞和巨噬细胞、中性粒细胞等炎症细胞分泌大量MMPs, 包括可降解弹力蛋白的MMP(-2, -9, -12)和胶原酶MMP(-1, -2, -9, -13), MT1-MMP, 以及ADAM-17, ADMATS(-4, -5)和组织蛋白酶, 促进血管细胞外基质蛋白降解和主动脉瘤及主动脉夹层的发生[86~88]. 本课题组[89,90]研究发现, 主动脉夹层患者血浆ADAMTS-1水平显著上升, 诱导敲除ADAMTS-1能抑制小鼠主动脉夹层的发生, 减少主动脉组织炎症细胞的浸润. 除基质蛋白异常降解外, 其遗传突变亦促进主动脉瘤和主动脉夹层的发生, 如fibrilin-1突变会导致TGFβ信号的过度激活和胸主动脉瘤(Marfan综合征)[91], Ⅲ型(a1)胶原删除突变易致胸主动脉瘤、主动脉夹层(Ehlers-Danlos综合征)发生[92], 弹性蛋白突变会导致Williams综合征及主动脉和肺动脉狭窄[93]. 此外, LOX基因突变或使用LOX抑制剂, 将使弹力蛋白和胶原的交联受抑制, 促进主动脉瘤和夹层的发病[94,95].

血管钙化常见于动脉粥样硬化、糖尿病、慢性肾功能衰竭及衰老的血管, 是一种血管病理性矿化. 细胞外基质的组成和表达发生变化, 参与血管钙化的主动调节. 病理情况下, Ⅰ型胶原合成增加, 其可促进血管平滑肌细胞向成骨样细胞分化, 从而促进血管钙化的发生[44]; 相反, Ⅳ型胶原表达减少, Ⅳ型胶原有抑制平滑肌细胞表型改变从而抑制钙化的功能. 在人动脉粥样硬化斑块中, 非胶原基质蛋白fibronectin和decroin与钙化区有共定位, 他们可以促使血管平滑肌细胞发生骨样表型转化[96~98]. 另有研究表明, 钙化血管中弹性蛋白降解增加, 使用MMPs抑制剂抑制弹性蛋白降解可明显缓解钙化发生[99].

降解血管基质的金属蛋白酶在动脉粥样硬化形成、血管再狭窄和动脉瘤的诸多环节中起重要作用, 它既是诊断和防治心血管病的重要生物标记物, 亦是研发心血管病药物的重要靶标. ADAMTSs是一类Zn^{2+}依赖的分泌型金属蛋白酶家族, 它区别于MMPs和其他金属蛋白酶的主要结构特点是羧基端含有至少一个TSP基序, 决定了其与底物结合的特异性, 底物谱相对狭窄[100]. 本课题组克隆了COMP的水解酶ADAMTS-7, 进而证实ADAMTS-7可一方面通过降解COMP, 明显促进平滑肌细胞的迁移, 另一方面通过降解TSP-1, 抑制内皮修复, 通过对内皮细胞和血管平滑肌细胞的“双刃剑”作用促进新生内膜的形成[101~105]. 金属蛋白酶ADAMTS-7虽然不影响血脂, 但可通过降解基质微环境中的保护性基质成分, 发挥促进动脉粥样硬化及再狭窄的作用, 这为目前以降脂为主的抗动脉粥样硬化

治疗提供了新的策略. *ADAMTS-7*后被发表在*Nature Genetics*和*The Lancet*的大规模人群研究证实是人类冠心病易感基因[106~108]. 三项全基因组关联分析(genome-wide association studies, GWAS)结果表明, 冠心病与染色体15q25上*ADAMTS-7*位点的单核苷酸多态性(single nucleotide polymorphisms, SNP)相关[109]. 后续研究证明, 在敲除*ADAMTS-7*或抑制ADAMTS-7催化活性的小鼠中, 或rs3825807的人组织细胞中, COMP降解减少, 平滑肌迁移减弱, 进而抑制动脉粥样硬化的发生发展[110~112]. ADAMTS-7是被基础和人群研究共同验证的重要心血管靶点[104].

6 展望

近20年来, 细胞外基质的研究取得了飞速发展, 随着蛋白质组学技术的进展, 人们发现了数以百计的新基质成分, 揭示了一系列基质分子突变造成的遗传性结缔组织病, 从基质成分中发展出了抗肿瘤药物Endostatin. 在心血管领域, 细胞外基质是血管中比例最大的组成成分, 但针对血管基质微环境的研究在国际上尚处于起始阶段. 基质组成及其生物学功能亟待一一确定; 其相互作用蛋白及网络调控体系尚未建立; 其合成和降解的关键物质在生理与病生理状态下的变化规律和作用机制远未被阐明; 其与人类重大心血管疾病不同发展阶段的关系和意义尚未明确. 无论是分子与结构, 合成与代谢, 聚合与离散, 可溶性与不可溶性, 分泌和机制, 降解与再利用, 信息的整合与传递, 组成与相互作用, 功能和调节, 病生理和临床意义, 检测技术和生物工程, 防治方法和新药开发都需要进一步研究. 从基质生物学出发, 从调控稳态的内源性血管活性物质着手, 通过高通量基质蛋白质组学和降解组学分析, 结合生物信息学手段, 从基质蛋白网络中筛选能促进血管稳态的基质分子或其结合蛋白, 围绕其功能、相互作用蛋白、信号转导和调控机制开展系列研究, 将有助于发掘新的防治重大心血管疾病的靶点和干预策略, 开拓未来心血管领域生物药物的发展空间.

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Extracellular matrix microenvironment and vascular homeostasis

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Cardiovascular diseases are the leading cause of death in China and the world, and their morbidity is continuously increasing. The occurrence and development of cardiovascular diseases are closely related to the imbalance of vascular homeostasis and pathological vascular remodeling. Recent studies have found that the interaction between extracellular matrix and vascular wall cells is involved in the regulation of vascular homeostasis. An in-depth understanding of the regulation mechanism of extracellular matrix microenvironment on vascular homeostasis and vascular remodeling is of great significance for guiding the exploration of the therapeutic drugs for cardiovascular diseases. We and our collaborators have carried out a series of research work, and have thoroughly explored the regulatory role of extracellular matrix proteins on the vascular structure and function under physiological and pathological conditions, supported by the National Natural Science Foundation of China "Regulatory Mechanism of Vascular Homeostasis and Remodeling". This review summarizes the effects of extracellular matrix microenvironment on vascular homeostasis and remodeling, focusing on the mechanism of extracellular matrix proteins regulating vascular homeostasis, aiming to provide new ideas and theoretical guidance for the prevention and treatment of cardiovascular diseases, such as hypertension, atherosclerosis, vascular restenosis, vascular calcification, and aneurysm.

vascular homeostasis, extracellular matrix microenvironment, extracellular matrix protein, cardiovascular disease

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