基质金属蛋白酶ADAMTS的研究进展

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摘要 ADAMTS是含有TSP基序的分泌性多结构域蛋白水解酶。*ADAMTS*基因的突变或过表达与多种生理学和病理学过程相关。*ADAMTS*基因的过表达促进了细胞外基质成分的降解, 加速了关节炎和动脉粥样硬化的疾病进程。*ADAMTS*基因的突变则与肿瘤的生长和侵袭以及遗传性发育紊乱等密切相关。该文将结合作者的研究工作, 重点对ADAMTS-7的当前研究概况进行综述, 讨论其结构、功能、调节及其在相关炎性疾病中的作用等。

关键词 ADAMTS; 金属蛋白酶; 关节炎; 细胞外基质; COMP

Research Advance of ADAMTS Proteinases

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Abstract The ADAMTS proteinases are a group of multi-domain and secreted metalloproteinase containing the thrombospondin motifs. Mutations in the *ADAMTS* gene or overexpression of *ADAMTS* gene is associated with a variety of physiological and pathological processes. Overexpression of *ADAMTS* gene promotes the breakdown of extracellular matrix and accelerates the development of arthritis and atherosclerosis. Mutations in the *ADAMTS* gene are closely related to cancer cells growth and metastasis and human genetic disorders. This review based on our results and provided an overview of current knowledge of ADAMTS-7, including its structure, function, gene regulation and inflammatory disease involvement.

Key words ADAMTS; metalloproteinase; arthritis; extracellular matrix; COMP

人类含I型血小板结合蛋白基序(thrombospondin, TSP)的解聚蛋白样金属蛋白酶(a disintegrin and metalloproteinase with thrombospondin-like motifs, ADAMTS)家族由19个分泌型多结构域蛋白水解酶组成, 参与多种生理学和病理学过程, 包括胞外基质的组装和降解、止血过程、器官生成、血管生成、人类遗传性疾病、关节炎和癌症等[1]。ADAMTS家族成员最早是作为炎症相关基因在小鼠中被克隆, 没有跨膜结构域, 含有I型TSP基序[2]。ADAMTS在结构上通常由四部分组成, 包括前体区、金属蛋白酶结构域、解聚蛋白样结构区和TSP序列重复区域[3]。前体区对于锌指依赖金属蛋白酶的正确折叠是必需的, 而且和保持酶活性的沉默有关。ADAMTS家族蛋白酶前体区通常存在弗林蛋白酶(furin)切割位点RX(K/R)R, 例如ADAMTS-1和ADAMTS-4在高尔基体中切割后释放具有活性的蛋白[4-5]。弗林蛋白酶基因敲除小鼠中, ADAMTS蛋白酶前体区的切除被完全阻断或严重抑制。ADAMTS的催化结构域序列具有高

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度同源性, 含有保守的Zn^{2+}结合基序HEXXHXXG/N/SXXHD。解聚蛋白样结构区的序列和蛇毒解聚蛋白序列相似, 解聚蛋白样结构区的功能可能与其活性调节有关, 提供了一个辅助底物结合的表面[6-7]。TSP序列重复区重复单位数目不一, 例如ADAMTS-20存在14个重复, 而ADAMTS-4缺乏TSP重复系列[8-9]。ADAMTS家族成员的具体生物学特性见表1, 根据序列比对结果和蛋白酶的功能不同分为四亚类: 第一亚类包括ADAMTS-1、ADAMTS-4、ADAMTS-5、ADAMTS-8、ADAMTS-9、ADAMTS-15和ADAMTS-20, 降解底物为聚蛋白聚糖。其中, ADAMTS-5可能是体内负责降解聚蛋白聚糖最主要的蛋白酶[10]。第二亚类包括ADAMTS-2、ADAMTS-3和ADAMTS-14, 降解底物包括I型、II型和III型原骨胶原的肽段[11-14]。ADAMTS-13为第三亚类, 是血管性血友病因子(von willebrand factor, vWF)的降解蛋白酶[15]。第四亚类包括4对蛋白酶: ADAMTS-19和ADAMTS-17、ADAMTS-18和ADAMTS-16、ADAMTS-12和ADAMTS-7、ADAMTS-10和ADAMTS-6, 每对蛋白结构特征相似[16]。总之, *ADAMTS*基因的异常表达和关节炎以及动脉粥样硬化等炎性疾病的致病过程密切相关, 而*ADAMTS*基因功能缺陷则容易引发遗传性疾病和多个组织器官发育异常。近年来, ADAMTS逐

表1 ADAMTS家族成员的生物学特性

Table 1 Biological characteristics of ADAMTS family members

基因 Gene	水解活性 Proteolytic activity	主要表达部位 Expression in human tissues	底物 Substrates	与疾病的关系 Relationship with diseases	参考文献 References
ADAMTS-1	+	Liver, endotheliocyte, skeletal muscle	Aggrecan	Cancer, atherosclerosis	[17-18]
ADAMTS-2	+	Connective tissue	Procollagen	Ehlhers-Danlos syndromes	[19-20]
ADAMTS-3	+	Skin, lung, brain	Procollagen	Dermatosparaxis	[13]
ADAMTS-4	+	Heart, lung, skeletal muscle	Aggrecan, brevican	Glioma, atherosclerosis	[21-22]
ADAMTS-5	+	Macrophage, bladder, oesophagus	Aggrecan	Arthritis, cancer	[21,23-24]
ADAMTS-6					
ADAMTS-7	+	Heart, liver, kidney, skeletal muscle	COMP	Arthritis, atherosclerosis	[25]
ADAMTS-8	+	Heart, lung	Aggrecan	Cancer	[22,26]
ADAMTS-9	+	Heart, lung, skeletal muscle	Aggrecan	Cancer, atherosclerosis	[27]
ADAMTS-10		Lens, cartilage, skin		Weill-Marchesani syndromes	[28]
ADAMTS-12	+	Chondrocyte	COMP	Cancer	[29-31]
ADAMTS-13	+	Liver, placenta, heart, skeletal muscle	von Willebrand factor (vWf)	Thrombotic thrombocytopenic purpura	[15]
ADAMTS-14	+	Brain, liver, placenta	Procollagen	Fibrosis	[32]
ADAMTS-15	+	Liver, kidney	Aggrecan	Cancer	[33]
ADAMTS-16	+	Cartilage, synovium, brain, ovary,		Cancer	[34]
ADAMTS-17		Epidermis, brain, heart		Weill-Marchesani syndromes	[35]
ADAMTS-18		Breast, endotheliocyte, chondrocyte		Abnormal development of eye and bone tissue, cancer	[36-37]
ADAMTS-19		Brain, liver, spleen		Spontaneous premature ovarian failure	[38]
ADAMTS-20		Ovary, heart, lung, placenta	Aggrecan	Abnormal development of elanoblast	[8]

渐成为这些相关领域的研究热点。本文将重点对ADAMTS-7的当前研究状况进行综述。

1 ADAMTS-7的结构

ADAMTS-7为ADAMTS蛋白酶家族的一员, 其蛋白结构从N端至C端依次为信号肽序列、前体区、金属蛋白酶催化结构域、解聚蛋白样结构域、间隔区1和间隔区2以及TSP重复基序(图1)。

2 ADAMTS-7在炎性疾病中的生物学功能

2.1 ADAMTS-7与关节炎

细胞外基质(extracellular matrix, ECM)除了提供细胞结构上的支架以外, 在调节细胞活性和细胞行为中也具有重要作用, 包括细胞塑型、存活、分化、运动、增殖和某些条件下的细胞死亡[40]。细胞外基质的降解和关节炎病理过程紧密相关, 骨关节炎(osteoarthritis, OA)早期软骨的病理学变化表现为细胞外基质成分的丢失和破坏。软骨寡聚基质蛋白(cartilage oligomeric matrix protein, COMP)是由五个多功能域糖蛋白亚基组成的524 kDa大小的五聚体, 为软骨中重要的细胞外基质成分。人类*COMP*基因C-末端球形结构域的突变导致骨骼畸形, 例如假性软骨发育不良以及多发性骨骺发育不良[41-43]。ADAMTS-7蛋白酶作为生理条件下COMP的降解酶被发现[44-45], 其可以选择性地和COMP蛋白EGF结构域结合, 二者共定位于软骨细胞的胞质和细胞表面。ADAMTS-7参与肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)和白细胞介素-1β(interleukin-1β, IL-1β)诱导的COMP蛋白降解, 而ADAMTS-7抗体能够阻断这种降解作用, 明显地减少110 kDa大小COMP降解片段的产生。此外, 基因沉默也证实了ADAMTS-7蛋白酶对COMP蛋白的体内降解作用[46]。

ADAMTS-7在正常人软骨和OA患者软骨之间的基因表达没有明显的差异, 而在OA和类风湿关节炎(rheumatoid arthritis, RA)患者的滑膜组织中*ADAMTS-7*基因存在异常表达[44-45]。OA和RA病人的关节软骨、滑囊液和血清中COMP降解片段增加。体外重组的ADAMTS-7能够体外降解COMP蛋白, 降解产生的片段和骨关节炎患者关节置换术后的软骨标本培养上清中的COMP降解片段的分子量大小相当[46], 这说明骨关节炎(OA)和类风湿关节炎(RA)患者软骨COMP的降解很有可能与ADAMTS-7的上调有关。研究发现, *ADAMTS-7*可以作为甲状旁腺激素相关蛋白(para-thyroid hormone-related peptide, PTHrP)信号的下游调节基因, 抑制软骨细胞分化和软骨内骨形成过程, 这种抑制作用与其酶降解活性以及C端4个TSP基序有关[47]。我们通过软骨细胞特异性的II型胶原蛋白启动子调控*ADAMTS-7*表达构建了*ADAMTS-7*转基因小鼠(transgenic mice)和Cre/loxp调控系统构建了*ADAMTS-7*下调小鼠(knockdown mice), 膝关节手术诱导的骨关节炎(OA)模型结果发现, *ADAMTS-7*转基因小鼠术后4周就出现明显的软骨基质成分丢失, 野生型小鼠在术后12周才出现中度软骨丢失, 而*ADAMTS-7*下调小鼠在术后12周还没有出现任何软骨基质成分的破坏, 说明*ADAMTS-7*过表达能够加速软骨基质成分的破坏和小鼠OA的疾病进程, *ADAMTS-7*水平下调则保护了小鼠骨关节炎的发生发展[48]。同时我们也发现, *ADAMTS-7*过表达也能够促进小鼠胶原蛋白诱导的类风湿关节炎(collagen-induced arthritis, CIA)的发生发展(未发表)。因此, 在手术诱导的骨关节炎(OA)模型和胶原蛋白诱导的类风湿关节炎(CIA)模型中, *ADAMTS-7*表达增加, 同时*ADAMTS-7*又上调了炎性因子的水平, 例如TNF-α[48-49]。*ADAMTS-7*增加后加速COMP的降解, 炎性因子水平上调又能刺激其

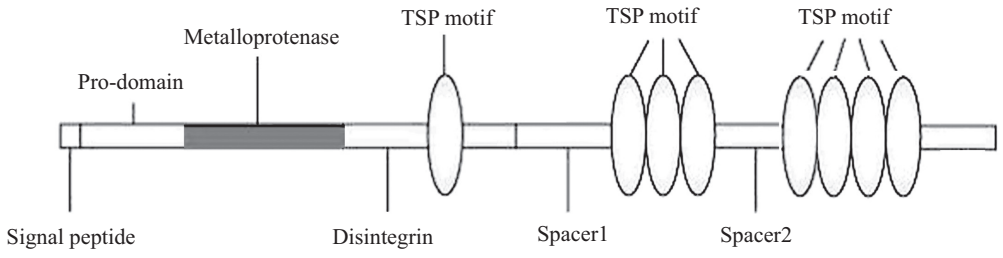

图1 ADAMTS-7的结构(根据参考文献[39]修改)

Fig.1 The structure of ADAMTS-7 (modified from reference [39])

他金属蛋白酶的表达增加, 包括MMP金属蛋白酶和ADAMTS蛋白酶, 最终加快了关节炎的疾病进程[48-49]。综上所述, ADAMTS-7可能通过降解细胞外基质成分COMP, 上调炎性因子和其他金属蛋白酶的表达, 从而参与关节炎的病理过程。

2.2 ADAMTS-7与心血管疾病

冠状动脉粥样硬化是引发冠心病的重要因素。动脉粥样硬化是一种进行性炎性疾病, 源于多种致病因素对血管内皮组织的损伤, 例如遗传易感病体质、高血压、吸烟、高血脂和2型糖尿病。在动脉粥样硬化病理过程中, 巨噬细胞和单核细胞能够分泌ADAMTS, 降解心血管系统组织和细胞中的细胞外基质成分, 从而影响动脉粥样硬化斑块的稳定性[50]。多种ADAMTS蛋白酶高表达在动脉粥样硬化斑块中, 例如ADAMTS-1高表达在迁移和增殖的血管平滑肌细胞中[51], ADAMTS-4出现在动脉粥样病变的巨噬细胞中, 而且炎性因子TNF-α和IFN-γ能够上调ADAMTS的表达[22]。*ADAMTS-1*转基因小鼠和*ApoE*基因敲除小鼠杂交所生后代的血管内膜比对照组明显增厚, 说明ADAMTS促进动脉粥样硬化病理进程的机制可能与加速血管细胞外基质成分的降解有关[51]。

最近的全基因组关联研究结果发现, *ADAMTS-7*和动脉粥样硬化的发生发展息息相关[52-53], *ADAMTS-7*基因单核苷酸多态性增加了冠心病(coronary artery disease, CAD)的患病风险。血管平滑肌细胞(vascular smooth muscle cells, VSMCs)迁移是动脉粥样硬化致病的一个重要步骤, 血管平滑肌细胞从动脉血管中层迁移到内膜, 并在内膜部位增殖和产生胞外蛋白, 所产生的胞外蛋白是动脉粥样硬化斑块的主要组分[54-55]。动脉机械力损伤后, *ADAMTS-7*首先在内膜部位表达和积累, 这说明在动脉粥样硬化病理过程中*ADAMTS-7*参与血管平滑肌细胞的迁移和增殖过程[25,56-57]。细胞外基质成分COMP可以通过和整合素蛋白α7β1相互作用保持血管平滑肌细胞的完整性和收缩性, 提示*ADAMTS-7*促进血管平滑肌细胞迁移的机制可能与降解COMP有关[58]。更为重要的是, *ADAMTS-7*通过加速COMP的降解, 促进血管平滑肌细胞的钙化过程, 表明*ADAMTS-7*可能作为靶点来干预治疗血管平滑肌细胞钙化导致的相关疾病[59]。综上所述, *ADAMTS-7*可能通过降解细胞外基质成分COMP, 促进血管平滑肌细胞迁移, 调节炎症反应, 从而参与动脉粥样硬化的发生发展过程。

3 *ADAMTS-7*基因表达的调节

在成年人的心脏、胰腺、肾脏、骨骼肌和肝脏标本中都能检测到*ADAMTS-7*基因的表达, 大小为5.5 Kb。在骨骼肌组织中还发现8.0 Kb和4.5 Kb大小的转录本, 说明存在基因的转录后调节[60-61]。SDS-PAGE蛋白电泳显示, 条带明显大于*ADAMTS-7*基因的理论推算分子量, 说明ADAMTS-7蛋白分泌后发生翻译后修饰。*ADAMTS-7*基因在多种组织中表达, 广谱表达的生物学意义有待于进一步的研究[60-61]。

炎性因子可以调节ADAMTS蛋白酶的表达[61]。例如肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)能够上调*ADAMTS-1*、*ADAMTS-6*和*ADAMTS-9*基因的mRNA水平[62], 白介素17(IL-17)能够刺激关节软骨细胞中*ADAMTS-4*基因表达增加[63], 且RA患者中ADAMTS-7蛋白的表达增加也与TNF-α水平的升高有关[44]。研究结果也发现, TNF-α能够诱导*ADAMTS-7*基因的表达, 染色质免疫沉淀(chromatin immunoprecipitation, ChIP)结果证实*ADAMTS-7*基因启动子区存在炎性转录因子NF-κB和AP-1的结合位点[58]。我们通过在*ADAMTS-7*转基因小鼠中建立胶原蛋白诱导的类风湿关节炎(CIA)模型和手术诱导的骨关节炎(OA)模型, 发现TNF-α通过NF-κB信号激活*ADAMTS-7*表达, 同时*ADAMTS-7*又可以上调TNF-α水平, 二者构成正反馈通路[48-49]。值得一提的是, 转化生长因子-β(transforming growth factor-β, TGF-β)可以上调关节软骨中*ADAMTS-4*的mRNA水平, 但是不能上调*ADAMTS-5*的mRNA水平, 说明不同ADAMTS的调节模式可能不同[64]。

通过选择性剪接的转录后调节模式已经在多种*ADAMTS*中报道, 例如*ADAMTS-6*、*ADAMTS-7*和*ADAMTS-9*[62,65]。最先预测认为, *ADAMTS-7*在1个C-端TSP重复基序后终止[66]。然而全长编码序列结果发现, *ADAMTS-7*编码4个C-端TSP重复基序、1个PLAC结构域和7个被黏蛋白样结构域分割的C-端TSP重复基序[67]。*ADAMTS-7*剪接变异体的存在说明转录后剪接可能是ADAMTS调节的重要机制。此外, ADAMTS还存在翻译后修饰的调节模式。ADAMTS以酶原的形式被合成, 然后在前体蛋白转化酶的作用下切除前体区, 例如在furin蛋白酶的作用下, 成为有活性的蛋白酶。分泌后的ADAMTS的

C-端可以进一步被切割加工, 例如ADAMTS-12黏蛋白样结构域内被切割后释放C-末端TSP重复基序[5]。

4 *ADAMTS*基因功能缺陷

*ADAMTS*基因突变和人类遗传性疾病密切相关。Ehlhers-Danlos综合征(EDS)是一种先天性结缔组织发育不全疾病, 特征为皮肤极度脆弱、关节松弛、皮肤松弛、脐带疝气和蓝色巩膜[68]。EDS综合征源于*ADAMTS-2*基因突变所导致的I型原骨胶原向胶原的加工过程缺陷[19], 皮肤松弛症状可能与ADAMTS-3和ADAMTS-14的功能过剩有关。*ADAMTS-17*基因突变和Weill-Marchesani样综合征密切相关, 患者表现为身材短小和晶状体移位, 但是无短指症出现[35]。尽管ADAMTS-17功能还不清楚, 临床和遗传学的结果表明, ADAMTS-10和ADAMTS-17在晶状体和结缔组织形成中具有关键的作用。Knobloch综合征是一种少见的发育紊乱性疾病, 特征为枕骨发育缺陷、高度近视和玻璃体视网膜退行性病变, 研究发现*ADAMTS-18*是Knobloch综合征患者唯一发生纯合子错义突变的基因[36]。此外, 通过纯合子作图和全外显子组测序, 结合体内实验功能分析, 发现ADAMTS-18还和遗传性视网膜营养不良及中枢神经系统并发症有关, 例如自闭症和神经发育延迟[37] 。*ADAMTS-18*基因敲除小鼠眼睛视网膜紫质比野生型小鼠减少了50%, 进一步支持了*ADAMTS-18*基因在人类遗传性视网膜营养不良中的病理学作用[37], *ADAMTS-18*基因突变会引发以小角膜和近视为主要特征的眼睛表型性病变[69]。*ADAMTS*在人类遗传性疾病中作用的鉴定, 有助于理解ADAMTS在胞外基质中的作用, 例如其结构组分和调节因子。

5 结语

ADAMTS家族共有19个成员, 是一类结构上不同于ADAM蛋白酶和MMP金属蛋白酶的新型蛋白酶, 在多种生理学和病理学过程中都发挥重要调节作用, 包括细胞外基质的重塑、器官生成、遗传性疾病、关节炎和肿瘤等。ADAMTS在这些研究领域的功能还需要进一步探索和研究, ADAMTS家族各成员之间的功能具有重叠性和独特性, 转基因小鼠的建立将有助于加快*ADAMTS*基因功能的研究步伐。多种因素都能调节ADAMTS家族的合成水平和生物学活性, 除了转录后剪接和翻译水平上的调节以外, 表观遗传学修饰也是*ADAMTS*基因调控的重要组成部分。ADAMTS-7在不同阶段通过不同机制参与了炎性疾病的病理过程, 例如关节炎和动脉粥样硬化, 有望成为这些疾病新的临床干预靶点。

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