钙蛋白酶在纤维化疾病中的研究进展

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【摘要】 纤维化作为一个生理性组织修复过程,几乎可发生在所有器官组织的创伤后修复中,与细胞多个病理生理过程密切相关,广泛参与多种疾病进展。目前认为体内促纤维化和抗纤维化系统处于动态调节过程,这一过程不仅可控,甚至可逆转。本文总结了钙蛋白酶(Calpain)家族在各器官纤维化中的最新研究进展,以及Calpain抑制剂对纤维化的临床前干预实验结果,旨在为研究Calpain家族在纤维化疾病的作用提供参考。

【关键词】 纤维化; 病理生理; 钙蛋白酶; 抑制剂
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Research progress of Calpain in fibrotic diseases

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【**Abstract**】 Calpain-mediated fibrosis, a physiological tissue repair process that almost occurs in most of tissues and organs, is closely related to multiple cellular pathways and is widely involved in the progression of diseases. It is believed that the pro- and anti-fibrotic systems are dynamic regulated *in vivo*, so pathological organ fibrosis still may be controlled and even reversed. This review summarizes the latest researches on the role of Calpain family in different organ fibrosis and the intervention of Calpain inhibitor in fibrosis progression, aiming to providing a reference for the research of Calpain family in fibrotic diseases context.

【**Key words**】 fibrosis; pathophysiology; Calpain; inhibitor
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纤维化既是组织损伤修复的生理过程,又是多种致病因素导致的不可逆的病理过程。纤维化几乎可以发生在所有器官组织的创伤后修复中,广泛参与各种疾病的进展、转化和终末衰竭,最终导致器官功能严重受损而衰竭[1]。在肝硬化、心肌重塑、间质性肺纤维化、肾脏损伤、血管粥样硬化、组织修复、移植后慢性血管硬化、心包疾病、关节强直等生理、病理过程中,纤维化是关键疾病表型。纤维化过程涉及到免疫细胞的激活、细胞因子的分泌、上皮间质转化(epithelial-mesenchymal transition,EMT)、成纤维细胞过度活化和细胞外基质(extracellular matrix,ECM)病理性蓄积等多种因素[2],是疾病研究中的热门表型。钙蛋白酶(Calpain)可通过调节多条胞内信号通路活性,正向或负向调控组织重塑,利用药物性抑制或基因敲除小鼠证实干预Calpain活性对纤维化有保护作用[3-7]。本文总结了Calpain的种类及其在多种纤维化疾病中的最新研究,旨在为发现临床治疗靶点提供参考。

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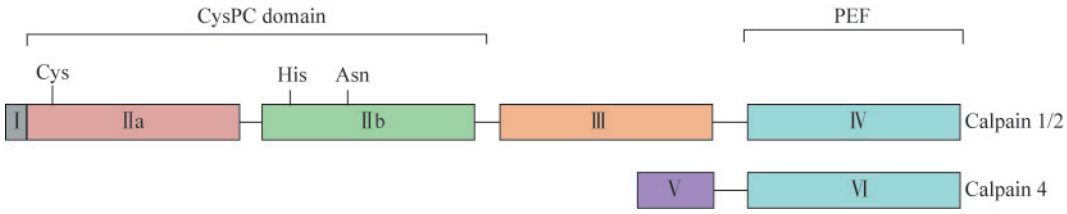
Calpain家族

经典Calpain成员及其内源性抑制剂Calpastatin

Calpain是一组可溶性中性半胱氨酸蛋白酶,主要功能是作为调节性酶参与底物剪切和功能修饰[8-9],在哺乳动物组织中广泛表达[10]。Calpain共有15个成员,其中Calpain 1和Calpain 2是经典的Calpain分子,分别需要微摩尔级和毫摩尔级的Ca^{2+}浓度来激活,故又被称为μ-Calpain和m-Calpain[8-9]。Calpain 1和Calpain 2在细胞内多以异源二聚体的形式表达,分别由*CAPN1*基因和*CAPN2*基因编码的催化性大亚基(相对分子质量为80 000)与由*CAPN4*(又称为*CAPNS1*)基因编码的调节性小亚基(相对分子质量为28 000)共同组成[8-9]。在两者催化大亚基的半胱氨酸酶结构域(cysteine protease domain, CysPC motif)中,包含由半胱氨酸残基-组氨酸残基-天冬酰胺残基构成的催化活性位点(图1),这是其蛋白结构的重要特点[8,10]。

目前已知唯一的内源性Calpain特异性抑制剂是钙蛋白酶抑制蛋白(Calpastatin)[11],由*CAST*基因编码,通常在胞质内与Calpain共表达[11-12]。Calpain-Calpastatin互相结合同样依赖Ca^{2+},且Ca^{2+}浓度阈值取决于Calpain的分子结构[8]。Calpastatin包含4个重复的抑制性结构域,在胞内表现出极强的抑制作用[12],此过程同样呈Ca^{2+}浓度依赖性[8]。同时,Calpain结合Calpastatin的亲和力被胞内多种因素调控,如激酶依赖的磷酸化修饰、膜结合、Calpain分子结构的紧密型、是否再定于线粒体或胞核等[8,10]。Calpain家族的其他成员缺少催化活性中心或关键氨基酸残基被替换,故被称为不典型Calpain[8]。

Calpain 1和Calpain 2的底物可同时被两酶中任意一个以不同酶解效率剪切[9]。但Calpain 1和Calpain 2对底物的识别仅呈现出轻度序列特异性[11,13]。然而,底物的剪切位点通常具有相同的空间构想[12]。被Calpain 1和/或Calpain 2酶解后,底物的活性和稳定性显著改变,从而导致结构和功能的修饰,影响信号转导分子而引起级联效应,参与多种细胞功能和疾病过程[12,14]。



Cys: Cysteine; His: Histidine; Asn: Asparagine; CysPC domain: Cysteine protease core domain; PEF: Penta EF-hand.

图1 钙蛋白酶家族成员结构图

Fig 1 Structural diagram of Calpain family members

其他Calpain成员 Calpain 3又称为p94,由*CAPN3*基因编码,是骨骼肌组织特异性单聚体Calpain成员[8,15],具有以下特征:(1)序列中的2个插入序列(insertion sequence, IS)使Calpain 3的相对分子质量从80 000增至94 000,故称为p94[15-16];(2)Calpain 3激活的必要条件是IS1自身裂解[16-17],这一过程依赖于钠离子,同时需要极低浓度的钾离子[18];(3)*CAPN3*的各种基因突变,包括错义突变、无义突变、移码突变和删除突变等超过400种序列改变,均可导致肢带肌型营养不良2A型(limb girdle muscular dystrophy type 2A, LGMD2A)[16,19],因此认为*CAPN3*是LGMD2A的致病基因。

Calpain 5和Calpain 6均含有2个特征性C端结构域(C-terminal domain, C2-domain),可参与脂质互相作用,并介导其膜定位[20]。其功能活性受Ca^{2+}浓度和S-脂酰化(S-acylation)调控[20-21]。Calpain 5在哺乳动物组织中广泛表达,线粒体Calpain 5通过C2结构域自身降解失活,提供组织保护、抗内质网应激(endoplasmic reticulum stress, ERS)[22-23]等作用。此外,*CAPN5*的蛋白酶核心突变导致蛋白酶高度激活,是常染色体显性遗传性新生血管炎性玻璃体视网膜病变(autosomal dominant neovascular inflammatory vitreoretinopathy, ADNIV)的致病原因[24]。Calpain 6缺乏PEF结构域,无蛋白酶活性[8,12],在胚胎发育中广泛表达于肌肉、心脏、肺、肾和胎盘,出生后其表达高度局限于胎盘[12]。

Calpain 7是不典型Calpain成员,缺乏PEF结构域,包含C2结构域和N端结构域[25-26],并由此介导其酶解活性和底物选择性[27]。Calpain 7与胞内运输所需的内体分选复合体(endosomal sorting

complex required for transport，ESCRT）系统蛋白IST1（ESCRT-Ⅲ复合体的关联因子）相互作用，发挥分选通路调节分子的作用[25,28]。

Calpain 8和Calpain 9分别称为nCL2和nCL4，是Calpain家族中Ca^{2+}依赖的组织特异性成员[29]，其蛋白二聚体高度局限于胃肠道表面黏膜细胞中，是构成胃肠黏膜屏障所必需的蛋白分子[30]。Calpain 8作用于质膜细胞器之间的膜泡转运过程，而Calpain 9则更多参与抑制胃肠道恶性肿瘤的发生和发展[30]。

Calpain 10由*CAPN10*基因编码，又称为非胰岛素依赖型糖尿病分子1（non-insulin dependent diabetes mellitus 1，NIDDM1），*CAPN10*单基因多态性（single nucleotide polymorphisms，SNP）是2型糖尿病（type 2 diabetes mellitus，T2DM）的易感基因之一[31]。Calpain 10由钙蛋白酶型β三明治结构域、微管相互作用及转运结构域和CysPC蛋白酶结构域组成，缺乏PEF结构域[32]，参与胰岛素抵抗、肥胖和高脂血症等[33]多种代谢综合征。

Calpain家族在纤维化疾病中作用

肝纤维化　在肝纤维化中，肝星状细胞（hepatic stellate cell，HSC）过度激活和肝实质细胞受损是主要致病的病理过程。Calpain激活介导双向调控，Ca^{2+}介导的Calpain 1和Calpain 2激活或过表达，通过上调*Bax*促凋亡基因表达、激活MAPK信号通路或细胞坏死级联反应，促进HSC死亡，进而阻止促纤维化作用，达到缓解肝脏过度胶原沉积和纤维化的效果[34-36]。然而，在肝库普弗细胞（Kupffer cells）中，Ca^{2+}内流引起的Calpain 1和Calpain 2激活通过NF-κB信号通路，可导致炎症介质释放而引起组织炎症和肝实质细胞、受损，进而促进肝脏纤维化过程[37]。此外，有研究表明*CAPN9*基因敲除（$CAPN9^{-/-}$）能提供肝纤维化保护作用[38]。

心脏纤维化　大量研究表明，Calpain异常过度激活促进了各种因素导致的心脏纤维化进展。在心梗模型中，*CAST*过表达（$CAST^{+/+}$）介导的Calpain过度激活降低了N-钙黏蛋白（N-Cadherin）表达，通过减少心肌闰盘的细胞间黏附，促进了心梗后心肌肥厚和纤维化[39-40]。心衰后纤维化过程中，Calpain表达上调促进成纤维细胞转化生长因子β（transforming growth factor-β，TGF-β）表达和胶原蛋白蓄积[11]。抑制Calpain活性或表达能在心脏疾病中提供抗纤维化作用。在1型糖尿病（type 1 diabetes mellitus，T1DM）小鼠模型中，*CAPN4*敲除（$CAPN4^{-/-}$）或*CAST*过表达（$CAST^{+/+}$）通过降低NF-κB信号通路和基质金属蛋白酶（matrix metalloproteinase，MMP）活性，可改善血管再生，减轻模型小鼠心肌肥厚和纤维化[41-42]。在心梗小鼠中，药物性抑制Calpain能减少心梗纤维化面积[43]。在高脂血症导致的心肌缺血中，抑制Calpain后通过JAK/STAT信号通路，影响黏蛋白和细胞骨架蛋白的表达，从而减轻慢性心肌纤维化，提供心功能保护作用[44]。

肺纤维化　在肺纤维化中，尤其是特发性肺纤维化（idiopathic pulmonary fibrosis，IPF），肺间质的胶原纤维累积和肺小血管的纤维化重塑均与Calpain 1密切相关。研究表明，Calpain 1表达上调通过损伤细胞间紧密连接[45]和PI3K/Akt信号通路导致EMT[46]，促进肺纤维化；反之，当抑制Calpain活性时，可缓解实验性肺纤维化的进展[47-48]。此外，Calpain还能介导胸膜间皮细胞迁移到肺实质，进而促进肺实质纤维化[49]。在肺小血管重建中，Calpain 1激活通过介导缺氧诱导因子1α（hypoxia-induced factor 1 alpha，HIF-1α）相关细胞因子分泌[50]和促进EMT[51]，引起肺血管纤维化和血管高压。

皮肤纤维化　Calpain在皮肤纤维化中的研究有限，主要集中在硬皮病和皮肤瘢痕中。硬皮病是典型的真皮纤维化疾病，通过敲除*CAPN4*阻止巨噬细胞M1极化，提供抗纤维化作用[52]；而药物性抑制Calpain活性能通过TGFβ1-Smad2/3通路，抑制成纤维细胞激活，从而改善硬皮病真皮和肺的纤维化程度[53]。在烧伤后皮肤增生性瘢痕形成的研究中，内源性钙蛋白酶抑制剂Calpastatin通过抑制Calpain活性发挥出显著的抗瘢痕、抗纤维化效果[54]，并通过抑制NF-κB-p65和CAPN2的活性，减轻肥厚性瘢痕成纤维化的生长，从而起到治疗作用[5]。

肾脏纤维化　Calpain在肾脏纤维化中的研究较少，研究表明髓系细胞中的机械敏感离子通道蛋白Piezo1对肾纤维化至关重要；而激活的Piezo1通过Calpain激活诱导骨髓来源的巨噬细胞发生炎症起作用，因此抑制Calpain活性可减轻肾脏纤维化[3]。Calpain1介导的自噬-溶酶体通路紊乱可能是肾结核病肾小管间质性纤维化的重要原因，因此

Calpain1有望成为肾小管间质纤维化的治疗靶点[55]。

Calpain抑制剂对纤维化的治疗作用 通常情况下Calpain对于纤维化进展有不同程度的促进作用,故抑制Calpain活性成为纤维化治疗的研究热点。在不同纤维化的疾病模型中,抑制Calpain活性为纤维化治疗的临床前研究和临床转化提供了一定的指导意义。在不同脏器纤维化中,文献报道明确有抗纤维化作用的Calpain抑制剂主要有衣霉素(tunicamycin)、乙酰亮氨酸亮氨酸去甲亮氨酸(acetyl leucyl leucyl norleucinal,ALLN)、选择性半胱氨酸蛋白酶抑制剂(MDL28170)、Calpeptin和选择性非肽类钙蛋白酶抑制剂(PD150606)等,对不同药物的分类、机制和纤维化疾病模型的总结如表1所示。

表1 Calpain抑制剂对不同纤维化模型的作用

Tab 1 Effects of Calpain inhibitors on different fibrosis models

Drug	Drug classification	Fibrotic disease model	Mechanism of fibrosis inhibiton	Animal type/ Reference
Tunicamycin	ERS inducer	Hepatic fibrosis	Induce HSCs apoptosis	Rat [35]
ALLN	Cysteine protease inhibitors	Hepatic fibrosis	Induce HSCs necrosis	Rat [36]
MDL28170	Cysteine protease inhibitors	Myocardial fibrosis	Disassembles cell-cell adhesion at intercalated discs by degrading N-cadherin	Mice [40]
Calpeptin	Cysteine protease inhibitors	Myocardial fibrosis	Inhibition of cardiac parenchymal cell apoptosis	Mice [44]
Calpeptin	Cysteine protease inhibitors	Pulmonary fibrosis	Decreased IL-6 dependent cell proliferation and angiopoietin-1 dependent cell migration	Mice [48]
Calpeptin	Cysteine protease inhibitors	Pulmonary fibrosis	Reverse TGFβ1-Smad2/3 mediated EMT	Mice [49]
MDL28170	Cysteine protease inhibitors	Pulmonary vascular fibrosis	Inhibition of HIF-1α signaling pathway	Mice [51]
MDL28170	Cysteine protease inhibitors	Pulmonary vascular fibrosis	Inhibition of PI3K/AKT-mediated EMT	Mice [52]
PD150606	Cysteine protease inhibitors	SSc-ILD pulmonary fibrosis	Inhibition of macrophage M1 polarizatio	Mice [53]
ALLN	Cysteine protease inhibitors	SSc-ILD pulmonary fibrosis	Inhibition of TGFβ1/Smad2/3 mediated EMT	Mice [54]

ERS: Endoplasmic reticulum stress; ALLN: Acetyl leucyl leucyl norleucinal; HSC: Hepatic stellate cell; EMT: Epithelial-mesenchymal transition; SSc-ILD: Systemic sclerosis- interstitial lung disease; HIF-1α: Hypoxia-induced factor 1 alpha.

结语 目前关于Calpain在纤维化疾病中的研究多局限于细胞和小鼠模型的探索,较少涉及人体样本,今后可通过人类样本表达量和活性的检测,从差异表达或差异活性中对患者的预后和生存率进行分群研究。另一方面,关于非典型性Calpain分子的研究在分子结构、亚细胞表达、是否存在酶解功能等方面尚存争议,未来可进一步推动对这些分子的探索,以期全面深入了解Calpain家族成员。随着作用机制研究的不断深入,以及Calpain抑制剂在各类小鼠模型的抗纤维化作用初见成效,Calpain有望成为新的治疗靶点。

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