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基质金属蛋白酶在缺血性脑白质损伤中的作用及药物干预研究进展

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摘要 脑白质损伤(white matter injury, WMI)是指大脑白质区域的结构或功能受到损害, 作为脑血管疾病中的一种常见病理现象, 严重影响老年人的认知功能和生活质量。近年来, 基质金属蛋白酶(matrix metalloproteinases, MMPs)在WMI中的作用引起了广泛关注。MMPs作为一类催化蛋白质水解的酶, 参与细胞外基质的降解和重塑, 在缺血性损伤过程中扮演关键角色。该文回顾了MMPs在WMI中的具体机制及其与病理过程的关联, 同时总结了现有药物对MMPs的调控作用, 旨在为WMI的预防和治疗奠定新的理论基石, 助力寻找更有效的治疗靶点。

关键词 脑白质损伤; 基质金属蛋白酶调控; 神经血管; 髓鞘; 靶向药物

The Role of Matrix Metalloproteinases in Ischemic White Matter Injury and the Research Progress of Drug Intervention

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Abstract WMI (white matter injury) refers to the damage to the structure or function of the brain's white matter region, which is a common pathological phenomenon in cerebrovascular diseases, significantly affecting the cognitive functions and quality of life in the elderly. In recent years, the role of MMPs (matrix metalloproteinases) in WMI has drawn widespread attention. MMPs, as a class of enzymes that catalyze protein hydrolysis, are involved in the degradation and remodeling of the extracellular matrix and play a crucial role in ischemic injury. This article reviews the specific mechanisms of MMPs in WMI and their association with pathological processes, while also summarizing the regulatory effects of existing drugs on MMPs. It aims to lay a new theoretical foundation for the prevention and treatment of WMI and facilitate the search for more effective therapeutic targets.

Keywords white matter injury; matrix metalloproteinase regulation; neurovascular; myelin; targeted drugs

脑白质占健康成人大脑体积的一半, 由神经元细胞的轴突、少突胶质细胞和星形胶质细胞组成, 负责不同脑区之间的信号转导和信息处理, 脑白质损伤(white matter injury, WMI)可以影响这些信号转导路径, 从而干扰大脑的正常功能[1-2]。WMI的发病隐蔽, 易被忽视, 最终可能发展为缺血性卒中, 并与

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阿尔茨海默病、多发性硬化症、血管性痴呆等神经系统疾病的发生、进展密切相关[3]。有研究表明, 在健康人的体内也存在不同程度的WMI, 且随着年龄的增长, 脑白质的萎缩也在加剧[4]。WMI常见的发病机制为慢性缺血性损伤、血脑屏障(blood brain barrier, BBB)破坏、神经细胞受损与凋亡、炎症因子破坏与氧化损伤等[5-6]。因脑室周围白质接受的侧支循环较少, 缺血性白质损伤最为常见[7]。基质金属蛋白酶(matrix metalloproteinase, MMP)是高度同源、多结构域、含锌(Zn^{2+})的金属蛋白酶, 具有降解几乎所有细胞外基质成分的能力, 其在病理状态下的过表达会导致各种疾病的发生[8-9]。最近的研究发现, MMP能够作用于中枢神经系统(central nervous system, CNS), 促进或抑制CNS疾病的发生发展[10]。WMI后的组织重塑、神经发生、血管生成、脱髓鞘和髓鞘再生等过程与大脑中MMP的表达水平增加有关[11]。本文在现有研究的基础上, 对MMPs的结构、作用于WMI的机制及靶向药物最新进展进行综述, 旨在为WMI高效治疗药物的研发及特异性疗法的探索提供理论依据。

1 MMP的结构及分类

MMPs家族成员由许多不同结构域构成, 从N-端到C-端, 其共同的核心结构包括信号肽序列、前肽结构域、催化结构域、一个可变长度的连接肽(铰链区)以及血红素样的结构域[12](图1)。信号肽由10~40个氨基酸构成, 可以被肽酶水解切割释放, 将MMP引导至分泌或质膜插入途径; 前肽结构域长度约为80个氨基酸, 包含半胱氨酸开关基序, 负责保持MMPs处于非活性状态[13]。催化结构域约有170个氨基酸, 含有锌结合位点, 其催化裂解作用需要通过破坏前肽结构域和催化结构域中锌离子之间的化学键来激活[14]。血红素样结构域由近200个氨基酸组成, 通过脯氨酸富集的柔性铰链区段与MMP分子的其他功能模块相联结, 是MMP多种功能特性(包括结合底物的特异性以及蛋白本身的激活或抑制等)的基础[15]。此外, 同一种MMP可降解多种细胞外基质成分, 而某一种细胞外基质成分又可被多种MMP降解, 但不同MMP酶的降解效率不同[16]。

MMP由结缔组织、促炎细胞和子宫胎盘细胞分泌, 成纤维细胞和白细胞是MMP的主要来源, 但由于MMP在细胞外基质重塑中起主要作用, 它们在大多数结缔组织中高度分布[17-18]。MMPs家族包括28个成员, 其中至少23个在人体组织中表达, 根据其底物特异性及结构域组成分为胶原酶(MMP-1、MMP-8、MMP-13和MMP-18)、明胶酶(MMP-2和MMP-9)、间质溶解素(MMP-3、MMP-10和MMP-11)、基质溶解因子(MMP-7和MMP-26)、膜型(membrane-type, MT) MMPs(MMP-14~MMP-17、MMP-24和MMP-25)和其他MMPs(MMP-12、MMP-19~MMP-23、MMP-27和MMP-28)[19-21]。

2 MMPs的活性调控

MMPs通常是以非活性的酶原形式分泌的, 随后可被包括其他MMPs在内的多种蛋白酶裂解激活, 形成具有催化功能的活性形式, 通过对细胞外基质的降解或结构性破坏, 参与CNS生理和病理过程[22-23]。在生理条件下, MMP的表达水平较低, 然而当脑组织出现损伤后, 其蛋白质水平迅速升高[24]。MMP的活性调节方式包括基因转录、酶原激活、与细胞外基质特定成分的相互作用以及内源性金属蛋白酶组织抑制剂(tissue inhibitor of matrix metalloproteinases, TIMPs)的作用[25]。在转录水平上, 新MMP的合成受细胞因子、生长因子和活性氧调控, 其启动子序列中含有顺式调节元件, 可通过各种刺激诱导表达[26]。此外, MMP基因的转录还受表观遗传机制如DNA甲基化和组蛋白

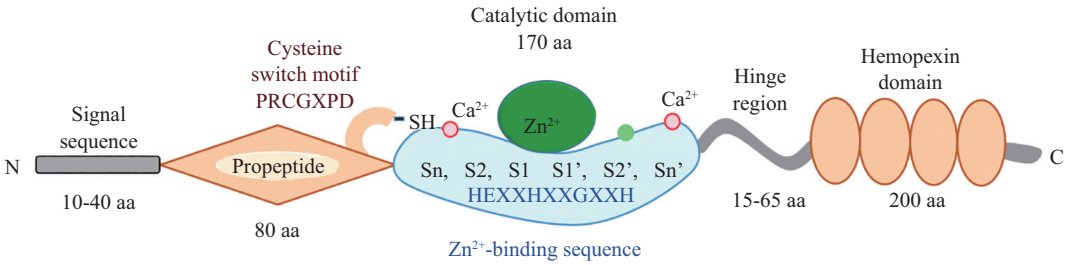


图1 经典MMP的结构示意图(根据参考文献[20]修改)

Fig.1 Structural diagram of the classical MMP (modified from the reference [20])

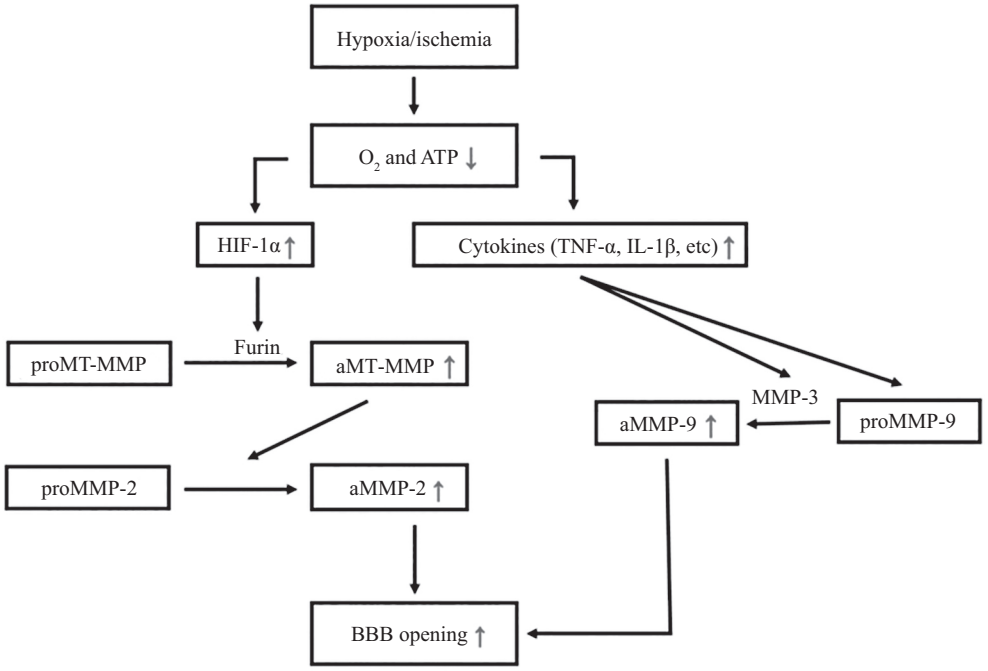
乙酰化调节[27]。MMP蛋白生成后，其活性取决于潜伏形式的激活以及内源性组织抑制剂如α2-巨球蛋白和TIMP的作用[28]。在出现WMI时，MMPs被广泛激活，白质受损，BBB破裂，进而导致毒副产物的释放并攻击髓鞘纤维，从而导致老年患者脑白质的慢性变化和血管认知障碍[29-31]。

3 MMPs在WMI中的作用

3.1 MMP在神经血管中的作用

3.1.1 MMP促进神经炎症 神经炎症在脑灌注不足所致的WMI及慢性认知功能障碍中起着关键作用，主要由CNS有害刺激引发，最终可能加重疾病，致使生物体处于慢性炎症状态[32]。MMP作为脑血管损伤的关键介质，在活化的小胶质细胞、星形胶质细胞及外渗白细胞(尤其是中性粒细胞)中迅速增多[33]。在神经炎症期间，白细胞从循环系统迁移至CNS，在小鼠实验性自身免疫性脑脊髓炎(experimental autoimmune encephalomyelitis, EAE，一种CNS炎症模型)中，发现白细胞利用MMP-2和MMP-9通过实质基底膜迁移[34]。研究表明，缺乏MMP-2和MMP-9表达的小鼠对EAE完全耐药，说明MMP-2和MMP-9是神经炎症过程的微调剂[35]。然而，*MMP-2*和*MMP-9*单基因敲除小鼠仍会出现EAE症状，这表明MMP-2和MMP-9具有互补功能，进一步强化了它们在神经炎症中的关键作用[34]。研究发现，MMP-2和MMP-9 在炎症边界的主要功能是提升炎症反应进程的效率(包括促进炎症细胞因子水平的快速调节，以及通过切割细胞外基质受体破坏实质边界稳定性，加速炎症细胞浸润)[36]。此外，MMP-2和MMP-9的作用具有局灶性，且它们会被快速灭活，从而形成一种快速开启/关闭的动态调节机制，以此精准调控炎症反应的强度和持续时间[36]。

3.1.2 MMP破坏血脑屏障 BBB是血液和CNS之间的高度选择性屏障，有助于维持大脑正常功能和稳态[37]。MMP是破坏BBB的重要因素，活性MMP能降解血管细胞外基质和紧密连接蛋白，导致BBB在病理状态下通透性增加[38-39]。MMP-2和MMP-9是主要的破坏者，分别影响早期和晚期BBB功能障碍[40](图2)。在早期脑血供不足的情况下，氧气与ATP供应随之减少，细胞内由于氧含量匮乏，致使缺氧诱导因子-1α(hypoxia-inducible factor 1 alpha, HIF-1α)蛋白无法像正常状态下那样被降解，而是在细胞内不断累积，随后HIF-1α转移至细胞核内，结合到特定的DNA序列上，通过与缺氧反应元件(hypoxia response element, HRE)结合，HIF-1α不仅能够招募转录起始复合



图中↑表示含量增加、活性增强，↓表示含量减少、活性减弱。

↑ indicates increased content or activity, ↓ indicates decreased content or activity.

图2 MMP在血脑屏障的作用机制(根据参考文献[50]修改)

Fig.2 Mechanism of MMP action in the BBB (modified from the reference [50])

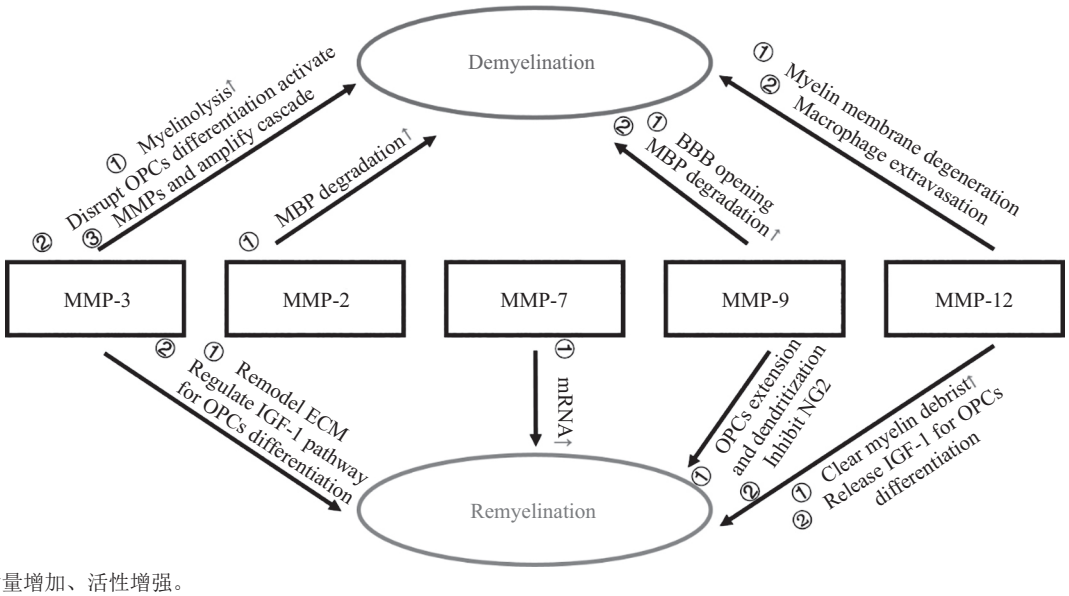
物以及RNA聚合酶II等, 直接启动*MMP-2*、*MMP-9*等基因的转录进程, 促进其表达, 还能通过上调促炎细胞因子激活NF-κB等下游信号通路, 或改变细胞代谢途径及微环境以间接影响MMP转录相关调控因子活性, 从而调控MMP转录[41-42]。HIF-1α激活MT-MMP, 后者再激活proMMP-2, 最终激活MMP-2[43]。神经炎症过程中, 肿瘤坏死因子-α和白细胞介素-1β可诱导MMP-9和MMP-3的表达上调并使其转化为活性形式, 其中proMMP-9可被MMP-3或氧化应激激活[44]。临床研究显示, 血浆MMP-9水平增加与WMI患者的神经功能衰退有关, 慢性脑灌注不足可诱导MMP-9分泌增加, 破坏BBB[45-46]。研究表明, 缺乏MMP-2的小鼠对WMI有抵抗力, MMP抑制剂可减轻慢性脑灌注不足引起的WMI[47-48]。大多数研究集中在MMP-2和MMP-9, 但MMP-3和MMP-12也与神经炎症引起的BBB破坏有关[49]。与野生型小鼠相比, *MMP-3*敲除小鼠在延迟重组组织型纤溶酶原激活剂(recombinant tissue plasminogen activator, rt-PA)静脉溶栓治疗后BBB泄漏减少[50]。在大鼠短暂性脑缺血模型中, MMP-12水平显著增加, 抑制MMP-12表达可降低BBB通透性[51-52]。这些结果表明, 靶向单个MMP调节BBB通透性具有复杂性, 其中MMP抑制剂的干预时间是关键, 开发减少MMP产生和激活的抑制剂对保护BBB至关重要。

3.1.3 MMP促进血管生成 在机体的正常生长发育、组织损伤修复以及各类疾病的发生发展进程中, 血管生成是一个高度复杂且至关重要的生理过程, 新生成的血管能够显著改善局部区域的氧气和营养供给, 尤其是在神经损伤或疾病背景下, 为维持细胞正常代谢与功能, 提供关键的能量支持[53]。而MMPs不仅可以直接降解血管基底膜和重塑细胞外基质, 为血管生成创造基础条件; 它还通过介导促血管生成因子, 调节血管内皮细胞的迁移、增殖以及管腔形成等过程来促进血管的形成和重塑[54-55]。研究表明, 在单侧颈动脉闭塞小鼠模型中, 自手术造模完成后持续观察4周期间, WMI区域的血管内皮生长因子A(vascular endothelial growth factor A, VEGF-A)水平显著升高, 这一变化可能为血管生成营造了适宜的微环境, 有力推动了神经血管的重塑[56]。同时, 表达VEGF-A的周细胞和星形胶质细胞在该模型的WMI区域表达MMP-3, 在患有皮质下缺血性脑血管病的人脑中也有类似现象[57-58]。此外, MMP-2和MMP-9在WMI后, 能够启动胶质细胞的迁移与分化, 助力髓鞘的修复进程, 实验表明在原代少突胶质细胞培养物中, 促炎细胞因子IL-1β可诱导MMP-9的表达上调与分泌, 经IL-1β处理并收集的少突胶质细胞条件培养基能显著促进脑内皮细胞的基质胶管形成, 这表明少突胶质细胞来源的MMP-9在体外具有促进血管生成的能力[59]。新生血管为胶质细胞供应充足的氧气和营养, 为其功能恢复与髓鞘再生提供了有力保障。

3.2 MMP在神经纤维中的作用

神经纤维由神经元的轴突或长树突以及包裹在轴突外的髓鞘构成, 主要功能是将信号从神经元传递到其他神经元或靶组织, 可被分为快速传导的有髓纤维与传导较慢的无髓纤维[60]。髓鞘作为包裹在轴突周围的绝缘层, 具有保护并电隔离轴突、促进动作电位跳跃传导的作用, 然而其易受到缺血、缺氧以及炎症等因素影响, 进而引发WMI[61]。多发性硬化症(multiple sclerosis, MS)属于CNS慢性炎症性疾病, 主要特征为大脑和脊髓髓鞘的慢性丢失, 从而导致WMI[62]。脱髓鞘所引起的功能丧失能够通过钠通道重新分布得到部分补偿, 但这种补偿只是暂时的, 持续的脱髓鞘会致使轴突损伤和变性, 而积累的轴突变性是疾病进展的主要原因[63]。髓鞘再生对于脱髓鞘轴突的存活至关重要, 不过在慢性MS中常常失败, 髓鞘再生需要MMPs表达水平增加, 因其能够调节少突胶质前体细胞(oligodendrocyte precursor cells, OPCs)的行为, 但其过度表达则可能导致脱髓鞘损伤加重[64](图3)。

3.2.1 MMP破坏神经纤维及信号转导 出现WMI时, MMPs尤其是MMP-2和MMP-9, 不仅通过降解神经外基质(层粘连蛋白和胶原蛋白)损伤神经纤维轴突, 还通过引发一系列炎症级联反应影响神经传导通路与神经递质传递[65]。MMPs激活后可促使炎症介质如肿瘤坏死因子-α、白细胞介素-6的释放, 这些介质不仅改变轴突膜的离子通透性, 导致轴突肿胀、变形, 还激活MAPK信号通路, 破坏轴突骨架蛋白, 最终引发轴突断裂[66-67]。进一步, MMPs还通过破坏BBB的完整性, 降解紧密连接蛋白增加BBB的通透性, 使得炎性细胞、细菌毒素及大分子物质进入脑白质, 导致局部炎症反应和氧化应激, 进而干扰神经信号的正常传递[68]。此外, MMPs通过重塑细胞外基质改变神经递质受体在突触后膜的分布和功能, 影响神经信号传递[69]。临床研究表明, 在缺血性脑白质患者中, 脑脊液中MMPs水平的升高与神经



图中↑表示含量增加、活性增强。

↑ indicates increased content or activity.

图3 MMP在髓鞘中的作用

Fig.3 Role of MMP in the myelin sheath

递质传递异常密切相关[70]。MMP过度激活可能导致神经纤维进一步损伤, 因此精准调控MMPs活性, 避免其过度降解神经基质, 对保护神经纤维、恢复神经传导功能及促进缺血后脑组织修复意义重大。

3.2.2 MMP促进脱髓鞘 在脱髓鞘进程中, MMPs的作用呈现出显著的时间依赖性与阶段性差异, MMP-3和MMP-9发挥着关键作用, 同时其他多种MMPs也参与其中, 共同影响着脱髓鞘的发展[71]。MMP-3在脱髓鞘初期, 其mRNA水平迅速升高, 至晚期则恢复至正常水平, 在此期间MMP-3可能直接作用于髓磷脂, 致使髓磷脂分解, 进而破坏髓鞘的正常结构[72]。更为关键的是, MMP-3能够通过调节生长因子信号, 干扰关键的分化信号通路, 如抑制Wnt/β-catenin等对OPCs分化至关重要的信号通路, 来抑制OPCs的分化与成熟[73]。由于OPCs是生成髓鞘的关键细胞, 其分化成熟受阻会直接影响髓鞘的正常修复与再生[64]。此外, MMP-3还具备激活其他MMPs的能力, 例如激活MMP-7和MMP-9, 从而引发级联放大的病理反应, 激活更多具有破坏作用的MMPs, 进一步加剧髓鞘的损伤[74]。MMP-9在脱髓鞘过程中在小胶质细胞和巨噬细胞中的蛋白表达量显著上调, 在MS患者的脑脊液和血清中, MMP-9水平亦明显升高, 向体内注入重组MMP-9后, 会引发BBB破裂以及髓鞘丢失[75]。这表明在脱髓鞘阶段, MMP-9的高表达及其活性增强, 能够直接降解髓鞘碱性蛋白(myelin basic protein, MBP)等关键髓鞘成分, 削弱髓鞘的稳定性; 同时破坏血脑屏障, 使更多炎性细胞和有害物质进入中枢神经系统, 进一步加重髓鞘损伤[46]。此外, 其他MMPs在脱髓鞘过程中也有特定表现, MMP-2的mRNA表达虽无变化, 但其蛋白水平在MS病变区域的巨噬细胞和浸润细胞中显著增加, 在受损轴突区域, MMP-2在MBP降解中最为活跃, 且在正常白质区域上调, 这表明其参与脱髓鞘病变, 不过其是否参与髓鞘再生仍有待研究[76-77]。MMP-12主要来源于小胶质细胞和巨噬细胞, 能够促进细胞迁移并参与髓鞘膜的变性, 在肿瘤微环境(tumor microenvironment, TME)中, MMP-12参与脱髓鞘和巨噬细胞外渗, 但与BBB损伤或细胞外基质重塑无关[78-79]。

3.2.3 MMP促进髓鞘再生 在髓鞘再生阶段, MMPs展现出截然不同的功能, 且其作用同样具有时间依赖性和复杂的功能切换特征[71]。MMP-3在这一阶段, 其mRNA和蛋白质水平再次升高, 它可能通过降解细胞外基质蛋白质以及髓磷脂碎片, 重塑细胞外基质, 为髓鞘再生创造有利条件[80]。此外, MMP-3还能激活胰岛素样生长因子-1(insulin-like growth factor 1, IGF-1)信号通路, 进一步促进OPCs的分化和髓鞘再生[81]。MMP-7在髓鞘再生阶段, 其表达量与健康对照白质相似, 在MS患者血清中也未见明显升高, 但其mRNA水平在髓鞘形成初期有所上升, 推测其可能通过重塑基底膜细胞外基质, 在单核细胞外渗和巨噬细

胞迁移过程中发挥作用[82-83]。与此不同, MMP-9在髓鞘再生阶段有助于少突胶质细胞的成熟, 其缺乏会导致少突胶质细胞的延伸和树突化减少, 并导致细胞活动定位错误[84]。小胶质细胞和巨噬细胞分泌的MMP-9能够降解神经/胶质抗原2(nerve/glial antigen 2, NG2), 这一过程有助于解除对少突胶质细胞成熟的抑制[85]。髓鞘再生阶段MMP-12由星形胶质细胞产生, 帮助清除髓鞘碎片和瞬时表达的细胞外基质蛋白, 创造有利于髓鞘再生的环境[86]。此外, MMP-12在CNS发育中通过释放IGF-1促进OPC分化[87]。

MMPs这种功能的动态调控和时间特异性, 源于不同阶段细胞内信号通路激活状态的差异。在脱髓鞘早期, 炎症等因素促使MMP-3和MMP-9表达, 以应对由炎症反应导致的神经传导功能损伤, 但却加剧髓鞘破坏。随着髓鞘损伤发展, 机体修复机制启动, 细胞内环境改变, 二者功能转向促进少突胶质细胞增殖分化、新髓鞘生成及神经纤维功能恢复等神经修复过程。对于靶向治疗而言, 精准把握MMPs功能切换至关重要。在疾病早期, 抑制MMPs的活性, 可减轻髓鞘损伤; 在髓鞘再生阶段, 适当增强其活性, 能促进髓鞘修复。

4 MMP靶向药物的研究进展

通过药物干预调控MMP活性, 不但能够有效遏制病情恶化, 还可为患者提供更有效的治疗方式, 进而提升整体治疗成效。此类药物在临床实践中展现出广阔前景与重要医学价值。

4.1 天然化合物

4.1.1 *姜黄素* 从姜黄(*Curcuma longa* L.)中分离出的姜黄素是备受广泛研究的植物分子之一, 因其具有强大的抗氧化及抗炎潜力, 被视作多种疾病有前景的治疗候选药物[88]。姜黄素处理可通过降低MMP-9表达水平, 有效抑制脂多糖诱导的星形胶质细胞活化, 影响BBB通透性, 促进白细胞渗入CNS并降解髓磷脂和神经元[89]。然而, 研究也表明姜黄素单独使用时并不抑制MMPs的活性或表达, 单一疗法难以提供大规模治疗效果, 而与阿苯达唑联合使用时, 姜黄素能够抑制MMPs的活性, 并降低血液和脑脊液中的嗜酸性粒细胞计数[90]。总体而言, 尽管姜黄素显示出对MMPs的调控潜力, 但其具体机制及临床效用仍需进一步研究明确。

4.1.2 *白藜芦醇* 白藜芦醇是一种存在于葡萄、苹果、蓝莓、李子和花生中的二苯乙烯化合物, 自1997年报道其具有强大抗癌特性以来, 作为药物和营养保健品化合物的生物活性及治疗潜力已被广泛研究[91]。研究表明, 白藜芦醇能够降低携带*APOE4*等位基因患者脑脊液样本中MMP-9的总水平, *APOE4*等位基因与胶质细胞炎症增加有关[92]。在阿尔茨海默病患者的脑脊液样本中, 白藜芦醇也可减少MMP-2和MMP-9的总水平[93]。此外, 白藜芦醇还能减少培养的小胶质细胞和星形胶质细胞在基础状态及脂多糖刺激下MMP和TIMP-1的释放[94]。综合上述结果可见, 白藜芦醇在抑制炎症相关胶质细胞释放MMP及TIMP-1方面展现出明确疗效, 为其作为治疗药物的研究提供了新方向。

4.1.3 *没食子儿茶素-3-没食子酸酯* 没食子儿茶素-3-没食子酸酯(epigallocatechin-3-gallate, EGCG)是绿茶中最重要的成分, 据报道具有抗氧化和抗癌活性[95]。EGCG可在多种MMPs的启动子区域, 对AP-1、Sp1和NF-κB等至少一种转录因子的结合位点活性产生下调作用, 这些转录因子通过信号通路被EGCG下调, 从而抑制MMP的生成, 且EGCG上调TIMPs的表达, 进而导致MMPs的抑制[96]。

4.2 合成化合物

4.2.1 Ilomastat 伊洛马司他(Ilomastat)是一种合成的肽基异羟肟MMPs抑制剂[97]。Ilomastat及其衍生物主要作用于MMP-9, 通过抑制MMP-9的活性, Ilomastat能够减轻由中性粒细胞入侵引起的组织破坏和炎症[98]。目前, 该药主要在研究领域中作为一种工具药物, 用于研究MMP在疾病中的作用。

4.2.2 *基质金属蛋白酶特异性抑制剂* TIMP家族(包括TIMP-1、TIMP-2、TIMP-3和TIMP-4)作为MMP的拮抗剂, 拥有相似的二级结构(由21个环组成), 这些环通过由3个高度保守的半胱氨酸残基形成的二硫键保持稳定, 分别对不同的MMP具有抑制作用[99]。TIMP具有很高的亲和力, 能够直接与活性的MMPs结合, 形成一对一的非共价复合物, 阻止MMP通过催化锌离子参与底物的水解反应[100]。此外, 通过占据MMP的活性位点, TIMP在空间上阻挡了MMP与其天然底物的接触, 抑制了MMP的酶促反应, 这一物理屏障效应确保了MMPs无法降解细胞外基质成分[101]。除了直接抑制MMPs外, TIMP还通过影响细胞信号通路间接调节MMP的表达和活性[102]。在CNS中, TIMP的较高表达与较低的BBB破坏相关,

这表明TIMP具有神经保护作用[103]。MMP和TIMP之间的平衡对于维持组织的结构完整性和功能至关重要, 它们也是许多疾病治疗中潜在的靶点。

4.2.3 双膦酸盐 双膦酸盐是一类能够抑制骨吸收的药物, 研究发现各种MMP在体外均被几种双膦酸盐(如氯膦酸盐、阿仑膦酸盐、帕米膦酸盐和唑仑膦酸盐)所抑制, 其机制可能涉及双膦酸盐充当阳离子螯合剂的能力, 值得注意的是双膦酸盐在约100 μmol/L的极低浓度下就能产生这种抑制作用[104]。双膦酸盐具有低毒性, 且在人类使用数年后被证明具有良好的耐受性, 有可能在不久的将来成为MMP相关人类疾病的主要MMP抑制剂之一。

4.2.4 3-羟基-3-甲基戊二酰辅酶-A还原酶抑制剂 3-羟基-3-甲基戊二酰辅酶-A还原酶抑制剂即他汀类药物, 属于降低血浆低密度脂蛋白胆固醇水平的常用处方药。研究显示, 他汀类药物可在转录和转录后水平改变MMP基因的表达, 进而影响MMP的激活[105]。洛伐他汀与赛洛他汀能够对人类血管平滑肌细胞中MMP-1、MMP-2、MMP-3及MMP-9的分泌起到抑制作用[106]。辛伐他汀能抑制大鼠肺泡巨噬细胞中MMP-9的表达[107]。上述研究结果表明, 长期应用他汀类药物或许会对多个相关的MMP基因转录控制产生影响。

早期研究主要聚焦于开发广谱MMP抑制剂, 然而在临床试验中, 因其选择性欠佳、毒副作用明显(例如肌肉骨骼疼痛等), 致使疗效不尽如人意。为降低副作用, 研究方向逐渐转为开发选择性MMP抑制剂。此外, 针对特定的MMPs, 一些天然产物被发现具有抑制作用, 如绿茶多酚、姜黄素、白藜芦醇等。总之, 尽管MMP抑制剂在临床应用中面临诸多难题, 但它巨大的治疗潜力与研究价值不容小觑。伴随技术的进步以及研究的深入, 针对MMPs的药物开发有望在多种疾病的治疗中发挥更为重要的作用, 进而提升患者的生活质量。

5 总结与展望

随着影像技术不断进步, 临床上检测到的WMI病例日益增多。尽管医疗技术持续发展, 但由WMI引发的认知功能障碍、情绪障碍和运动功能障碍仍未得到显著改善。若不能真正实现对白质的保护, 就难以达成持久的神经恢复。已有研究表明, MMPs在WMI的病理过程中发挥关键作用, 尤其在神经血管和髓鞘方面, 其活性与损伤程度紧密相关。多种靶向MMPs的药物在实验模型中呈现出不同程度的保护效果, 展现出临床治疗的潜力。

未来的研究应进一步深入探究MMPs在WMI中的作用机制, 特别是不同类型MMPs的功能及其调控途径。由于WMI的病理生理学涉及多种机制、通路和分子, 单一靶点治疗可能难以取得理想效果。因此, 未来研究还应探索多靶点治疗或联合使用MMP抑制剂与传统神经治疗药物, 以减轻WMI的影响。现有的大多数研究是在年轻动物上进行的, 而WMI主要影响老年人, 这限制了研究的临床应用价值。故而, 未来需要更多的研究来测试MMPs抑制剂在老年和有合并症的动物中的有效性, 评估其对这些患者的潜在益处。此外, 鉴于MMP-3、MMP-9等蛋白酶于髓鞘中的作用呈现双重性, 即既能加剧早期脱髓鞘, 又能推动后续髓鞘再生。针对这些蛋白酶的不同活性位点, 可设计小分子抑制剂或单克隆抗体, 对其特定活性位点进行选择性抑制, 从而研发出具有时控释放或定向激活功能的药物。此类药物能够选择性靶向并抑制在损伤后发挥负面作用的MMPs, 同时维持对髓鞘修复有益的MMPs正常功能, 确保MMP抑制剂在WMI修复过程中发挥最优效应, 进而改善患者预后。

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