

基质金属蛋白酶家族调控乳腺癌发展机制研究进展

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摘 要

目的: 了解基质金属蛋白酶(matrix metalloproteinases, MMPs)家族调控乳腺癌发展及其机制研究的进展, 以期为基础研究及临床的诊断和治疗提供借鉴和帮助。方法: 对近年来国内外关于MMPs调控乳腺癌发生、发展及其机制研究的相关文献进行综述。结果: MMPs家族中大多数成员的非正常表达均可导致细胞外基质降解、细胞侵袭和附着并显著加速上皮间质转化进程, 从而促进HCC的侵袭及转移。目前与乳腺癌发展相关研究较多的MMPs包括MMP-1、2、3、7、9、10、11、13、14、26, 其余MMPs家族成员与乳腺癌发展相关的研究还相对较有限。结论: MMPs家族(尤其是MMP-1、2、3、7、9、10、11、13、14、26)在增殖、侵袭、转移等进展过程中起十分重要的作用。进一步探索MMPs家族所有成员与乳腺癌发展可能存在的内在联系, 对预测乳腺癌转移潜力和预后情况及开发新的或改进乳腺癌当前靶向抗癌疗法至关重要。

关键词

乳腺癌, 基质金属蛋白酶, 机制, 研究进展

Advances in the Study of Mechanisms by Which the Matrix Metalloproteinase Family Regulates the Development of Breast Cancer

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Abstract

Objective: To understand the research progress of the matrix metalloproteinases (MMPs) family regulating breast cancer development and its mechanisms, aiming to provide references and assistance for basic research, clinical diagnosis, and treatment of breast cancer. **Methods:** Recent domestic and international literature on the regulation of breast cancer occurrence and development by MMPs and their mechanisms was reviewed. **Results:** The abnormal expression of most members of the MMPs family can lead to extracellular matrix degradation, cell invasion, and attachment, significantly accelerating the epithelial-mesenchymal transition process, thereby promoting the invasion and metastasis of breast cancer. Currently, the MMPs most frequently studied in relation to breast cancer development include MMP-1, 2, 3, 7, 9, 10, 11, 13, 14, and 26, while research on other MMPs family members in relation to breast cancer development is relatively limited. **Conclusions:** The MMPs family (especially MMP-1, 2, 3, 7, 9, 10, 11, 13, 14, and 26) plays a crucial role in the proliferation, invasion, and metastasis of breast cancer. Further exploration of the potential intrinsic connections between all members of the MMPs family and breast cancer development is essential for predicting metastasis potential and prognosis of breast cancer, as well as for developing new or improved current targeted anti-cancer therapies for breast cancer.

Keywords

Breast Cancer, Matrix Metalloproteinases, Mechanism, Research Progress

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1. 引言

恶性肿瘤已成为严重威胁我国人群健康的主要疾病之一。根据 2022 年我国恶性肿瘤发病与年龄分布特征发现乳腺癌发病率位居女性所有恶性肿瘤第二, 是中国 45~59 岁女性中发病率最高的恶性肿瘤类型, 其发病年龄也呈年轻化趋势[1]。近年来, 随着乳腺癌手术治疗的发展以及多学科协作的背景下乳腺癌的病死率逐年下降[2], 但相当一部分患者术后出现器官转移而复发, 这已成为导致乳腺癌患者不良预后的关键因素。基质金属蛋白酶(matrix metalloproteinases)在包括乳腺癌等诸多恶性肿瘤的发生与发展中起到了极其重要的作用, 它促进广泛的过程, 包括细胞增殖和迁移, 并且在细胞凋亡、血管生成, 组织再生和免疫反应中发挥重要作用[3]。本篇将综述对 MMPs 家族部分成员与乳腺癌细胞调控乳腺癌发展及其机制研究的进展, 以期为乳腺癌的基础研究及临床的诊断和治疗提供借鉴和帮助。

2. MMPs 简介

基质金属蛋白酶(MMPs)是一大类钙依赖性含锌内肽酶, 至少有 23 种在人体组织中表达[4]-[6]。MMPs 对组织的稳态有十分重要的意义, 并且参与生成血管、胚胎发生和伤口修复等各种生理过程, 是组织重塑及再生过程中的关键物质[4]。MMPs 在各种细胞中表达, 如结缔组织中成纤维细胞中表达, 也在嗜中性粒细胞、单核细胞、巨噬细胞和内皮细胞中表达, 它们的主要作用是降解细胞外基质(ECM)蛋白、糖蛋白、膜受体、细胞因子和生长因子[7]。此外, 心肌梗死、纤维化疾病、骨关节炎和癌症组织的生长、转移和侵袭, 此外, 它们还可以通过调节免疫细胞的分化和活性以及募集巨噬细胞和中性粒细胞来影响

免疫系统。许多疾病的病理生理机制和疾病专归过程都与其有密切关系[8] [9]。

MMPs 具有共同的功能域和激活机制。根据其底物或类似的结构部分, 它们被细分为胶原酶(MMP1、MMP8、MMP13)、明胶酶(MMP2、MMP9)、溶血素(MMP3、MMP10、MMP11)、基质溶血素(MMP7、MMP26)、膜型 MMP (MMP14)和其他 MMP。

MMPs 通常被合成为无活性酶原合成并且以此形式分泌, 锌离子可以与其催化位点相结合, 产生相互作用与其前肽结构域[10], 通过蛋白水解过程, 暴露该结构域的蛋活性位点, 使酶原被激活为活性酶[11]。在 MMP 蛋白水解的过程中, 金属蛋白酶内源性组织抑制剂(TIMP)是控制该过程的关键因素, 因此, MMP 实际活性的变化取决于 MMPs 的产生和激活与 TIMP 的局部水平之间的平衡[12] [13]。

3. MMPs 与乳腺癌

MMPs 家族各成员由于具有不同的生物学活性, 所以在乳腺癌的侵袭、转移等发展过程中也发挥着不同的调控作用, 下面乳腺组织中现已发现的 MMPs 进行阐述。

3.1. MMP-1

MMP-1 (基质金属蛋白酶 1), 又称间质胶原酶, 是最广泛表达的基质金属蛋白酶之一, 可以降解 I 型、II 型和 III 型胶原。MMP-1 的异常表达与肿瘤的侵袭和转移密切相关, 其在乳腺癌的早期发生及肿瘤生长中可能起重要作用, 在晚期乳腺癌中经常被上调, 与肿瘤分化相关, 有报道指出 MMP-1 参与 ECM 降解, 迁移, 侵袭, 从而导致转移[14], 被认为是乳腺癌转移的预测标记物以及与不良预后相关[15] [16]。MMP-1 可以通过激活 G 蛋白偶联受体 PAR1 和释放信号分子前体如 pro-TGF α 、pro-TGF β , 来促进肿瘤的转移。

3.2. MMP-2 与 MMP-9

MMP-2 与 MMP-9 分别被称为明胶酶 A 及明胶酶-B, MMP-9 常被认为与 MMP 2 是一致的肿瘤进展标志物, 其共同作用都是推动它是肿瘤细胞分解基底膜, 有利于肿瘤细胞的局部浸润和远处转移[17], 根据 Jeleniewicz 等学者研究[18]表明: MMP-2 表达的增加与人类多种恶性肿瘤侵袭、转移以及预后紧密相关, 是恶性肿瘤进展的标志物之一。LI [19]等学者通过检测 80 例乳腺癌组织和 40 例癌旁正常组织标本中 MMP-2 和 MMP-9 的表达水平, 研究结果表明乳腺癌组织中 MMP-2 和 MMP-9 的表达明显高于乳腺癌旁正常组织, 癌组织中 MMP-2 和 MMP-9 的表达水平与淋巴结转移和肿瘤分期有关, 且影响乳腺癌患者的预后。王娜[20]等研究结果也提示 MMP-2 和 MMP-9 的表达与乳腺癌的发生、发展, 恶性细胞的侵袭、转移密切相关。Ramos 等研究结果显示乳腺癌病人中, MMP-2 阳性表达者较阴性表达者更差。Aman [21]学者通过对 48 名乳腺癌患者和 13 名良性乳腺疾病患者进行对比研究得出 MMP-9 的表达水平在乳腺癌患者组织中显著升高, 乳腺癌患者术前 MMP-2 和 MMP-9 表达水平较根治术后显著升高。根据国内学者周梅、周虹等研究[22] [23], 乳腺癌组织中 MMP-2 的表达水平明显高于正常乳腺组织或乳腺良性疾病组织。

3.3. MMP-3

基质金属蛋白酶 3 (MMP-3), 又称基质分解素-1, 可降解层粘连蛋白、I、III、IV 和 V 型纤维连接蛋白, 在细胞外基质的降解和重塑过程中起着关键作用, 并以此调节促进肿瘤侵袭和转移。MMP-3 的合成和活化是 MMPs 介导的降解过程的第一步, 它在激活 MMP-1、MMP 7 和 MMP-9 的过程中起着至关重要的作用[24]。MMP-3 与乳腺癌细胞的增殖、凋亡、侵袭与转移密切相关, 并且在乳腺癌中与高死亡率和晚期肿瘤相关, 不仅在肿瘤最初的发展和进展中有都重要作用[25] [26]。

3.4. MMP-7

MMP-7 也称为基质溶血素, 它可切割组成细胞外基质的许多蛋白质成分, 包括胶原蛋白、骨桥蛋白、纤连蛋白、层粘蛋白、弹性蛋白和蛋白聚糖[27], 研究显示[28], 乳腺癌组织中 MMP-7 蛋白的高表达能促进乳腺癌细胞侵袭和迁移。另研究发现, 与正常乳腺组织相比, 乳腺浸润性导管癌和导管原位癌 MMP-7 的阳性表达率显著升高。此外, 它与乳腺癌的组织学分型, 临床分期和淋巴结转移密切相关, 这再次证实 MMP-7 不仅参与了乳腺癌的发生和发展, 同时参加了乳腺癌的转移进程。

3.5. MMP-8

MMP-8, 也称为胶原酶-2 或中性粒细胞胶原酶, 与 MMP-1 同属于胶原酶家族, 其促癌机制主要是通过毛细血管样网络结构的发展在细胞增殖、迁移以及血管生成中发挥作用[29]。

MMP-8 在炎症刺激下从中性粒细胞颗粒中释放, 降低基底膜和组织的连接, 帮助中性粒细胞到达炎症部位参与炎症响应, 如肺损伤、也血管疾病、关节炎等疾病的炎症反应[30]。然而, 癌症中 MMP-8 的作用不尽相同, 其在不同癌症类型和癌症阶段有可能截然相反, 需要谨慎辩证看待。有临床研究也显示, 乳腺癌病人高表达 MMP-8 将预示着更低的转移发生和良好预后[31]。

3.6. MMP-10

MMP-10, 或称为基质溶质-2, 主要存在于上皮细胞中, 通过分解细胞外基质成分(如胶原、明胶、弹性蛋白、纤连蛋白、蛋白聚糖和层粘连蛋白)参与肿瘤细胞侵袭和转移[32], 除了蛋白水解活性 MMP-10 还被证明具有催化某些酶原的活性包括 MMP-1、MMP-7、MMP-8、MMP-9、MMP-13 以及触发胶原酶(如 MMP-1)活性的能力。MMP-10 通过靶向其他几种 MMP 催化其酶原的能力被认为是左右激活与抑制平衡的关键[33] [34], 在乳腺癌的侵袭转移中发挥协同作用。

3.7. MMP-11

MMP-11, 也称为基质溶质-3, 其过表达是各种人类癌症预后不良的一个因素, 有研究报道这种蛋白酶本身并不在恶性细胞中表达, 而是由细胞基质中的间充质细胞分泌[35], 然而, 一些研究却证实了 MMP-11 不仅在细胞基质中表达, 同时也在肿瘤细胞中表达[36] [37]。MMP-11 其在抑制细胞凋亡、增强肿瘤的侵袭和转移活性的能力却被其他研究所证实[38]。MMP-11 在乳腺癌组织中显著上调, 提示乳腺癌有发展成为浸润性癌的可能性, 并且认为 MMP-11 可能是乳腺癌一个新的标志物。MMP-11 除了在侵袭性原发性癌中的表达, 还被发现在淋巴结转移病灶中表达[39] [40]。在肿瘤细胞中, 肿瘤细胞与肿瘤相关的成纤维细胞之间的细胞相互作用过程中能促进 MMPs 的表达与激活[41]。在乳腺癌肿瘤细胞与基质成纤维细胞中, 与乳腺癌预后相关的因子 P53, 雌激素受体、孕激素受体以及人表皮生长因子 HER2 与 MMP-11 的表达具有相关性[42]。这些发现认为 MMP-11 可能通过某一信号通路或者未知的生物学行为, 扮演着比蛋白水解酶更复杂的角色。

3.8. MMP-13

MMP-13 在肿瘤或间质细胞中的过表达和癌症的演变进展之间存在一定的因果关系。MMP-13 作为基质金属蛋白酶家族的一员, 主要降解 I、II、III、IV、X 型胶原纤维以及粘蛋白、纤维连接蛋白、蛋白多糖和原纤维蛋白, 在多种恶性肿瘤中表达, 如结直肠癌、皮肤癌、乳腺癌、基底细胞癌等, 并且与肿瘤的生物行为 and 预后有关[43] [44]。研究发现 MMP-13 在溶骨性骨转移中起着关键作用, 主要因为肿瘤细胞诱导的抑癌蛋白 M 和载脂蛋白 SAA3 在成骨细胞产生的急性反应中发挥作用, 而成骨细胞分泌的胶原酶

是 MMP-13 的主要作用底物, 这些胶原酶促进破骨细胞介导的骨吸收, 使破骨细胞活化肿瘤发生骨转移[45][46]因此开发有效的 MMP-13 抑制剂, 阻断其诱导的骨转移, 有望为乳腺癌的临床诊治提供新的靶点。早期开发的广谱 MMPs 抑制剂马立马司他, 因严重的不良反应在临床研究中未能取得成功。近年 Piecha 等[47]发现了两种高效高选择性非 Zn²⁺结合的 MMP-13 抑制剂 ALS 1-0635 和 ALS 1-1087, 在动物模型中可有效抑制软骨细胞的骨转移, 但缺少进一步的人体实验; 另外新发现的一种 MMP-13 特异性的抑制剂 Cmpd-1 [48]在乳腺癌肿瘤细胞生长及骨转移过程中起抑制性作用, 可明显降低溶骨性骨损伤。

3.9. MMP14

MMP-14 是为膜型 MMP, 通过降解细胞外基质, 增加 MMP-2 和 MMP-9 的分泌以及与 TIMP 相互作用, 是癌症侵袭和转移期间细胞外基质和组织破坏背后的驱动力; 同时, MMP-14 还通过调节许多质膜锚定和细胞外蛋白的活性来影响细胞间和细胞-基质通讯[49]。有研究表明 MMP-14 在调节肿瘤细胞生长环境、诱导多种细胞因子表达方面发挥重要作用。该研究认为, MMP-14 蛋白和 c-myc 基因存在内部联系, 共同影响乳腺癌的发生, 并且实癌组织 MMP-14 蛋白和 c-myc 基因阳性表达率显著高于癌旁正常组织($P < 0.05$)。提示, MMP-14 蛋白和 c-myc 基因发挥促进肿瘤生长的作用[49]。另有研究表明过表达的 miR-584-5p 通过下调 MMP-14 抑制乳腺癌细胞的增殖、迁移和侵袭, 提示该机制可能成为乳腺癌治疗的潜在靶点

3.10. MMP-26

MMP-26, 也称为基质溶解素-2, 可以分解数个细胞外基质组成物质并通过激活 MMP-9 来发挥其生物学功能[50]。病理状态下, MMP-26 主要表达于上皮源性的恶性肿瘤中, Zhao YG 等通过免疫组化及 PCR 技术对乳腺癌组织进行研究时发现, MMP-26 在乳腺导管原位癌中 mRNA 和蛋白的表达量明显升高, 其表达水平高于乳腺浸润型导管癌[51]。Strongin 等研究也证实, MMP-26 在乳腺癌导管原位癌中呈高表达, 且雌激素阳性患者的生存期明显高于雌激素阴性患者[52]。

4. 总结与展望

乳腺癌已经成为影响广大女性健康的主要疾病之一。目前针对乳腺癌的治疗多种多样, 也取得了很大进展, 但乳腺癌转移以及治疗耐药严重困扰着临床医师, 随着 MMPs 家族成员不断被发现, MMPs 家族成员中大多数成员的非正常表达均可导致细胞外基质分解、细胞侵袭和附着并显著加速上皮细胞间充质化进程, 这足以说明 MMPs 家族在乳腺癌的增殖、侵袭、转移等进展过程中起着十分重要的促进作用。若能进一步证实患者血清或肿瘤的细胞外基质中 MMPs 的表达水平与乳腺癌发生或转移的相关性, 可能存在一定临床意义。对于 MMPs 家族成员与乳腺癌发展的深层机制的探索有望对开发新的或改进乳腺癌当前靶向抗癌疗法提供新的思路和理论依据。

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