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MMP-9与ICAM-1在COPD中作用机制及临床应用潜力

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摘　要

慢性阻塞性肺疾病(COPD)是一种以持续气流受限为特征的慢性呼吸系统疾病，其病理改变主要表现为气道或肺泡异常。其患病率及死亡率居高不下，已成为我国重要公共卫生问题。大量研究证实基质金属蛋白酶-9 (MMP-9)可通过降解细胞外基质参与气道重塑，也可诱导炎症介质的表达，细胞间粘附分子-1 (ICAM-1)则能介导炎症细胞浸润与粘附，也可参与气道重塑，二者在COPD的炎症进展、肺组织损伤及疾病恶化进程中发挥关键调控作用。本文就MMP-9、ICAM-1在COPD中的作用机制及临床应用潜力等研究现状进行综述，深入阐明上述分子调控机制，能为其新型诊断指标与治疗靶点的发掘奠定重要理论基础。

关键词

慢性阻塞性肺疾病，基质金属蛋白酶-9，细胞间粘附分子-1

Mechanisms and Clinical Application Potential of MMP-9 and ICAM-1 in COPD

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Abstract

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized by

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persistent airflow limitation, with pathological changes mainly manifested as abnormalities in the airways or alveoli. The prevalence and mortality of COPD are both high, making it a significant public health concern. Numerous studies have confirmed that matrix metalloproteinase-9 (MMP-9) can contribute to airway remodeling by degrading the extracellular matrix and can also induce the expression of inflammatory mediators. Intercellular adhesion molecule-1 (ICAM-1) can mediate the infiltration and adhesion of inflammatory cells and also participate in airway remodeling. Both play key regulatory roles in the inflammatory progression, lung tissue damage, and disease exacerbation of COPD. This article reviews the current research on the mechanisms and clinical application potential of MMP-9 and ICAM-1 in COPD, providing an in-depth explanation of the regulatory mechanisms of these molecules, and laying an important theoretical foundation for the development of new diagnostic markers and therapeutic targets.

Keywords

Chronic Obstructive Pulmonary Disease, Matrix Metalloproteinase-9, Intercellular Adhesion Molecule-1

1. 引言

COPD 作为一种临床表现多样的慢性呼吸系统疾病，临床以呼吸困难、咳嗽、咳痰、喘息为典型表现，其核心病理生理特征为持续进展且无法完全逆转的气流[1]。流行病学数据显示，全球 COPD 流行趋势日益严峻，预计到 2050 年患者规模将接近 6 亿例，较 2020 年增长约 23% [2]。COPD 作为一项全球性的重大公共卫生难题，不仅患病率、发病率和死亡率居高不下，同时也对患者家庭、医疗系统及社会经济构成了持续且沉重的负担[3]。

2. COPD 发病机制

慢性阻塞性肺疾病的发展涉及多重因素交互作用，其发病机制较为复杂，香烟烟雾是其最常见的危险因素，非吸烟者也可能因空气污染、生物燃料烟雾等环境因素而患病[4]。其核心病理机制为持续性肺部炎症与氧化应激，二者相互促进共同推动疾病进程，氧化应激可激活炎症相关通路，慢性炎症会促进活性氧(ROS)进一步生成，二者形成恶性循环，共同导致气道结构改变与肺功能不可逆损害[5]。例如氧化应激可增加 ICAM-1 表达[6]，从而促进炎症细胞在气道与肺血管内皮的粘附，并加剧肺部慢性炎症[7]。在免疫机制方面，下呼吸道异常免疫反应在 COPD 发病进程中起关键作用，其进展与先天和适应性炎性免疫细胞浸润肺部及淋巴滤泡形成有关[8]。在结构上，COPD 与蛋白酶－抗蛋白酶系统失衡密切相关，炎症反应可打破该系统稳态，进而引起气道结构发生进行性损伤与重塑。基质金属蛋白酶(MMPs)可通过直接与间接途径参与肺气肿形成，其中 MMP-9 在肺部炎症中发挥重要作用，机制包括降解细胞外基质、促进中性粒细胞趋化以及加剧炎症反应等[9]。COPD 的影响具有全身性，其肺部病理过程可加速心血管疾病等合并症的进展[10]。因此，深入探讨 COPD 相关的关键分子，如 MMP-9 与 ICAM-1 的作用机制，可能为未来治疗靶点的开发提供新方向。

3. MMP-9 的定义和一般功能

MMP-9，即基质金属蛋白酶-9，属于 MMPs 家族中的明胶酶亚类，也称为明胶酶 B，是一种依赖锌

离子的内肽酶[11]。它通常以无活性前体形式分泌，需经酶解或化学激活转化为活性形式[12]，且需钙离子辅助维持活性，主要通过降解细胞外基质(ECM)中的蛋白质发挥作用[13]。其主要功能是参与 ECM 重塑，通过降解 ECM 中的胶原、层粘连蛋白、纤维连接蛋白等成分在组织发育、修复及再生过程中发挥关键作用[14]。MMP-9 可通过蛋白水解活性直接降解肺组织中 ECM 成分，导致肺组织破坏和肺气肿形成，其过度表达会打破蛋白酶/抗蛋白酶平衡，这也是 COPD 小气道和肺实质进行性结构损伤的核心病理特征[15]。在伤口愈合过程中，适量 MMP-9 可促进组织修复，过度表达则会导致 ECM 过度降解进而延缓愈合[16]。在病理生理方面，MMP-9 在炎症与免疫反应中可调节免疫细胞迁移和细胞因子激活[13]。在肿瘤进展中则能促进肿瘤侵袭、转移及血管生成[17]。在神经系统中，其可影响血脑屏障通透性和突触可塑性，且与神经发育障碍及中枢神经系统感染相关[18]。MMP-9 还可通过调节 p38MAPK、uPA 等信号通路影响细胞迁移、增殖与凋亡[19]，它与同属明胶酶亚家族的 MMP-2 (明胶酶 A)相比，在炎症和肿瘤相关病理过程中作用更显著[20]，其活性受金属蛋白酶组织抑制剂(TIMPs)调控，MMP-9/TIMP-1 比例失衡与多种疾病的发生发展相关[21]。综上所述，MMP-9 是一种具有多重生物学功能蛋白酶，能够通过降解 ECM 与调控细胞信号等途径，在多种生理与病理过程中发挥广泛作用[22]。

4. ICAM-1 的定义和一般功能

ICAM-1 是一种跨膜糖蛋白，属于免疫球蛋白超家族成员，也被称为 CD54 [7] [23]。它由特定基因编码，可在内皮细胞、中性粒细胞和免疫细胞等多种细胞表面表达[24]。在炎症或病理状态下，其表达显著升高，并可被剪切为可溶性形式 sICAM-1 进入循环[25]。有研究发现，sICAM-1 在各系统炎症反应中均呈高表达状态[26]，其含有与整合素(如 LFA-1 和 Mac-1)结合的结合域，从而介导细胞间的粘附作用[27]。ICAM-1 能够介导细胞粘附与信号传导，通过结合整合素 LFA-1 和 Mac-1 促进白细胞跨内皮迁移及组织浸润，是白细胞招募的关键分子[28]。该分子也可增强炎症中 T 细胞与靶细胞的粘附，同时协调免疫细胞的迁移与激活[29]。ICAM-1 作为内皮炎症的核心生物标志物，其表达上调与多种炎症性疾病相关，例如脑小血管病中，它与 VCAM-1 共同参与内皮炎症反应[30]；ICAM-1 在肿瘤发展中具有双重功能，其既可促进免疫细胞浸润与免疫突触形成以增强抗肿瘤免疫[31]，也能参与肿瘤免疫逃逸，例如肿瘤外泌体可通过 ICAM-1 与 PD-L1 共定位来抑制 CD8 T 细胞活性[32]。在心血管疾病中，ICAM-1 是血管炎症和内皮功能障碍的关键调节因子，例如在动脉粥样硬化过程中它参与单核细胞募集和斑块形成[33] [34]。在各类呼吸系统炎症性疾病中，ICAM-1 的表达水平均显著升高[35]，有研究发现，COPD 患者肺功能水平与 ICAM-1 血清水平有关[36]。它可通过介导炎症细胞的浸润与活化等，在 COPD 的进展中发挥重要作用[37]。一项哮喘小鼠实验发现，IgE 能够促使血管内皮细胞表面 ICAM-1 表达增加，从而增强单核细胞黏附功能[38]。综上，ICAM-1 是一种介导细胞粘附和信号传导的跨膜糖蛋白，参与多种炎症性疾病、肿瘤及心血管疾病的发生发展，同时也是慢性阻塞性肺疾病病理过程的关键分子。

5. MMP-9 在 COPD 病理中的核心作用机制

MMP-9 在 COPD 病理机制中的重要作用已得到广泛研究证实。其主要通过降解 ECM 参与 COPD 的气道重塑与肺组织破坏。COPD 患者肺组织中细胞外基质过度降解，表现为 MMP-9 蛋白水解活性直接降解胶原和弹性蛋白，引发肺组织破坏及肺气肿形成。MMP-9 过度表达破坏了蛋白酶－抗蛋白酶平衡，导致小气道和肺实质出现进行性结构损伤[39]。MMP-9 还能调节中性粒细胞和巨噬细胞等免疫细胞的迁移活化，促进炎症介质释放并放大炎症级联反应，其与氧化应激的相互作用进一步加剧慢性肺损伤，COPD 患者体内 MMP-9 可能通过氧化应激促进巨噬细胞极化从而加重肺损伤[40]。Agraval 等人发现，COPD 患者体内 MMP-9 可能通过氧化应激促进巨噬细胞极化从而加重肺损伤。此外，MMP-9 通过促进上皮－间

质转化参与气道重塑，导致气道纤维化与管壁增厚，并能通过此过程增加 COPD 相关肺癌风险，提升恶性转化潜能[41]。多项研究证实，COPD 患者的多种生物样本中均存在显著的 MMP-9 水平升高。Przysucha 等人发现，COPD 患者痰液中的 MMP-9 水平升高，并与疾病严重程度及炎症标志物(如 IL-8)正相关[42]。还有研究在小鼠模型中观察到，COPD 小鼠肺泡灌洗液内 MMP-9 水平呈现上升趋势[43]。一项前瞻性队列研究表明高血浆 MMP-9 水平与肺功能下降及 COPD 发病风险增加显著相关[44]，但其样本量有限，结论需通过大样本研究进一步验证，且 MMP-9 影响肺功能的具体机制仍不明确，未来可通过扩大样本量并深入探究其作用机制开展研究。当前关于 MMP-9 在 COPD 中作用研究已取得一定进展，但仍有改进空间，如目前研究支持 MMP-9 在 COPD 中的致病作用，但有研究发现，MMP 抑制剂在既往临床试验中屡屡失败，其核心原因可归结为三大方面：药物本身缺乏选择性、不良的药代动力学特性以及对生理修复过程的干扰。广谱 MMP 抑制剂通常同时靶向多个 MMP 家族成员，这些蛋白酶不仅在病理过程中被激活，也广泛参与维持正常组织稳态、促进伤口愈合和调节免疫应答等关键生理功能。这种非选择性的广泛抑制也会破坏上述保护性作用，进而引发一系列严重的副作用，例如肌肉骨骼综合征、肝毒性等，这些不良反应最终严重限制了该类药物的临床应用前景[13] [17] [45]。现多数研究证实了 MMP-9 水平与疾病严重程度具有相关性，但尚缺乏确凿证据证明其因果性，无法明确其升高是驱动疾病恶化的原因还是组织损伤的结果。且 MMP-9 作为独立生物标志物在诊断与预后评估中价值有限，且检测方法尚未实现标准化，未来可将 MMP-9 联合影像组学特征及其他分子标志物，以提高早期诊断与病情分级的精准度。

6. ICAM-1 在 COPD 病理中的核心作用机制

ICAM-1 是与吸烟暴露密切相关的生物学标志物。在 COPD 的病理过程中，ICAM-1 也扮演了关键角色，其核心作用机制主要体现在介导炎症细胞浸润、参与内皮免疫调节、氧化应激损伤以及与 ECM 重塑等方面。作为跨膜糖蛋白，ICAM-1 通过与白细胞表面的整合素结合，促进白细胞与内皮细胞黏附及跨内皮迁移，驱动炎症细胞向肺组织浸润[7]。ICAM-1 在 COPD 中表达上调会加剧中性粒细胞和巨噬细胞等炎症细胞的聚集，从而驱动慢性气道炎症[23]。ICAM-1 还参与氧化应激与内皮屏障损伤过程。例如，纳米铅氧化物等环境毒素通过增加细胞内活性氧生成并降低抗氧化酶活性，诱导 ICAM-1 与 VCAM-1 表达升高，导致内皮屏障功能障碍[6]。在血小板–内皮相互作用与血管重塑方面，ICAM-1 也发挥关键作用，肺动脉内皮细胞表面的 ICAM-1 与血小板糖蛋白 IIb/IIIa 结合可激活血小板并释放 PDGF-BB，进而促进肺动脉平滑肌细胞增殖迁移，参与 COPD 的肺血管重塑[46]。ICAM-1 在免疫调节及细菌感染过程中具有双重功能。一方面它通过促进免疫细胞与上皮细胞黏附参与宿主防御反应[23]，另一方面外泌体 ICAM-1 与 PD-L1 共定位可能与 LFA-1 结合抑制 $CD8^+$ T 细胞功能，进而导致免疫逃逸[32]。Shukla 等人发现，吸烟者气道上皮均出现 ICAM-1 高表达，且在 COPD 患者气道中，ICAM-1 的表达水平也显著升高[47]。亦有研究发现，COPD 患者诱导痰中 ICAM-1 表达显著增高[48]。当前研究受限于生物标本类型较少且样本规模不足，未来可通过扩充样本量、扩展生物标本类型等方式开展进一步探索，例如测定肺泡灌洗液、血液等样本中 ICAM-1 的表达水平。基于上述机制，靶向 ICAM-1 或其调控通路展现出治疗潜力，例如化合物 XJ8 可通过抑制 JNK/Stat3 和 NF-κB 通路下调 ICAM-1 表达，减少单核–内皮细胞黏附[49]。综上，ICAM-1 通过调控炎症细胞募集、氧化应激反应以及血管重塑等多种机制，在 COPD 的发生发展中发挥核心作用，成为潜在的治疗靶点。但是目前研究有很大局限性，现有研究多数为动物模型或体外实验，ICAM-1 在人体 COPD 病程中的动态作用尚需在大规模前瞻性人群研究进一步确认，且现有研究多聚焦于 ICAM-1 的粘附功能，而其在信号转导及可溶性形式 sICAM-1 方面的功能在 COPD 中研究尚不充分。针对 ICAM-1 的单克隆抗体及其他抑制剂在 COPD 治疗中的临床应用仍处于初步探索阶段，其疗效与安全性有待更多大型临床试验验证。

7. MMP-9 与 ICAM-1 在 COPD 的潜在协同作用和研究进展

MMP-9 和 ICAM-1 在 COPD 的发病机制中具有显著的潜在协同作用。其协同作用与研究进展主要体现在以下几个方面：首先，二者在炎症与免疫细胞浸润中存在协同调控。MMP-9 作为锌依赖性内肽酶，参与 ECM 重塑、血管生成及免疫细胞迁移[13]；而 ICAM-1 是介导白细胞与内皮细胞黏附的关键分子[27]。ICAM-1 与 MMP-9 共同参与细胞外基质重塑和炎症反应。例如在心肌缺血再灌注损伤模型中，ICAM-1 与 MMP-9 的表达水平呈相关性升高[50]。其次，二者协同参与气道重塑与组织损伤。MMP-9 的活性失调直接导致 ECM 的过度降解，是促进气道纤维化和肺气肿形成的关键机制[41]；而 ICAM-1 通过介导炎症细胞与内皮/上皮细胞的相互作用，不仅加重局部炎症，也进一步放大了 MMP-9 的促纤维化与组织破坏效应[51] [52]。有研究证实，COPD 患者血清中 MMP-9 与 ICAM-1 水平呈显著正相关，且二者浓度与疾病严重程度呈正相关[53]。基于上述机制，靶向 MMP-9 与 ICAM-1 已成为潜在的治疗探索方向。但是目前关于 MMP-9 与 ICAM-1 在 COPD 中的直接相互作用机制的研究较少，多数研究仅单独探讨两者的作用。我们提出以下假设：香烟烟雾等刺激激活 NF-κB 通路同步上调 ICAM-1 和 MMP-9，MMP-9 进一步活化或切割 ICAM-1，从而放大炎症反应和组织破坏，但此信号通路的具体细节，仍是未来研究的关键方向。

8. 总结和展望

本文系统阐述了 MMP-9 与 ICAM-1 在 COPD 中的病理机制。MMP-9 主要通过破坏 ECM 稳态、促进气道重塑和放大炎症反应推动疾病发展；ICAM-1 则通过介导炎症细胞的募集与浸润，启动并维持慢性炎症状态，二者存在显著的协同作用，然而 MMP-9 与 ICAM-1 之间信号交叉调控的具体分子通路尚未明确，并且需要更大规模的研究，联合检测 MMP-9 与 ICAM-1 在 COPD 早期诊断、病情严重程度评估、急性加重风险预测及治疗反应监测中的临床应用价值。总之，MMP-9 与 ICAM-1 是参与 COPD 炎症、组织破坏与重塑两大核心病理过程的关键分子。深化对其协同作用机制的理解，不仅有助于揭示 COPD 的疾病本质，更可能为开发新的诊疗方案开辟有前景的道路。

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