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FGF23、Klotho在慢性阻塞性肺疾病中的研究进展

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摘　要

慢性阻塞性肺疾病(Chronic Obstructive Pulmonary Disease, COPD)是全球高发病率和死亡率的重要原因，造成了巨大的经济和社会负担。近年来研究发现，成纤维细胞生长因子23 (Fibroblast Growth Factor 23, FGF23)、Klotho除了参与体内的钙磷代谢调节外，同时与COPD发病机制密切相关。FGF23、Klotho的深入研究有望为临床治疗COPD带来新的突破。

关键词

慢性阻塞性肺疾病，成纤维细胞生长因子23，Klotho

The Research Progress of FGF23 and Klotho in Chronic Obstructive Pulmonary Disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is an important cause of high morbidity and mortality in the world which results in a huge economic and social burden. In recent years, it has been found that fibroblast growth factor 23 (FGF23) and Klotho are not only involved in the regulation

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of calcium and phosphorus metabolism *in vivo*, but also related to the pathogenesis of COPD. The further study of FGF23 and Klotho may bring a new breakthrough in the clinical treatment of COPD.

Keywords

Chronic Obstructive Pulmonary Disease, Fibroblast Growth Factor 23, Klotho

1. 引言

慢性阻塞性肺疾病(Chronic Obstructive Pulmonary Disease, COPD)简称慢阻肺，是一种与年龄相关的慢性气道炎性疾病，主要特征是持续存在的呼吸道症状和不可逆的气流受限，大多数病例与接触香烟烟雾有关[1]。成纤维细胞生长因子 23 (Fibroblast Growth Factor 23, FGF23)是一种与全身炎症和代谢改变相关的激素，参与磷酸盐代谢平衡，还与炎性因子(白介素 IL-6、IL-1β、C 反应蛋白)产生、铁－红细胞生成、诱导心肌细胞肥大致左心室肥厚、胰岛素抵抗及游离脂肪酸代谢有关[2] [3]。Klotho 作为 FGF23 的辅助受体，提高 FGF23 与成纤维细胞生长因子受体(FGFR)的亲和力[4]。近年来研究发现，FGF23、Klotho 与 COPD 发病机制密切相关，本文即对该领域相关研究进展进行综述，有可能为临床中寻找 COPD 新型生物标志物及药物开发提供新思路。

2. FGF23、Klotho 简介

2.1. FGF23 简介

FGF23 属于成纤维细胞生长因子家族(Fibroblast Growth Factors, FGFs)中的一员，主要由骨细胞和成骨细胞合成和分泌，维持体内磷酸盐代谢平衡[5] [6]。FGF23 分子结构中除了包含 FGFs 家族同源 N 端，是其受体(Fibroblast Growth Factor Receptor, FGFR)结合域，还包含与 Klotho 结合的特异性 C 端[4] [7]。在肾脏组织中，FGF23 通过 FGFR1 和辅助受体(Klotho)发挥作用，减少肾小管对磷酸盐的重吸收及维生素 D 依赖的肠道摄取磷酸盐方式[4]。目前 FGF23 作为磷酸盐调节激素的作用已得到充分确立，研究还发现 FGF23 参与铁代谢、炎症、胰岛素抵抗、急性肾损伤等过程[3]。

2.2. Klotho 简介

Klotho 基因表达缺陷的小鼠会出现寿命缩短、动脉硬化、皮肤萎缩、骨质疏松症、肺气肿、性腺功能减退等过早衰老的表型特征[8]，因此 Klotho 最初被定义为抗衰老基因，主要在人体肾小管、大脑脉络丛、甲状旁腺表达，其编码的 Klotho 蛋白为单次跨膜蛋白，该蛋白与 FGFR 结合，作为 FGF23 的联合受体发挥作用，维持机体磷酸盐、钙、维生素 D 稳态[9]；Klotho 蛋白的胞外区脱落和分泌后，作为分泌型形式，可以调节胰岛素/胰岛素样生长因子-1 (IGF-1)和 Wnt 等信号通路，还可以通过抑制细胞凋亡、氧化应激及衰老路径发挥抗衰老、抗氧化作用[10] [11] [12]。故 Klotho 在调节钙磷平衡、抗氧化应激及抗衰老等方面有关键作用。

在经典的靶器官肾脏和甲状旁腺中，FGF23 通过与 FGFR1-Klotho 结合后激活 Ras/丝裂原活化蛋白

激酶(MAPK)信号通路介导其生物学活性[13] [14]。然而，一些研究发现 FGF23 还可以靶向缺乏 Klotho 的细胞，FGF23 可以直接激活 FGFR4 并诱导随后的磷脂酶 Cγ (PLCγ)/活化的 T 细胞核因子(NFAT)信号传导通路。这种机制介导的病理生理作用表现在 FGF23 诱导心肌细胞肥大和促进肝细胞中炎性细胞因子的产生[15] [16] [17]。

3. FGF23、Klotho 与 COPD 发病机制

3.1. FGF23 与 COPD 发病机制

炎症是慢性阻塞性肺疾病发病的关键机制，FGF23 参与 COPD 的炎症信号传导通路。COPD 患者血浆 FGF23 水平升高，和血浆白细胞介素 6 (IL-6)水平存在显着的正相关[18]。肺部表达四种 FGFR [19]，有研究发现 FGFR4 在 COPD 支气管上皮细胞暴露于香烟烟雾后表达水平升高[20]，FGF23 可直接激活 FGFR4/磷脂酶 Cγ (PLCγ)/钙调神经磷酸酶/活化的 T 细胞核因子(NFAT)信号通路诱导气道炎症，合成和释放大量白细胞介素 1β (IL-1β)，此过程并不依赖 Klotho [18]。此外，给予可溶性 Klotho 抑制 FGF23 介导的炎症信号，减少 IL-1β 分泌而减弱炎症反应。Klotho 基因缺陷的小鼠气道上皮细胞和血浆中 FGF23 表达增加，激活己糖胺生物合成途径(HBP)及 O-β-N-乙酰氨基葡萄糖(O-GlcNAc)所介导的氧化应激、炎症反应，参与肺气肿的发病过程[21]。相似的研究发现，FGF23 刺激人支气管上皮细胞同样通过己糖胺生物合成途径，产生 O-GlcNAc 修饰蛋白质，导致 NFAT 信号通路的下游激活后分泌 IL-6，参与气道炎症[22]。还有研究发现，FGF23 介导肺血管平滑肌细胞中促炎细胞因子 IL-1β 表达，参与 COPD 香烟烟雾相关全身血管炎症途径[20]。然而，Ishii 等[23]却发现 FGF23 非同义编码核苷酸多态序列(rs7955866)中的 A 等位基因通过降低血清 FGF23 蛋白浓度，促进肺气肿的形成。因此，FGF23 在 COPD 的炎症机制和肺气肿形成过程起重要作用。

3.2. Klotho 与 COPD 发病机制

3.2.1. Klotho 与氧化应激

氧化应激启动炎症反应，诱导细胞凋亡或导致肺损伤，这同样是 COPD 的关键发病机制[24]。研究发现 Klotho 主要沿人气道上皮细胞表达，其水平在健康吸烟者的肺部有所减少，在 COPD 患者的肺部中进一步降低[25]。相似的研究发现，COPD 患者肺泡巨噬细胞和外周血单核细胞中的 Klotho 蛋白水平也降低[26]。巨噬细胞被认为是 COPD 慢性炎症反应的主要协调者[27]。COPD 患者的巨噬细胞释放出更高水平的促炎细胞因子如肿瘤坏死因子 α (TNF-α)、白细胞介素 6 (IL-6)及基质金属蛋白酶 9 (MMP-9) [28]。气道上皮细胞内 Klotho 缺乏导致其对香烟烟雾诱导炎症的敏感性增加，研究观察到细胞内增强的 MAPK 磷酸化和 p65/核因子 κB(NF-κB)核转位，促炎细胞因子 IL-8、IL-6 和单核细胞趋化蛋白 1 (MCP-1)表达增加[25]。Klotho 表达水平降低与氧化应激、炎症导致细胞凋亡增加相关，且进一步加重了肺部慢性炎症和氧化损伤，加剧 COPD 的进展，这些过程是由 NF-κB 介导的。NF-κB 是一种重要的转录因子，控制细胞增殖、氧化应激、免疫和炎症反应等过程[29] [30]。在小鼠肺泡巨噬细胞中，Klotho 负性调节 NF-κB 通路减少促炎因子的转导，抑制炎症介质(MMP-9、TNF-α 和 IL-6)的表达[26]。研究还发现 Notch 信号通路介导的 Klotho 高甲基化抑制了肺泡巨噬细胞和气道上皮细胞中 Klotho 的表达，从而促进与 COPD 发展相关的炎症反应和细胞凋亡[31]。香烟烟雾通过产生增加的活性氧(ROS)水平诱导肺组织的氧化应激，导致肺部炎症和细胞凋亡[32]，Klotho 可降低肺泡上皮细胞 ROS 水平发挥抗氧化作用[33]。Klotho 还可以增加核因子红细胞衍生的 2 相关因子(Nrf2)转录活性，防止氧化应激[12]。综上，Klotho 蛋白作为一种抗氧化剂，参与肺部促炎细胞因子释放、应激抵抗调节，COPD 中 Klotho 低水平表达与氧化应激机制密切相关。

3.2.2. Klotho 与细胞衰老

细胞衰老会导致肺部细胞增殖减少、肺泡结构破坏和肺气肿，COPD 发病与肺部细胞衰老相关[34]。香烟烟雾通过增加细胞周期抑制剂 p21 的表达水平来阻止细胞周期向 S 期发展，导致肺上皮细胞过早衰老[35]，参与 COPD 的发病[36]。p21 被认为是衰老的生物标志物，香烟烟雾在体内和体外均可诱导 p21 表达显着增加[37]。使用 RNAi 敲低 Klotho 表达对人成纤维细胞进行的研究，观察到 p21 表达显着增加，导致生长停滞和细胞衰老[38]。研究发现体外 Klotho 过表达可抑制 p21 表达，降低人肺上皮细胞对香烟烟雾诱导的细胞死亡的敏感性[39]。故 Klotho 可抑制香烟烟雾诱导的 COPD 细胞衰老过程。

3.2.3. Klotho 与自噬

自噬是肺组织对香烟烟雾暴露后的早期反应，它介导细胞凋亡并最终促进细胞死亡，在 COPD 发病机制中发挥重要作用。与正常组织相比，COPD 患者肺组织中的自噬增加[40]。在长期吸入香烟烟雾的小鼠肺上皮细胞中发现了类似的自噬体增加。吸烟者的肺泡巨噬细胞显示出自噬体和 p65 积聚，是由于自噬体和溶酶体的融合受阻及长寿命蛋白的清除减少，最终导致异常自噬、线粒体功能异常和细菌清除缺陷[41]。研究表明，Klotho 预处理的小鼠肺泡巨噬细胞减弱了香烟烟雾诱导的自噬，然而 Klotho 的敲低则会增强自噬[42]，这项研究将 COPD 的发病机制与 Klotho 下调引起的异常自噬联系起来。故 Klotho 在香烟烟雾诱导的自噬中起着双重调节作用。

4. FGF23 与 COPD 磷酸盐代谢

COPD 患者有低磷血症的倾向[43]，FGF23 作为磷酸盐代谢调节激素，与 COPD 患者磷酸盐代谢的关系值得关注。磷是一种重要的电解质，在肌肉收缩、维持细胞的完整性及能量代谢的过程中发挥着重要的作用。COPD 患者肌肉和循环中的磷酸盐水平低，可能是其呼吸肌和骨骼肌无力的原因，预示着 AECOPD 患者的不良预后[44]。COPD 低磷血症有不同诱因，包括：摄入不足、药物使用、肾脏或肠道排泄磷增加及细胞分布异常[45]。一项研究发现 COPD 患者肾磷阈(TMP/GFR)明显降低，肾磷酸盐排泄增加，其次 COPD 中升高的 FGF23 对肾小管产生磷酸尿化作用，增加磷酸盐的流失，这些均导致血磷降低[46]。这项研究还观察到 COPD 患者的甲状旁腺素(PTH)和碱性磷酸酶(ALP)水平显著升高。然而在另一项研究中却发现 COPD 患者血清磷酸盐、FGF23、PTH 水平均低于对照组[47]。目前关于这方面研究较少，结论并不一致，FGF23 在 COPD 的低磷血症中具体作用机制并不清楚。

5. FGF23 与 COPD 临床相关性

5.1. FGF23 与 COPD 临床

肺功能检查是临床诊断 COPD 必备条件，可检出早期 COPD 患者，且有助于评估 COPD 的进展、预后及评定药物疗效。研究表明 COPD 患者 FGF23 血浆水平与第一秒用力呼气容积(FEV1)和肺弥散量(DLCO)存在明显负相关，与残气量/肺总量(RV/TLC)之间存在正相关，显着关系是最强的是 DLCO [48]，目前认为 DLCO 与组织学评估的肺气肿严重程度密切相关[49]。相似的研究发现，COPD 患者血浆 FGF23 与 FEV1 呈负相关，但是按 GOLD 分级后 FGF23 水平并无统计学意义[46]。还有研究表明 COPD 患者血浆 FGF23 的 C 末端水平与肺总量(TLC)之间存在显着负相关[47]。Gulati 等人[50]观察到频繁加重的 COPD 患者的 FGF23 水平更高，认为血浆 FGF23 与 COPD 频繁加重表型独立相关。综上，FGF23 与肺功能下降及频繁加重表型相关，有望成为 COPD 肺气肿表型和频繁加重表型的新型生物标志物。

5.2. Klotho 与 COPD 临床

COPD 患者更好的临床状况与更高的 Klotho 表达相关，但研究发现康复训练中 COPD 患者运动能力

和临床参数明显改善，但 Klotho 水平没有发生显著变化，也不与临床参数相关[51] [52]。也有研究发现，Klotho 在骨骼肌中表达，并且其水平在吸烟者中降低，但是已确诊肌肉萎缩的 COPD 患者 Klotho 蛋白水平反常地升高[53]。因此 Klotho 蛋白的血浆水平可能不能用作 COPD 稳定的生物标志物。

6. FGF23、Klotho 在 COPD 治疗中应用展望

FGF23 通过 FGFR4 发出的信号与 COPD 炎症变化有关，Klotho 在肺部具有抗氧化、抗炎、抗衰老功能。FGF23/Klotho 信号通路有可能成为 COPD 抗衰老和抗炎治疗的一条可行的靶向途径。目前已开发出一种 FGFR4 阻断抗体和小分子抑制剂用于治疗肝细胞癌[54]。抑制 FGFR4 或 Klotho 补充剂可能成为 COPD 的一种新型抗炎策略[18]。

7. 小结

综上所述，FGF23、Klotho 在 COPD 发病机制中扮演着重要角色，相信随着对其信号通路及调控机制等研究的逐渐深入，FGF23/Klotho 信号通路有可能成为 COPD 抗衰老和抗炎治疗的一条可行的靶向途径，为未来临床治疗提供新思路。

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