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代谢相关脂肪性肝病与胰腺癌相关性的研究进展

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摘　要

2020年，非酒精性脂肪性肝病(NAFLD)已更名为代谢相关脂肪性肝病(MAFLD)，它是世界上慢性肝病最常见的原因。胰腺癌是MAFLD肝外常见的并发症之一。近年来，大量研究显示MAFLD患者发生胰腺癌的风险较高，其中机制尚未完全明确，可能与炎症反应、肠道菌群等因素有关。本文综述MAFLD和胰腺癌的相关性，以期为预测MAFLD和胰腺癌的发病及治疗提供帮助。

关键词

代谢相关脂肪性肝病，胰腺癌，相关性

Research Progress on the Relationship between Metabolic-Associated Fatty Liver Disease and Pancreatic Cancer

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Abstract

In 2020, non-alcoholic fatty liver disease (NAFLD) has been renamed metabolic-associated fatty liver disease (MAFLD), which is the most common cause of chronic liver disease in the world. Pancreatic cancer is one of the common extrahepatic complications of MAFLD. In recent years, a large

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number of studies have shown that patients with MAFLD have a higher risk of pancreatic cancer, and the mechanism has not been fully understood, which may be related to inflammatory reaction, intestinal flora and other factors. This article reviews the correlation between MAFLD and pancreatic cancer in order to provide help for predicting the incidence and treatment of MAFLD and pancreatic cancer.

Keywords

Metabolic-Associated Fatty Liver Disease, Pancreatic Cancer, Relevance

1. 引言

2020 年，一个由 22 个国家肝病学专家组成的国际专家小组提出将非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)更名为代谢相关性脂肪性肝病(metabolic-associated fatty liver disease, MAFLD) [1]。NAFLD 是指除外饮酒和其他明确的肝脏损害因素所导致的肝内脂肪过度沉积，它采用的是一种“排他式”诊断方式，然而，随着该疾病的患病率持续上升(2005 年 NAFLD 的患病率为 15%，到目前已上升至 25% [2])，临床和社会经济负担持续增加，NAFLD 的命名已经不能反映当前的医疗知识水平，需要更准确的标准来诊断该疾病。因此，国际专家小组发布了 MAFLD 新定义的国际专家共识声明，该定义标准基于肝脏脂肪堆积(肝脏脂肪变性)的组织学(肝组织活检)、影像学或血液生物标志物证据，以及以下 3 个标准之一，即超重/肥胖、2 型糖尿病(T2DM)或代谢功能障碍，代谢功能障碍定义为至少存在两种代谢风险异常因素[1]。新命名的 MAFLD 的诊断标准采用了“肯定性”的诊断方式，既全面又简单，更适用于 MAFLD 的诊断，并且独立于其他肝病。MAFLD 已成为世界上慢性肝病最常见的原因之一，影响着全世界约 25%的人口[3]。它的发病率和流行率在全球范围内不断增加，据估计，到 2030 年，中国 MAFLD 患病率总体和相对增幅最大，2030 年 MAFLD 病例数估计为 3.1458 亿例，增幅为 29.1% [4]，这极大程度地增加了临床负担和医疗压力。

胰腺癌(PC)是一种极具侵袭性和致命性的恶性肿瘤，预后差，到 2020 年，胰腺癌已成为全球第 14 大常见癌症，占所有新发癌症病例数的 2.6%，所有癌症死亡数的 4.7%，总体 5 年相对生存率约为 10% [5] [6] [7]。近年来，MAFLD 与胰腺癌之间的关系引起了研究人员的广泛关注。胰腺癌症的危险因素主要包括与个人特征、生活方式和环境以及疾病状况相关的因素[8]。现在有越来越多的证据表明，MAFLD 是一种影响肝外器官的多系统疾病，它的发病率正在全球范围内迅速增加，并成为了胰腺癌的危险因素之一[9]。本文将综述 MAFLD 与胰腺癌的相关性，以及这两种疾病之间的潜在分子机制。

2. MAFLD 与胰腺癌的相关性

MAFLD 是一种代谢紊乱疾病，其主要特征是肝脏脂肪变性和炎症反应。MAFLD 的疾病发展范围从非酒精性脂肪肝到非酒精性脂肪性肝炎(NASH)、纤维化、肝硬化，最后到肝细胞肝癌[10] [11]。MAFLD 与肥胖、糖尿病和代谢综合征等代谢异常密切相关，同时，这些代谢异常也被认为是胰腺癌的危险因素之一。因此，人们开始研究 MAFLD 与胰腺癌之间的关系，并且发现二者之间存在着密切的相关性。

多项研究表明，MAFLD 患者发生胰腺癌的风险比非 MAFLD 患者高。一项横断面病例匹配研究发

现，MAFLD 的组织病理学方面与胰腺癌的发生之间存在显著关联[12]。一项针对美国人群的研究发现，MAFLD 患者的胰腺癌发病率是非 MAFLD 患者的两倍[13]。一项韩国全国性的队列研究发现，与没有 MAFLD 的患者相比，MAFLD 患者患胰腺癌症的风险增加 0.36 倍[14]。此外，研究人员还发现，MAFLD 患者的胰腺癌发病率与 MAFLD 严重程度相关，表明 MAFLD 的严重程度可能对胰腺癌产生影响[15]。相反，也有研究表明，患有 MAFLD 患者的胰腺癌发病率与非 MAFLD 患者相比没有显著差异[16]。一项包含 3 篇研究文章的荟萃分析发现，MAFLD 患者会比非 MAFLD 患者增加 85%的胰腺癌发生风险[17]。

3. MAFLD 与胰腺癌的潜在机制

尽管 MAFLD 与胰腺癌之间的关系已被确认，但其具体的分子机制尚未完全阐明。目前，有一些假说试图解释 MAFLD 与胰腺癌之间的关系。

1) 慢性炎症假说

炎症是 MAFLD 和胰腺癌发生关联的一种重要机制。MAFLD 患者肝脏中脂肪积聚导致肝细胞损伤和炎症反应，释放出一系列炎症介质和生长因子。这些炎症因子和生长因子能够通过多种复杂的炎症信号通路，如 WNT/β-连环蛋白通路、NF-κB 通路、TGF-b 信号通路等，促进肿瘤细胞的生长和转移，从而增加胰腺癌的风险[18] [19] [20] [21] [22]。

2) 肝胰轴假说

肝胰轴假说认为，MAFLD 引起肝脏炎症和纤维化，进而导致肝胆酸紊乱和胆汁淤积，胆汁淤积会导致胆汁中的毒素和代谢产物积聚，增加胰腺癌的发生风险。胆汁酸代谢功能障碍是胆结石形成的一个原因，胆结石的形成又会进一步阻碍胆汁流动，可能导致胆汁酸回流到胰腺导管和上皮细胞或腺泡细胞中，因此会诱发和导致胰腺炎的发生发展，这是胰腺癌的一个危险因素，增加了胰腺癌的发病风险[23] [24]。

3) 肠道菌群假说

肠道菌群假说认为，肠道微生物群可以通过多种途径(包括炎症、免疫、代谢、激素稳态等)影响肿瘤进展。肠道微生物失调可能是 MAFLD 发病机制的一部分，生物失调会增加肠道对细菌产物的渗透性，并增加肝脏对有害物质的暴露，从而增加肝脏炎症和纤维化。MAFLD 患者肠道菌群失调导致代谢产物和炎症介质的释放，这些代谢产物和炎症介质可以促进肝脏和胰腺的炎症反应，从而增加胰腺癌的风险[25] [26]。

4) 胰腺脂肪浸润假说

胰腺脂肪浸润假说认为，MAFLD 患者肝脏脂肪浸润可能导致胰腺脂肪浸润，从而进一步导致胰腺炎，最终发展成为胰腺癌。此外，脂肪浸润和炎症反应可能导致胰腺细胞分化和增殖异常，从而增加胰腺癌的发生风险[27] [28]。

5) 其他

除了以上的假说外，还有一些其他的假说在解释 MAFLD 与胰腺癌之间的关系。这些假说包括胰岛素抵抗、脂肪酸合成和氧化应激等等[29]。

4. 结论

总的来说，MAFLD 与胰腺癌之间存在着密切的关系，MAFLD 患者发生胰腺癌的风险较高，这可能与慢性炎症、肝胰轴假说、肠道菌群失调、胰腺脂肪浸润等多种机制有关。因此，对于 MAFLD 患者，应该重视其胰腺癌的筛查和治疗，及时进行相关的检查和干预措施。此外，对于预防 MAFLD 和胰腺癌的发生，也应该从生活方式、饮食习惯、体重控制等方面入手，提高公众的健康意识，降低肝脏和胰腺疾病的发生率。

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