·综述·

DOI：10.12449/JCH250123

脂肪因子与代谢相关脂肪性肝病及其相关肝癌的关系

张熠潇，孙建光，蒋博文

山东中医药大学第一临床医学院，济南 250013

通信作者：孙建光，sdutcmsjg03@163.com（ORCID：0009-0001-5251-341X）

摘要：随着生活中不健康饮食结构的出现，代谢相关脂肪性肝病（MAFLD）逐渐成为我国第一大慢性肝病，MAFLD相关肝癌的发生也逐渐增多。脂肪组织不仅具有能量储存功能，而且其分泌的脂肪因子在MAFLD及其相关肝癌的发生发展中亦起到重要作用。脂肪因子作用机制相关研究为MAFLD的预防与治疗提供了重要的帮助，大量研究显示，脂肪因子的异常分泌不仅与MAFLD相关，其在肝癌的发生发展中也发挥了重要作用。脂肪因子不仅在基因层面被调控，也可通过特定途径与基因相互作用，共同调控MAFLD及其相关肝癌的炎症、代谢、免疫、细胞增殖等病理生理过程。本文就脂肪因子与MAFLD及其相关肝癌关系的最新研究进行综述，以期为肝癌发病机制的进一步研究提供新的方向。

关键词：代谢相关脂肪性肝病；肝肿瘤；脂肪因子类

基金项目：山东省重点研发计划（2021CXGC010510）

Research advances in the association of adipokines with metabolic associated fatty liver disease and its associated liver cancer

ZHANG Yixiao, SUN Jianguang, JIANG Bowen

The First Clinical Medical College of Shandong University of Traditional Chinese Medicine, Jinan 250013, China

Corresponding author: SUN Jianguang, sdutcmsjg03@163.com (ORCID: 0009-0001-5251-341X)

Abstract: With the emergence of unhealthy dietary structures in people's life, metabolic associated fatty liver disease (MAFLD) has gradually become the most important chronic liver disease in China, and there is also a gradual increase in the cases of MAFLD-associated liver cancer. Adipose tissue not only has the function of energy storage, but also secretes adipokines that play an important role in the development and progression of MAFLD and its associated liver cancer. Studies on the mechanism of adipokines have provided important help for the prevention and treatment of MAFLD, and a large number of studies have shown that the abnormal secretion of adipokines is associated with MAFLD and plays an important regulatory role in the development and progression of liver cancer. Adipokines are not only regulated at the gene level, but they can also interact with genes through specific pathways to co-regulate pathophysiological processes such as inflammation, metabolism, immunity, and cell proliferation in MAFLD and its associated liver cancer. This article reviews the latest studies on the association of adipokines with MAFLD and its associated liver cancer, in order to provide new directions for further research on the pathogenesis of liver cancer.

Key words: Metabolism-Associated Fatty Liver Disease; Liver Neoplasms; Adipokines

Research funding: Shandong Province Key R & D Program (2021CXGC010510)

最新研究[1]显示，肝癌死亡率居全球癌症死亡的第4位，且具有明显的地区与性别差异。2020年我国肝癌死亡率为17.2/10万，仍处亚洲最高[1]。除肝炎病毒感染以外，酗酒、黄曲霉素及代谢相关脂肪性肝病（metabolism-associated fatty liver disease，MAFLD）等代谢因素也是引起肝癌的重要因素[2]。在临床工作中，部

分肝脏恶性肿瘤病因不甚明确，临床将其称为隐源性肝癌，为排除性诊断，目前尚无统一的指南及共识。早期研究[3]显示，隐源性肝硬化及肝癌的发生与非酒精性脂肪性肝病（non-alcoholic fatty liver disease，NAFLD）有密切关系，NAFLD的定义强调饮酒情况而较少描述代谢因素所带来的疾病进展风险，而大量研究[4-5]表明，NAFLD与代谢综合征密不可分，因此2020年由国际专家提出了MAFLD的新定义[6]，减弱了对饮酒的限制，而将代谢因素如超重/肥胖、2型糖尿病、代谢功能障碍等作为诊断要点，且将这部分病因所致肝硬化及肝癌患者纳入MAFLD疾病谱中。

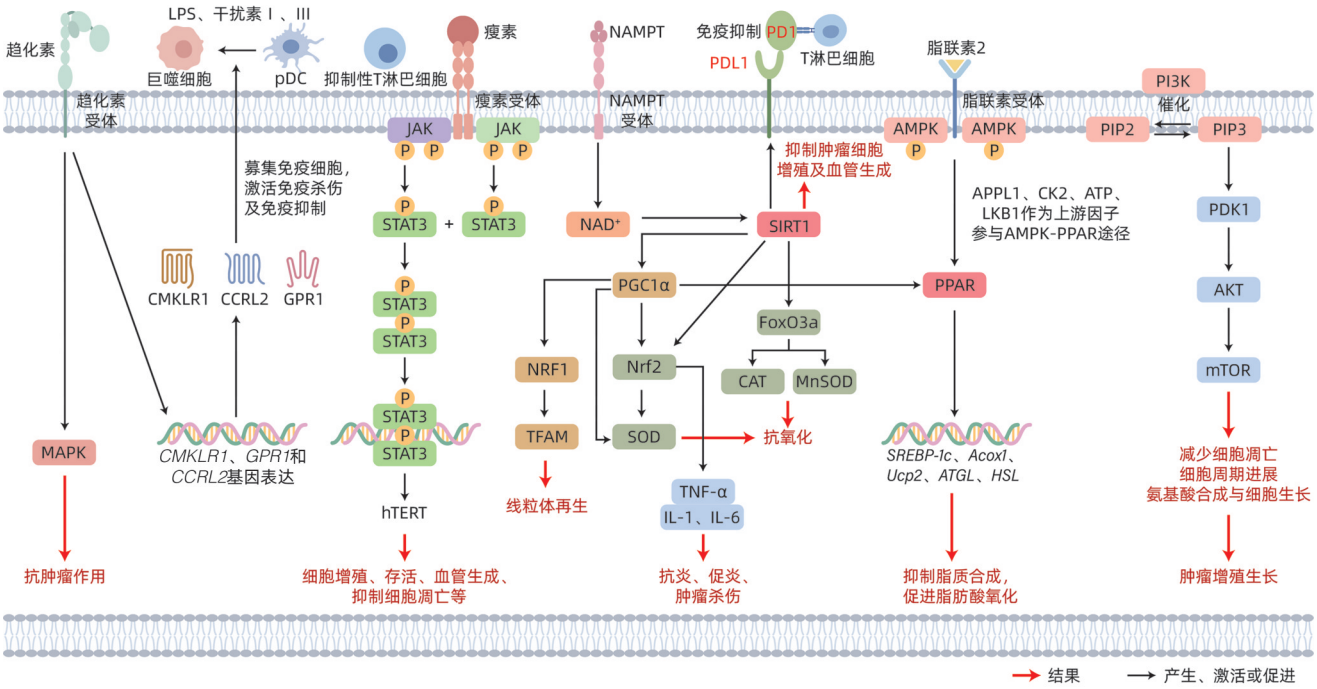
2000—2010年，英国MAFLD相关肝癌患病率上升至34.8%；美国MAFLD相关肝癌的发病率逐年增长9%；1991—2010年，亚洲非病毒感染原因相关肝癌增长约14.1%[7]。非健康饮食结构引起的超重与肥胖对MAFLD及其相关肝癌的患病率上升有重要影响，大量临床和数据研究[8-12]显示，腰围是MAFLD的确切风险因素，腰臀比和睾酮水平为其潜在风险因素。此外，MAFLD与NAFLD定义在脂肪变性风险方面相似，对于NAFLD而言，脂肪分布于腹腔相较于腹壁发病风险更大[13]，因此内脏脂肪组织对发病发挥着重要的作用。

人体脂肪组织中含有大量脂肪因子，由脂肪细胞、免疫细胞和内皮细胞分泌，包括激素、细胞因子、生长因子、胞外基质等。根据脂肪因子的功能，大致可分为免疫反应类脂肪因子、抗炎症细胞因子、脂质代谢调节因子、类固醇激素代谢酶类、调节血管稳态血管活性因子。目前脂肪因子已在NAFLD人群及动物模型中被广泛研究[14-15]，且其与脂质代谢异常也通过多种机制作用于癌症的发生[16-19]。脂肪组织可以分泌多种物质对靶器官的代谢、炎症、免疫等功能进行调控。目前，瘦素、脂联素等经典脂肪因子在肥胖和2型糖尿病等代谢类疾病中的重要作用已被广泛认可[20]，在癌症方面的作用也被广泛研究，明确其作用机制对MAFLD及其相关肝癌具有重要临床意义。本文主要对近3～8年内脂肪因子与MAFLD及肝癌相关临床和试验研究进行分析总结，就烟酰胺磷酸糖苷转移酶（nicotinamide phosphoribosyltransferase，NAMPT）、脂联素、趋化素、丝氨酸蛋白酶抑制剂（Vaspin）等脂肪细胞因子与MAFLD及其相关肝癌的关系进行综述，以期为MAFLD疾病谱的认识及肝癌的发生机制提供更多研究思路。

1 脂肪因子在MAFLD及其相关肝癌发病中的作用

1.1 瘦素 瘦素是在对小鼠进行克隆操作时所发现[21]，其作为一种肽类激素，可以控制食欲消耗能量，同时在促进细胞增殖、血管生成等方面对癌症相关进展发挥作用[22]。基因组研究[23-24]显示，在肝细胞纤维化及癌变过程中，JAK2-STAT3途径是重要的促癌通路，瘦素可以激活此途径，引起肝细胞癌变[25]，而人端粒酶逆转录酶被认为是该通路的一个重要靶位[26]（图1）。瘦素水平可随MAFLD患者疾病严重程度加重而升高[27]。伊朗的一项研究[28]发现，通过藏红花干预，可以降低瘦素水平改善MAFLD炎症指标，提高抗氧化能力。然而，尽管瘦素早期升高会对MAFLD脂肪变性起到一定的保护作用，但长期升高可引起瘦素抵抗[29]。综上可见，MAFLD在进展过程中瘦素可能累积升高，增加肝癌的发生风险。Zhang等[30]使用替米沙坦喂养MAFLD大鼠后发现替米沙坦可以下调瘦素mRNA的表达，降低血清及组织中的瘦素水平（$P<0.01$），这为代谢综合征相关药物治疗MAFLD相关肝癌提供了临床参考。

1.2 NAMPT NAMPT又称为内酯素，是一种细胞代谢限速酶，可在哺乳动物烟酰胺腺嘌呤二核苷酸（nicotinamide adenine dinucleotide，NAD）合成补救途径中催化烟酰胺单核苷酸的产生。NAMPT分为细胞内NAMPT（iNAMPT）和细胞外NAMPT（eNAMPT），是控制NAD代谢的关键酶，主要由eNAMPT作为细胞因子发挥作用，与多种代谢、炎症类疾病及肿瘤有关，其在细胞中的功能较为复杂且存在争议。2019年，一项研究[31]对211例NAFLD患者进行检测，发现NAFLD组血清NAMPT水平低于非NAFLD组，且与NAFLD风险呈负相关（$OR=0.30$，95%CI：0.10～0.91，$P<0.05$），提示NAMPT可能对肝细胞代谢功能具有保护作用。郭娅棣等[32]研究亦获得同样的结论。NAMPT活性缺乏会影响线粒体功能和脂质代谢，使脂滴合成增加，造成脂肪合成与分解的失衡[33]。杨丽等[34]分析了66例NAFLD患者的部分代谢学指标，发现NAFLD患者NAMPT水平与肝纤维化程度也呈明显的负相关关系（$P<0.05$）。最新研究[35]显示，NAMPT/NAD/SIRT1通路可显著缓解非酒精性脂肪性肝炎（non-alcoholic steatohepatitis，NASH）小鼠肝脏炎症的加重，同时降低整个肠肝系统中总胆汁酸水平，且激活的NAMPT/NAD/SIRT1可抑制肿瘤细胞的增殖和血管的形成[36]（图1）。然而也有研究结论与之相反，例如Sun等[37]通过对NAFLD受试者的血清学及组织学检测发现，与健康对照组相比，NAFLD受试者NAMPT表达明显增加，血浆中eNAMPT、IL-6、血管生成素-2和白细胞介素-1受体拮抗剂（IL-1RA）的水平明显升高。通过使用Toll样受体4（Toll-like receptor 4，TLR4）配体中和eNAMPT，发现配体试验组NASH相



注：LPS，脂多糖；pDC，浆细胞样树突状细胞；NAMPT，烟酰胺磷酸糖苷转移酶；PD1，程序性死亡受体1；PDL1，程序性死亡配体1；JAK，非受体型酪氨酸蛋白激酶；AMPK，腺苷酸活化蛋白激酶；PI3K，磷脂酰肌醇3-激酶；PIP2，二磷酸磷脂酰肌醇；PIP3，三磷酸磷脂酰肌醇；PDK1，3-磷酸肌醇依赖的蛋白激酶-1；AKT，蛋白激酶B；mTOR，哺乳动物雷帕霉素靶蛋白；PPAR，过氧化物酶体增殖物激活受体；*SREBP-1c*，固醇元件调节结合蛋白基因；*Acox1*，酰基辅酶A氧化酶1基因；*Ucp2*，线粒体偶联蛋白2基因；*ATGL*，甘油三酯脂肪酶基因；*HSL*，激素敏感性脂肪酶基因；NAD^+，烟酰胺腺嘌呤二核苷酸；SIRT1，沉默调节蛋白1；APPL1，脂联素受体1结合蛋白；CK2，酪蛋白激酶2；ATP，三磷酸腺苷；LKB1，肝激酶B1；FoxO3a，叉头框蛋白a；CAT，过氧化氢酶；MnSOD，锰超氧化物歧化酶；PGC1α，过氧化物酶体增殖物激活受体γ共激活因子1α；Nrf2，核因子E2相关因子2；SOD，超氧化物歧化酶；TFAM，线粒体转录因子A；TNF-α，肿瘤坏死因子α；IL-1，白细胞介素1；IL-6，白细胞介素6；NRF1，核呼吸因子1；STAT3，信号传导转录激活因子3；hTERT，人端粒酶逆转录酶；CMKLR1，趋化样因子受体1；GPR1，G蛋白偶联受体1；CCRL2，趋化因子（C-C基元）受体样2；MAPK，丝裂原活化蛋白激酶。

图1　脂肪因子与肝癌发生相关分子机制

Figure 1　Molecular mechanisms associated with adipokines and hepatocarcinogenesis

关指标均明显下降，提示eNAMPT/TLR4炎症通路的激活导致了NAFLD/肝纤维化。此外，NAMPT在不同肿瘤细胞中的功能也不相同，如在结肠癌[38]、胶质瘤[39]、胰腺瘤[40]、胃腺癌等肿瘤中其表达上调，有研究[41]显示NAMPT可促进肿瘤细胞增殖和新生血管形成。而在肝细胞癌及膀胱癌中NAMPT表达下调，NAMPT能够刺激肿瘤微环境中免疫细胞表面因子的表达，且可以促进TNF、穿孔素、NKG2D（自然杀伤细胞活化性受体）、CD40的表达和分泌，从而诱导免疫细胞杀伤及癌细胞凋亡[42]。若肿瘤长期存在，NAMPT还会诱导肿瘤细胞表面免疫检查点程序性死亡配体1的表达，产生自然选择作用，导致免疫逃逸（图1）。

1.3　脂联素　脂联素早在小鼠分化的脂肪细胞中被发现[43]。作为一种由脂肪组织分泌的蛋白质，脂联素分为人脂联素1和人脂联素2，后者主要存在于肝部[44]。在肝组织中，脂联素主要与脂联素受体1和脂联素受体2结合，通过激活AMPK信号通路产生抗炎、调节脂肪代谢的作用[45]，促进脂肪酸氧化。在脂联素刺激下，脂联素受体1结合蛋白、酪蛋白激酶2和肝激酶B1作为上游因子，乙酰辅酶A羧化酶及过氧化物酶体增殖物激活受体α（peroxisome proliferator-activated receptor α，PPARα）作为下游因子，参与脂联素增强脂肪酸氧化作用的进程[46-49]。此外，在酒精性肝病中，脂联素主要通过SIRT1-AMPK轴来促进脂肪酸氧化[50]。脂联素也可以通过激活AMPK-PPARα途径影响*SREBP-1c*、*Acox1*、*Ucp2*等基因的表达来抑制脂质的合成[51]，作用于甘油三酯脂肪酶和激素敏感性脂肪酶产生降脂作用[52]（图1）。脂联素的表达与肥胖呈负相关[53]。研究[54]表明，脂联素水平过低会增加肝细胞癌变的风险，并通过促进蛋白激酶释放及激活蛋白酶激酶p38-AMPK途径促进肝癌进展。大多数肿瘤细胞的表面都可表达脂联素受体，正常情况下脂联素可以通过激活PI3K/AKT/mTOR、JAK/STAT[55]和Akt1/FoxO1通路[56]抑制炎症进展及肿瘤增殖生长。许瀚元等[57]研究发现，脂联素对HepG2细胞*FAS*启动子的

活性影响呈剂量依赖性和时间波动性，对*HSL*启动子的活性呈剂量依赖性，时间上则可一直呈促进作用，这为脂联素调控肝脏脂代谢的模式提供了更加详细的实验依据及模型构建。

1.4 *趋化素* 趋化素是一种近年发现的由白色脂肪组织分泌的趋化因子，可通过影响胰岛素受体通路的表达导致胰岛素抵抗，与代谢综合征具有强相关性[58]。研究[59]发现，在肥胖的NAFLD及纤维炎症活动的患者中，趋化素与炎性因子如TNF-α、IL-6水平均呈正相关，这与趋化素的炎性趋化作用有关。但2017年Pohl等[60]研究认为趋化素会在部分情况下产生抗炎作用，其与肝纤维化和NASH评分呈负相关，且与脂肪变性无关。这表示趋化素可能在MAFLD不同病理阶段与细胞内外环境影响下会发挥不同的生理功能。因此，趋化素在MAFLD相关肝癌中的作用也有不同，其可通过趋化样因子受体1（chemokine-like receptor 1，CMKLR1）、G蛋白偶联受体1（G-protein coupled receptor 1，GPR1）和趋化因子（C-C基元）受体样2（C-C chemokine receptor-like 2，CCRL2）募集免疫细胞，如巨噬细胞、自然杀伤细胞、浆细胞样树突状细胞（plasmacytoid dendritic cells，pDC）等，从而发挥肿瘤杀伤与抑制作用，同时也会募集免疫抑制性的调节T淋巴细胞及骨髓源性抑制细胞促进肿瘤免疫逃逸，这种免疫调节影响着肿瘤的进展[61]（图1）。趋化素受体广泛存在于正常癌组织及免疫细胞中。pDC可产生脂多糖及干扰素Ⅰ、Ⅲ。此类炎症因子可增强巨噬细胞中*CMKLR1*的转录表达，转化为M1型巨噬细胞杀伤肿瘤。然而，肿瘤产生时，pDC产生的干扰素会减少甚至缺失，从而利于肿瘤微环境的形成[62]。研究[63-65]发现，趋化素可刺激早期生长应答因子1（early growth response protein 1，EGR1）发挥作用，EGR1具有生长抑制及促凋亡的功能，趋化素可通过CMKLR1及GPR1激活血清反应因子，刺激EGR1产生活性，从而抑制肿瘤的进展。此外，趋化素通过趋化素受体促进β抑制素2表达，并抑制β-连环蛋白和丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）活性产生抗肿瘤作用[66-67]。然而，趋化素还能够促进p38-MAPK通路活性以及升高细胞外调节蛋白激酶的磷酸化水平，上调血管内皮生长因子及基质金属蛋白酶7的表达，从而促进肿瘤组织的形成[68]。趋化素根据不同的细胞通路对不同类型肿瘤的发生发展起到调节作用，而目前研究[69-70]大多肯定了其在肝癌中的抗肿瘤作用，但仍需进一步探究其在不同细胞通路中对肝癌发生发展影响的详细机制。

1.5 Vaspin Vaspin是一种由白色脂肪组织产生的与血糖脂质代谢密切相关的脂肪因子，可特异性结合激肽释放酶，抑制其生物活性，从而减缓胰岛素降解，改善糖耐量水平。这项功能的发挥有赖于Vaspin的生物活性[71]。吴光秀等[72]研究发现，Vaspin可以通过抑制肝脏脂肪合成的关键限速酶，促进脂肪分解限制酶来调控脂肪的代谢。陈香梅等[73]研究显示，Vaspin在NAFLD患者肝组织中表达升高且与血清低密度脂蛋白、空腹血糖呈正相关，临床可用于提示NAFLD的病情进展。Vaspin可明显降低血管平滑肌细胞内TNF-α的活性，从而抑制核因子-κB、蛋白激酶C的激活和活性氧的产生来减少淋巴细胞的募集，同时抑制MAPK、PI3K/Akt等通路来减少血管内皮细胞的增生[74]。然而马欢[75]通过观察内生痰湿体质对小鼠血清Vaspin的影响，发现Vaspin与IL-6呈直线相关关系，提示Vaspin可能与促进炎症反应有关。一项对56例重度肥胖NAFLD女性受试者的研究[76]结果显示，肝脏的Vaspin基因表达水平与疾病严重程度呈正相关，特别是在肝纤维化及NASH患者中其表达水平升高明显，表明Vaspin mRNA的表达具有非线性的特点，而即使考虑到混杂因素，也不能排除Vaspin高表达的有害作用，或者与其他因子作用而产生促炎或其他有害作用的可能。一项Vaspin对Hep-3B细胞的凋亡试验[77]证明，Vaspin对Hep-3B细胞具有剂量依赖性的保护作用，当Vaspin剂量为5～10 ng/mL时，细胞活力增加。Vaspin处理后，Hep-3B细胞簇氧化应激减弱，使细胞凋亡减少。提示Vaspin能够下调Hep-3B细胞的凋亡通路，抑制其促炎反应与氧化应激过程，加重肿瘤进展。同时，Vaspin对肿瘤细胞的增殖具有刺激作用，且在肝病病程中Vaspin对新生血管生成的保护机制亦被认为在肝细胞癌的发生发展中起重要作用[78-81]。

2 *P53*基因调控脂质代谢影响肝癌的发生

*P53*是最常见的抑癌基因之一，主要通过调控下游靶基因发挥作用[82]，可对细胞损伤如癌基因激活、DNA损伤、氧化应激、蛋白质错误折叠等作出及时反应，被活化刺激所激活，是控制细胞凋亡、抑制肿瘤的重要分子[83]。大量研究表明*P53*不仅是基因组异常的调控枢纽，还调控着代谢稳态的平衡，可同时参与调控机体糖脂代谢、脂肪酸氧化产能、乙醇代谢、氨基酸代谢及核苷酸代谢的过程，是重要的调控基因。

脂肪参与机体能量代谢和储存，同时也是细胞增殖分化不可或缺的营养物质。*P53*作为肥胖的主要调节因子，其与脂质代谢及脂肪因子的关系密不可分。研究[84]

显示，NAFLD或代谢综合征发生发展的同时可能伴随高*P53*表达，这可能是大量脂肪被吸收所诱导，同时伴随脂肪因子共同作用，通过P53/PXR-SCD1调控轴及其他通路等途径促进脂滴形成加重炎症进展。肝细胞癌变主要源自细胞内原癌基因激活、抑癌基因失活以及多种信号通路的共同作用[85]。作为一种抑癌基因，*P53*可以通过抑制苹果酸酶2活性[86]和*SREBP-1*的表达[87]、降低NADPH（还原型辅酶Ⅱ）水平[83]、激活骨桥蛋白[88]等途径抑制脂肪合成，也可以通过编码β3-肾上腺素能受体基因分解脂肪[89]，进而影响脂肪组织细胞功能。癌变的肝细胞*P53*基因表达会受到抑制，为满足增殖生长需要，脂滴分解、脂质合成、脂肪变性减轻。此外，研究[90]显示，P53凋亡刺激蛋白2分子N段可与SIRT1分子结合协同抑制肝癌HepG2细胞脂质的合成及脂滴的分解，抑制肿瘤细胞的增殖。

可见*P53*基因作为抑癌基因通过调控脂肪组织细胞脂质代谢对MAFLD及其相关肝癌产生重要影响，同时脂肪组织细胞可分泌各种脂肪因子发挥功能，与P53蛋白共同调控细胞的炎症、癌变及转移进程。

3 小结与展望

在MAFLD发病过程中，脂肪组织发挥重要作用，通过脂肪因子参与肝病的发生发展，随着大量营养物质的摄入和脂肪组织的扩张，血管系统对脂肪细胞供血负担导致细胞缺血缺氧从而诱导脂肪组织产生炎症趋化因子[91-92]，同时游离脂肪酸增加，导致脂肪组织中DNA损伤、*P53*表达上调[93]，激活炎症通路，选择性调控多种脂肪因子的表达，参与肝脏炎症发生发展。充足的营养物质、高糖环境及炎症刺激提高了细胞癌变的敏感性，多数肝癌细胞更倾向于促进脂质代谢及合成以满足自身快速增殖生长的能量供给，因此脂质的异常代谢及合成影响着脂肪细胞的功能，而脂肪细胞影响肝脏的抗炎、抗氧化、解毒、调控代谢及免疫等功能。抑癌基因如*P53*可以从源头上参与脂质的代谢调控，从而影响脂肪组织的代谢功能。NAFLD或代谢综合征可能会伴随高*P53*表达，抑制脂质的合成及脂滴的分解，从而抑制肿瘤细胞的增殖。然而高糖引起的血管内皮细胞再生及高脂环境为肝细胞癌变提供了物质和能量基础，提高了细胞癌变的敏感性。在MAFLD及其相关肝癌的进展过程中，脂肪因子作用机制复杂，肝脏炎症或免疫等因素在脂肪因子影响肝病的过程中发挥的作用不甚明确，研究结果也存在差异，故存在较多争议，这也与变量的控制、研究对象本身特性及混杂因素的排除相关。因此，基于更深层次的理论进行严谨的研究与试验探讨脂肪因子的作用机制及其相互作用可以更进一步揭示争议之下存在的必然机制，为临床控制MAFLD及其相关肝癌提供更加有力的证据。

利益冲突声明：本文不存在任何利益冲突。

作者贡献声明：张熠潇负责撰写论文，资料分析，修改论文；蒋博文参与文献检索，收集数据，修改论文；孙建光负责拟定写作思路，指导撰写文章并最后定稿。

参考文献：

[1] CAO MM, LI H, SUN DQ, et al. Global epidemiology of liver cancer in 2020[J]. Chin J Cancer Prev Treat, 2022, 29(5): 322-328. DOI: 10.16073/j.cnki.cjcpt.2022.05.03.
曹毛毛, 李贺, 孙殿钦, 等. 全球肝癌2020年流行病学现状[J]. 中华肿瘤防治杂志, 2022, 29(5): 322-328. DOI: 10.16073/j.cnki.cjcpt.2022.05.03.

[2] NING L, SUN JG. Research progress of traditional Chinese medcine and western medicine in precancerous lesions of primary hepatic carcinoma[J]. Mod Tradit Chin Med Mater Med World Sci Technol, 2021, 23(10): 3590-3598. DOI: 10.11842/wst.20210506008.
宁麟, 孙建光. 原发性肝癌癌前病变中西医研究进展[J]. 世界科学技术-中医药现代化, 2021, 23(10): 3590-3598. DOI: 10.11842/wst.20210506008.

[3] WANG GH. Clinical and pathological features of cryptogenic liver cancer[D]. Changchun: Jilin University, 2016.
王国华. 隐源性肝癌的临床特点及病理特征分析[D]. 长春: 吉林大学, 2016.

[4] KÄRÄJÄMÄKI AJ, BLOIGU R, KAUMA H, et al. Non-alcoholic fatty liver disease with and without metabolic syndrome: Different long-term outcomes[J]. Metabolism, 2017, 66: 55-63. DOI: 10.1016/j.metabol.2016.06.009.

[5] ZHANG YY, ZHANG T, ZHANG CQ, et al. Identification of reciprocal causality between non-alcoholic fatty liver disease and metabolic syndrome by a simplified Bayesian network in a Chinese population [J]. BMJ Open, 2015, 5(9): e008204. DOI: 10.1136/bmjopen-2015-008204.

[6] XUE R, FAN JG. Brief introduction of an international expert consensus statement: A new definition of metabolic associated fatty liver disease[J]. J Clin Hepatol, 2020, 36(6): 1224-1227. DOI: 10.3969/j.issn.1001-5256.2020.06.007.
薛芮, 范建高. 代谢相关脂肪性肝病新定义的国际专家共识简介[J]. 临床肝胆病杂志, 2020, 36(6): 1224-1227. DOI: 10.3969/j.issn.1001-5256.2020.06.007.

[7] JIANG TT, SUN FF, ZENG Z, et al. Progress on metabolic associated fatty liver disease related liver cancer[J/CD]. Chin J Liver Dis (Electronic Version), 2022, 14(3): 14-17. DOI: 10.3969/j.issn.1674-7380.2022.03.004.
蒋婷婷, 孙芳芳, 曾湛, 等. 代谢相关脂肪性肝病相关肝癌研究进展[J/CD]. 中国肝脏病杂志(电子版), 2022, 14(3): 14-17. DOI: 10.3969/j.issn.1674-7380.2022.03.004.

[8] JARUVONGVANICH V, SANGUANKEO A, RIANGWIWAT T, et al. Testosterone, sex hormone-binding globulin and nonalcoholic fatty liver disease: A systematic review and meta-analysis[J]. Ann Hepatol, 2017, 16(3): 382-394. DOI: 10.5604/16652681.1235481.

[9] WANG S, ZHANG J, JIANG XZ, et al. Relationship between waist circumference trajectory and new-onset non alcoholic fatty liver dis-

ease in the non-obese population[J]. Chin J Epidemiol, 2020, 41(6): 824-828. DOI: 10.3760/cma.j.cn112338-20190630-00479.
王珊, 张健, 蒋晓忠, 等. 非肥胖人群的腰围轨迹与新发非酒精性脂肪肝的相关性[J]. 中华流行病学杂志, 2020, 41(6): 824-828. DOI: 10.3760/cma.j.cn112338-20190630-00479.

[10] SARKAR M, YATES K, SUZUKI A, et al. Low testosterone is associated with nonalcoholic steatohepatitis and fibrosis severity in men[J]. Clin Gastroenterol Hepatol, 2021, 19(2): 400-402. DOI: 10.1016/j.cgh.2019.11.053.

[11] LEE JH, JEON S, LEE HS, et al. Cutoff points of waist circumference for predicting incident non-alcoholic fatty liver disease in middle-aged and older Korean adults[J]. Nutrients, 2022, 14(14): 2994. DOI: 10.3390/nu14142994.

[12] NING L, SUN JG. Associations between body circumference and testosterone levels and risk of metabolic dysfunction-associated fatty liver disease: A Mendelian randomization study[J]. BMC Public Health, 2023, 23(1): 602. DOI: 10.1186/s12889-023-15467-4.

[13] FRANCHITTO A, CARPINO G, ALISI A, et al. The contribution of the adipose tissue-liver axis in pediatric patients with nonalcoholic fatty liver disease after laparoscopic sleeve gastrectomy[J]. J Pediatr, 2020, 216: 117-127. DOI: 10.1016/j.jpeds.2019.07.037.

[14] POLYZOS SA, KOUNTOURAS J, MANTZOROS CS. Adipose tissue, obesity and non-alcoholic fatty liver disease[J]. Minerva Endocrinol, 2017, 42(2): 92-108. DOI: 10.23736/S0391-1977.16.02563-3.

[15] ÁLVAREZ-MERCADO AI, BUJALDON E, GRACIA-SANCHO J, et al. The role of adipokines in surgical procedures requiring both liver regeneration and vascular occlusion[J]. Int J Mol Sci, 2018, 19(11): 3395. DOI: 10.3390/ijms19113395.

[16] YANG T, XUE JL. Research progress on the pathogenesis and carcinogenesis of colorectal polyps in patients with type 2 diabetes mellitus[J]. Chin J New Clin Med, 2024, 17(1): 113-118. DOI: 10.3969/j.issn.1674-3806.2024.01.21.
杨腾, 薛君力. 2型糖尿病患者结直肠息肉发病及癌变机制的研究进展[J]. 中国临床新医学, 2024, 17(1): 113-118. DOI: 10.3969/j.issn.1674-3806.2024.01.21.

[17] XU Y, LI ZX, MA Y, et al. Cancer disease burden attributable to type 2 diabetes mellitus among adults in China, 1990-2019[J]. China Cancer, 2022, 31(12): 959-966. DOI: 10.11735/j.issn.1004-0242.2022.12.A004.
徐英, 李志学, 马艳, 等. 1990—2019年中国成年人归因于2型糖尿病的癌症疾病负担研究[J]. 中国肿瘤, 2022, 31(12): 959-966. DOI: 10.11735/j.issn.1004-0242.2022.12.A004.

[18] CHEN XY, CHEN JH, YANG YL. Research progress on the mechanism, prevention and treatment of obesity-related tumors[J/OL]. Electron J Metab Nutr Cancer, 2022, 9(6): 714-720. DOI: 10.16689/j.cnki.cn11-9349/r.2022.06.006.
陈系羽, 陈京浩, 杨雁灵. 肥胖相关肿瘤发生机制和防治研究进展[J/OL]. 肿瘤代谢与营养电子杂志, 2022, 9(6): 714-720. DOI: 10.16689/j.cnki.cn11-9349/r.2022.06.006.

[19] WANG H. Risk factors and mechanism of cancer in type 2 diabetes patients in Changchuna[D]. Changchun: Jilin University, 2023.
王欢. 长春地区2型糖尿病患者伴发癌症的危险因素分析及机制探讨[D]. 长春: 吉林大学, 2023.

[20] DONATO J Jr. Programming of metabolism by adipokines during development[J]. Nat Rev Endocrinol, 2023, 19(7): 385-397. DOI: 10.1038/s41574-023-00828-1.

[21] ZHANG Y, PROENCA R, MAFFEI M, et al. Positional cloning of the mouse obese gene and its human homologue[J]. Nature, 1994, 372(6505): 425-432. DOI: 10.1038/372425a0.

[22] LIN TC, HUANG KW, LIU CW, et al. Leptin signaling axis specifically associates with clinical prognosis and is multifunctional in regulating cancer progression[J]. Oncotarget, 2018, 9(24): 17210-17219. DOI: 10.18632/oncotarget.24966.

[23] KAN ZY, ZHENG HC, LIU X, et al. Whole-genome sequencing identifies recurrent mutations in hepatocellular carcinoma[J]. Genome Res, 2013, 23(9): 1422-1433. DOI: 10.1101/gr.154492.113.

[24] TONG HV, BOCK CT, VELAVAN TP. Genetic insights on host and hepatitis B virus in liver diseases[J]. Mutat Res Rev Mutat Res, 2014, 762: 65-75. DOI: 10.1016/j.mrrev.2014.06.001.

[25] ZHANG B, ZHONG DW, WANG QW, et al. Study on correlation of JAK/STAT signal pathway with progression and prognosis in hepatocellular carcinoma[J]. Chin J Cell Mol Immunol, 2010, 26(4): 368-370, 373. DOI: 10.13423/j.cnki.cjcmi.005452.
张斌, 钟德玠, 王群伟, 等. JAK/STAT信号通路与肝细胞性肝癌的肿瘤进展和预后的相关性研究[J]. 细胞与分子免疫学杂志, 2010, 26(4): 368-370, 373. DOI: 10.13423/j.cnki.cjcmi.005452.

[26] GAO PL, LI HY, YANG XF, et al. JAK/STAT3 signaling system regulates hTERT through leptin in hepatocellular carcinoma cells[J]. World Chin J Dig, 2015, 23(35): 5613-5619.
高培亮, 李海洋, 杨晓峰, 等. JAK/STAT3信号系统通过瘦素调控hTERT在肝癌细胞中的作用[J]. 世界华人消化杂志, 2015, 23(35): 5613-5619.

[27] LONARDO A, NASCIMBENI F, MAURANTONIO M, et al. Nonalcoholic fatty liver disease: Evolving paradigms[J]. World J Gastroenterol, 2017, 23(36): 6571-6592. DOI: 10.3748/wjg.v23.i36.6571.

[28] POUR FK, ARYAEIAN N, MOKHTARE M, et al. The effect of saffron supplementation on some inflammatory and oxidative markers, leptin, adiponectin, and body composition in patients with nonalcoholic fatty liver disease: A double-blind randomized clinical trial[J]. Phytother Res, 2020, 34(12): 3367-3378. DOI: 10.1002/ptr.6791.

[29] HU LP, CAI H, LI QJ, et al. Study on the pathogenesis of metabolism associated fatty liver disease[J]. J Med Inf, 2023, 36(23): 174-179. DOI: 10.3969/j.issn.1006-1959.2023.23.044.
胡丽平, 蔡华, 李情娇, 等. 代谢相关脂肪性肝病发病机制的研究[J]. 医学信息, 2023, 36(23): 174-179. DOI: 10.3969/j.issn.1006-1959.2023.23.044.

[30] ZHANG QZ, LIU YL, WANG YR, et al. Effects of telmisartan on improving leptin resistance and inhibiting hepatic fibrosis in rats with non-alcoholic fatty liver disease[J]. Exp Ther Med, 2017, 14(3): 2689-2694. DOI: 10.3892/etm.2017.4809.

[31] QIU Y, WANG SF, YU C, et al. Association of circulating adipsin, visfatin, and adiponectin with nonalcoholic fatty liver disease in adults: A case-control study[J]. Ann Nutr Metab, 2019, 74(1): 44-52. DOI: 10.1159/000495215.

[32] GUO YD, DENG YJ, SUN HL, et al. To investigate the levels of adipsin, visfatin and irisin in patients with nonalcoholic fatty liver disease (NAFLD)and their correlation[J]. J Pract Med, 2020, 36(17): 2376-2380. DOI: 10.3969/j.issn.1006-5725.2020.17.012.
郭娅棣, 邓玉杰, 孙洪林, 等. 非酒精性脂肪肝患者血清脂肪素、内脂素和鸢尾素水平及其相关性[J]. 实用医学杂志, 2020, 36(17): 2376-2380. DOI: 10.3969/j.issn.1006-5725.2020.17.012.

[33] GUO X, JIAO L, YI Y, et al. NAMPT regulates mitochondria function and lipid metabolism during porcine oocyte maturation[J]. J Cell Physiol, 2024, 239(1): 180-192. DOI: 10.1002/jcp.31156.

[34] YANG L, ZHI SS. Relationship between the serum levels of CK-18, visfatin and liver fibrosis indexes in patients with NAFLD[J]. Hebei Med J, 2019, 41(11): 1726-1728. DOI: 10.3969/j.issn.1002-7386.2019.11.032.
杨丽, 智深深. NAFLD患者血清CK-18、内脂素水平变化与纤维化指标的关系[J]. 河北医药, 2019, 41(11): 1726-1728. DOI: 10.3969/j.issn.1002-7386.2019.11.032.

[35] YANG N, SUN RB, ZHANG XL, et al. Alternative pathway of bile acid biosynthesis contributes to ameliorate NASH after induction of NAMPT/NAD^+/SIRT1 axis[J]. Biomed Pharmacother, 2023, 164: 114987. DOI: 10.1016/j.biopha.2023.114987.

[36] MA R, WU YS, ZHAI YS, et al. Exogenous pyruvate represses histone gene expression and inhibits cancer cell proliferation *via* the NAMPT-NAD^+-SIRT1 pathway[J]. Nucleic Acids Res, 2019, 47(21):

11132-11150. DOI: 10.1093/nar/gkz864.
[37] SUN BL, SUN XG, KEMPF CL, et al. Involvement of eNAMPT/TLR4 inflammatory signaling in progression of non-alcoholic fatty liver disease, steatohepatitis, and fibrosis[J]. FASEB J, 2023, 37(3): e22825. DOI: 10.1096/fj.202201972RR.
[38] LUCENA-CACACE A, OTERO-ALBIOL D, JIMÉNEZ-GARCÍA MP, et al. NAMPT is a potent oncogene in colon cancer progression that modulates cancer stem cell properties and resistance to therapy through Sirt1 and PARP[J]. Clin Cancer Res, 2018, 24(5): 1202-1215. DOI: 10.1158/1078-0432.CCR-17-2575.
[39] LUCENA-CACACE A, OTERO-ALBIOL D, JIMÉNEZ-GARCÍA MP, et al. NAMPT overexpression induces cancer stemness and defines a novel tumor signature for glioma prognosis[J]. Oncotarget, 2017, 8(59): 99514-99530. DOI: 10.18632/oncotarget.20577.
[40] LV HW, LV GS, CHEN CA, et al. NAD^+ metabolism maintains inducible PD-L1 expression to drive tumor immune evasion[J]. Cell Metab, 2021, 33(1): 110-127. DOI: 10.1016/j.cmet.2020.10.021.
[41] ADYA R, TAN BK, CHEN J, et al. Nuclear factor-kappaB induction by visfatin in human vascular endothelial cells: Its role in MMP-2/9 production and activation[J]. Diabetes Care, 2008, 31(4): 758-760. DOI: 10.2337/dc07-1544.
[42] CHANG Q. Immunomodulatory role of nicotinamide phosphoribosyltransferase (NAMPT) in chronic hepatitis B and hepatocellular carcinoma[D]. Jinan: Shandong University, 2023.
常晴. 烟酰胺磷酸核糖转移酶(NAMPT)在慢性乙型肝炎和肝癌中的免疫调节作用[D]. 济南: 山东大学, 2023.
[43] SCHERER PE, WILLIAMS S, FOGLIANO M, et al. A novel serum protein similar to C1q, produced exclusively in adipocytes[J]. J Biol Chem, 1995, 270(45): 26746-26749. DOI: 10.1074/jbc.270.45.26746.
[44] PAL CHINA S, SANYAL S, CHATTOPADHYAY N. Adiponectin signaling and its role in bone metabolism[J]. Cytokine, 2018, 112: 116-131. DOI: 10.1016/j.cyto.2018.06.012.
[45] LIU QQ, GAUTHIER MS, SUN L, et al. Activation of AMP-activated protein kinase signaling pathway by adiponectin and insulin in mouse adipocytes: Requirement of acyl-CoA synthetases FATP1 and Acsl1 and association with an elevation in AMP/ATP ratio[J]. FASEB J, 2010, 24(11): 4229-4239. DOI: 10.1096/fj.10-159723.
[46] YOON MJ, LEE GY, CHUNG JJ, et al. Adiponectin increases fatty acid oxidation in skeletal muscle cells by sequential activation of AMP-activated protein kinase, p38 mitogen-activated protein kinase, and peroxisome proliferator-activated receptor alpha[J]. Diabetes, 2006, 55(9): 2562-2570. DOI: 10.2337/db05-1322.
[47] FANG XP, PALANIVEL R, CRESSER J, et al. An APPL1-AMPK signaling axis mediates beneficial metabolic effects of adiponectin in the heart[J]. Am J Physiol Endocrinol Metab, 2010, 299(5): E721-E729. DOI: 10.1152/ajpendo.00086.2010.
[48] TOMAS E, TSAO TS, SAHA AK, et al. Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: Acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation [J]. Proc Natl Acad Sci U S A, 2002, 99(25): 16309-16313. DOI: 10.1073/pnas.222657499.
[49] DENG DT, WANG YM, CHENG Y, et al. Adiponectin activates AMP-activated protein kinase via LKB1 pathway[J]. Chin J Endocrinol Metab, 2012, 28(7): 578-583. DOI: 10.3760/cma.j.issn.1000-6699.2012.07.014.
邓大同, 王佑民, 程媛, 等. 脂联素通过LKB1途径激活腺苷酸活化蛋白激酶[J]. 中华内分泌代谢杂志, 2012, 28(7): 578-583. DOI: 10.3760/cma.j.issn.1000-6699.2012.07.014.
[50] YOU M, ROGERS CQ. Adiponectin: A key adipokine in alcoholic fatty liver[J]. Exp Biol Med (Maywood), 2009, 234(8): 850-859. DOI: 10.3181/0902-MR-61.
[51] YAMAUCHI T, NIO Y, MAKI T, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions[J]. Nat Med, 2007, 13(3): 332-339. DOI: 10.1038/nm1557.
[52] KIM SJ, TANG TY, ABBOTT M, et al. AMPK phosphorylates desnutrin/ATGL and hormone-sensitive lipase to regulate lipolysis and fatty acid oxidation within adipose tissue[J]. Mol Cell Biol, 2016, 36(14): 1961-1976. DOI: 10.1128/MCB.00244-16.
[53] ANTUNA-PUENTE B, FEVE B, FELLAHI S, et al. Adipokines: The missing link between insulin resistance and obesity[J]. Diabetes Metab, 2008, 34(1): 2-11. DOI: 10.1016/j.diabet.2007.09.004.
[54] MANIERI E, HERRERA-MELLE L, MORA A, et al. Adiponectin accounts for gender differences in hepatocellular carcinoma incidence [J]. J Exp Med, 2019, 216(5): 1108-1119. DOI: 10.1084/jem.20181288.
[55] DALAMAGA M, DIAKOPOULOS KN, MANTZOROS CS. The role of adiponectin in cancer: A review of current evidence[J]. Endocr Rev, 2012, 33(4): 547-594. DOI: 10.1210/er.2011-1015.
[56] XIE X, YAN D, LI HB, et al. Enhancement of adiponectin ameliorates nonalcoholic fatty liver disease *via* inhibition of FoxO1 in type I diabetic rats[J]. J Diabetes Res, 2018, 2018: 6254340. DOI: 10.1155/2018/6254340.
[57] XU HY, ZHU HJ, PAN H, et al. Effects of adiponectin on the gene promoter activities of fatty acid synthase and hormone sensitive lipase in HepG2 cells[J]. Basic Clin Med, 2021, 41(1): 13-19. DOI: 10.16352/j.issn.1001-6325.2021.01.005.
许瀚元, 朱惠娟, 潘慧, 等. 脂联素对HepG2细胞中脂肪酸合成酶及激素敏感性脂肪酶基因启动子活性的影响[J]. 基础医学与临床, 2021, 41(1): 13-19. DOI: 10.16352/j.issn.1001-6325.2021.01.005.
[58] EBERT T, GEBHARDT C, SCHOLZ M, et al. Relationship between 12 adipocytokines and distinct components of the metabolic syndrome[J]. J Clin Endocrinol Metab, 2018, 103(3): 1015-1023. DOI: 10.1210/jc.2017-02085.
[59] SELL H, DIVOUX A, POITOU C, et al. Chemerin correlates with markers for fatty liver in morbidly obese patients and strongly decreases after weight loss induced by bariatric surgery[J]. J Clin Endocrinol Metab, 2010, 95(6): 2892-2896. DOI: 10.1210/jc.2009-2374.
[60] POHL R, HABERL EM, REIN-FISCHBOECK L, et al. Hepatic chemerin mRNA expression is reduced in human nonalcoholic steatohepatitis [J]. Eur J Clin Invest, 2017, 47(1): 7-18. DOI: 10.1111/eci.12695.
[61] GALON J, ANGELL HK, BEDOGNETTI D, et al. The continuum of cancer immunosurveillance: Prognostic, predictive, and mechanistic signatures[J]. Immunity, 2013, 39(1): 11-26. DOI: 10.1016/j.immuni.2013.07.008.
[62] MITCHELL D, CHINTALA S, DEY M. Plasmacytoid dendritic cell in immunity and cancer[J]. J Neuroimmunol, 2018, 322: 63-73. DOI: 10.1016/j.jneuroim.2018.06.012.
[63] ROURKE JL, DRANSE HJ, SINAL CJ. CMKLR1 and GPR1 mediate chemerin signaling through the RhoA/ROCK pathway[J]. Mol Cell Endocrinol, 2015, 417: 36-51. DOI: 10.1016/j.mce.2015.09.002.
[64] KRONES-HERZIG A, ADAMSON E, MERCOLA D. Early growth response 1 protein, an upstream gatekeeper of the p53 tumor suppressor, controls replicative senescence[J]. Proc Natl Acad Sci U S A, 2003, 100(6): 3233-3238. DOI: 10.1073/pnas.2628034100.
[65] NAIR P, MUTHUKKUMAR S, SELLS SF, et al. Early growth response-1-dependent apoptosis is mediated by p53[J]. J Biol Chem, 1997, 272(32): 20131-20138. DOI: 10.1074/jbc.272.32.20131.
[66] LIU-CHITTENDEN Y, JAIN M, GASKINS K, et al. RARRES2 functions as a tumor suppressor by promoting β-catenin phosphorylation/degradation and inhibiting p38 phosphorylation in adrenocortical carcinoma[J]. Oncogene, 2017, 36(25): 3541-3552. DOI: 10.1038/onc.2016.497.
[67] RAGHUWANSHI SK, NASSER MW, CHEN XX, et al. Depletion of beta-arrestin-2 promotes tumor growth and angiogenesis in a murine model of lung cancer[J]. J Immunol, 2008, 180(8): 5699-5706. DOI: 10.4049/jimmunol.180.8.5699.
[68] WANG CH, WU WKK, LIU XD, et al. Increased serum chemerin level promotes cellular invasiveness in gastric cancer: A clinical and experimental study[J]. Peptides, 2014, 51: 131-138. DOI: 10.1016/j.peptides.2013.10.009.

[69] LIN W, CHEN YL, JIANG L, et al. Reduced expression of chemerin is associated with a poor prognosis and a lowed infiltration of both dendritic cells and natural killer cells in human hepatocellular carcinoma[J]. Clin Lab, 2011, 57(11-12): 879-885.
[70] MENYHÁRT O, NAGY Á, GYŐRFFY B. Determining consistent prognostic biomarkers of overall survival and vascular invasion in hepatocellular carcinoma[J]. R Soc Open Sci, 2018, 5(12): 181006. DOI: 10.1098/rsos.181006.
[71] KLÖTING N, KOVACS P, KERN M, et al. Central vaspin administration acutely reduces food intake and has sustained blood glucose-lowering effects[J]. Diabetologia, 2011, 54(7): 1819-1823. DOI: 10.1007/s00125-011-2137-1.
[72] WU GX, ZHOU ZH, SUN JJ, et al. Effect of Vaspin on liver lipid aggregation in mice fed with high fat[J]. Chin J Gerontol, 2018, 38(13): 3206-3209. DOI: 10.3969/j.issn.1005-9202.2018.13.054.
吴光秀, 周泽华, 孙建娟, 等. Vaspin对高脂喂养小鼠肝脏脂质聚集的影响[J]. 中国老年学杂志, 2018, 38(13): 3206-3209. DOI: 10.3969/j.issn.1005-9202.2018.13.054.
[73] CHEN XM, ZHANG L, QI LM, et al. The expression and clinical significance of adipokine Vaspin in nonalcoholic fatty liver disease[J]. China J Mod Med, 2021, 31(6): 37-43. DOI: 10.3969/j.issn.1005-8982.2021.06.008.
陈香梅, 张亮, 齐立明, 等. 脂肪因子Vaspin在非酒精性脂肪性肝病中的表达及其临床意义[J]. 中国现代医学杂志, 2021, 31(6): 37-43. DOI: 10.3969/j.issn.1005-8982.2021.06.008.
[74] LI HL, PENG WH, ZHUANG JH, et al. Vaspin attenuates high glucose-induced vascular smooth muscle cells proliferation and chemokinesis by inhibiting the MAPK, PI3K/Akt, and NF-κB signaling pathways[J]. Atherosclerosis, 2013, 228(1): 61-68. DOI: 10.1016/j.atherosclerosis.2013.02.013.
[75] MA H. Effect of endogenous phlegm-dampness on fat factor Vaspin in serum of CIA mice[D]. Shenyang: China Medical University, 2022.
马欢. 内生痰湿对CIA小鼠血清中脂肪因子Vaspin的影响[D]. 沈阳: 中国医科大学, 2022.
[76] WALUGA M, KUKLA M, ŻORNIAK M, et al. Vaspin mRNA levels in the liver of morbidly obese women with nonalcoholic fatty liver disease[J]. Pol J Pathol, 2017, 68(2): 128-137. DOI: 10.5114/pjp.2017.69688.
[77] SKONIECZNA M, HUDY D, HEJMO T, et al. The adipokine vaspin reduces apoptosis in human hepatocellular carcinoma (Hep-3B) cells, associated with lower levels of NO and superoxide anion[J]. BMC Pharmacol Toxicol, 2019, 20(1): 58. DOI: 10.1186/s40360-019-0334-6.
[78] BOOTH A, MAGNUSON A, FOUTS J, et al. Adipose tissue, obesity and adipokines: Role in cancer promotion[J]. Horm Mol Biol Clin Investig, 2015, 21(1): 57-74. DOI: 10.1515/hmbci-2014-0037.
[79] KUKLA M, MAZUR W, BUŁDAK RJ, et al. Potential role of leptin, adiponectin and three novel adipokines—visfatin, chemerin and vaspin—in chronic hepatitis[J]. Mol Med, 2011, 17(11-12): 1397-1410. DOI: 10.2119/molmed.2010.00105.
[80] ERDOGAN S, SEZER S, BASER E, et al. Evaluating vaspin and adiponectin in postmenopausal women with endometrial cancer[J]. Endocr Relat Cancer, 2013, 20(5): 669-675. DOI: 10.1530/ERC-13-0280.
[81] FAZELI MS, DASHTI H, AKBARZADEH S, et al. Circulating levels of novel adipocytokines in patients with colorectal cancer[J]. Cytokine, 2013, 62(1): 81-85. DOI: 10.1016/j.cyto.2013.02.012.
[82] LACROIX M, RISCAL R, ARENA G, et al. Metabolic functions of the tumor suppressor p53: Implications in normal physiology, metabolic disorders, and cancer[J]. Mol Metab, 2020, 33: 2-22. DOI: 10.1016/j.molmet.2019.10.002.
[83] MAO YX, JIANG P. The crisscross between p53 and metabolism in cancer[J]. Acta Biochim Biophys Sin (Shanghai), 2023, 55(6): 914-922. DOI: 10.3724/abbs.2023109.
[84] LIN YM. The role and mechanism of p53/PXR-SCD1 axis in nonalcoholic fatty liver disease[D]. Hangzhou: Zhejiang University, 2020.
林一鸣. p53/PXR-SCD1调控轴在NAFLD中的作用及机制研究[D]. 杭州: 浙江大学, 2020.
[85] DENG Y, DUAN Y. Research progress on pathogenesis and drug therapy of primary liver cancer[J]. Hebei Med, 2024, 30(2): 345-348. DOI: 10.3969/j.issn.1006-6233.2024.02.034.
邓燕, 段勇. 原发性肝癌发病机制和药物治疗的研究进展[J]. 河北医学, 2024, 30(2): 345-348. DOI: 10.3969/j.issn.1006-6233.2024.02.034.
[86] LI W, KOU JJ, ZHANG ZX, et al. Cellular redox homeostasis maintained by malic enzyme 2 is essential for MYC-driven T cell lymphomagenesis[J]. Proc Natl Acad Sci U S A, 2023, 120(23): e2217869120. DOI: 10.1073/pnas.2217869120.
[87] MOON SH, HUANG CH, HOULIHAN SL, et al. p53 represses the mevalonate pathway to mediate tumor suppression[J]. Cell, 2019, 176(3): 564-580. DOI: 10.1016/j.cell.2018.11.011.
[88] GÓMEZ-SANTOS B, SAENZ DE URTURI D, NUÑEZ-GARCÍA M, et al. Liver osteopontin is required to prevent the progression of age-related nonalcoholic fatty liver disease[J]. Aging Cell, 2020, 19(8): e13183. DOI: 10.1111/acel.13183.
[89] KANG JG, LAGO CU, LEE JE, et al. A mouse homolog of a human TP53 germline mutation reveals a lipolytic activity of p53[J]. Cell Rep, 2020, 30(3): 783-792. DOI: 10.1016/j.celrep.2019.12.074.
[90] WANG H. The role of ankyrin-repeat-containing, SH3-domain-containing, and proline-rich-region- containing protein 2 (ASPP2) in lipid metabolism in hepatocellular carcinoma[D]. Shanghai: Second Military Medical University, 2017.
汪浩. p53凋亡刺激蛋白2调控肝癌脂质代谢的研究[D]. 上海: 第二军医大学, 2017.
[91] FOLKMAN J, HAHNFELDT P, HLATKY L. Cancer: Looking outside the genome[J]. Nat Rev Mol Cell Biol, 2000, 1(1): 76-79. DOI: 10.1038/35036100.
[92] KANDA H, TATEYA S, TAMORI Y, et al. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity[J]. J Clin Invest, 2006, 116(6): 1494-1505. DOI: 10.1172/JCI26498.
[93] SHIMIZU I, YOSHIDA Y, KATSUNO T, et al. p53-induced adipose tissue inflammation is critically involved in the development of insulin resistance in heart failure[J]. Cell Metab, 2012, 15(1): 51-64. DOI: 10.1016/j.cmet.2011.12.006.

收稿日期：2024-04-29；**录用日期：**2024-06-14
本文编辑：葛俊

引证本文： ZHANG YX, SUN JG, JIANG BW. Research advances in the association of adipokines with metabolic associated fatty liver disease and its associated liver cancer[J]. J Clin Hepatol, 2025, 41(1): 151-158.
张熠潇, 孙建光, 蒋博文. 脂肪因子与代谢相关脂肪性肝病及其相关肝癌的关系[J]. 临床肝胆病杂志, 2025, 41(1): 151-158.