酒精相关肝癌发病机制研究进展

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摘要：原发性肝癌是危害我国人民健康的主要肿瘤之一。酒精是导致肝癌的重要原因。酒精相关肝癌与个体遗传背景有关。在此基础上酒精可通过乙醇和乙醛的直接毒性作用导致肝癌的发生。此外酒精还可通过表观遗传学修饰、氧化应激损伤、影响抗肿瘤免疫以及作用于肠道微生态等多种途径导致肝癌的发生与发展。明确酒精导致肝癌的可能机制有助于发现酒精相关肝癌防治的新靶点与药物研发。

关键词：酒精相关肝病；乙醛；原发性肝癌；表观遗传学；肠道微生态

Research progress on pathogenesis of alcohol related liver cancer

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Abstract: Primary hepatic cancer (PHC) is one of the most common tumors endangering in China's mainland. Alcohol is an important cause of PHC. Risk of alcohol related PHC is related to genetic susceptibility. Besides, ethanol and acetaldehyde may induce PHC through direct toxicity. Pathogenesis of alcohol related PHC also involves epigenetic modification, oxygen stress injury, impaired anti-tumor immunity and disturbed intestinal microecology. Clarifying the possible mechanism of alcohol related PHC can help identify new targets and drug development for the prevention and treatment of alcohol related liver cancer.

Key words: Alcohol related liver disease; Acetaldehyde; Primary hepatic cancer; Epigenetics; Intestinal microecology

原发性肝癌是危害人类健康的主要肿瘤之一，2016年我国新发原发性肝癌36.4万例，死亡33.6万例[1]。在我国引起肝癌的病因以乙型肝炎病毒感染为主[2]，但酒精相关肝癌的发病率呈上升趋势[3]。酒精相关肝癌发病机制与乙型肝炎相关肝癌不完全相同，有一些其特有的致病机制，涉及遗传易感性、酒精及代谢产物的毒性作用、表观遗传学异常、氧化应激损伤、抗肿瘤免疫受损与肠道微生态紊乱等多个方面。近年来对酒精相关肝癌机制的研究不断进展，本文就相关内容综述如下。

1 酒精相关肝癌的遗传易感性

酒精相关肝癌的发生与多个基因的多态性有关，其中包括Patatin样磷酯酶结构域蛋白3（patatin-like phospholipase domain-containing 3，*PNPLA3*）[4]、跨膜蛋白6超家族成员2（transmembrane 6 superfamily member 2，*TM6SF2*）[4]、羟基类固醇17β脱氢酶13（hydroxysteroid 17-beta dehydrogenase 13，*HSD17B13*）[5]、*WNT3A-WNT9A*[4]与端粒酶逆转录酶（telomerase reverse transcriptase，*TERT*）[6]等。*PNPLA3*基因rs738409位点是研究最深入的与酒精相关肝癌相关的基因多态性位点[7]。Stickel等[8]对比了751例发生肝细胞癌（hepatocellular carcinoma，HCC）的酒精相关肝硬化患者和1165例无HCC的酒精相关肝硬化患者在*PNPLA3* rs738409的单核苷酸多态性（single nucleotide polymorphism，SNP），结果提示*PNPLA3* rs738409位点多态性与酒精相关肝癌发生风险相关（*OR* = 1.84，95%*CI*：1.55～2.18）。同样，Trépo等[4]对2107例欧洲酒精相关肝病（alcohol related liver disease，ARLD）患者进行两步法病例对照全基因组关联研究（genome-wide association study，GWAS），结果表明*PNPLA3*的rs738409位点多态性与酒精相关肝癌的发生显著相关（$P = 9.29 \times 10^{-7}$）。分析*PNPLA3*多态性与酒精相关肝癌风险相关的原因，考虑可能与*PNPLA3*的rs738409

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多态性影响机体脂代谢等相关[4]。PNPLA3本身是一种具有三酰甘油脂酶和酰基甘油-O-酰基转移酶活性的酶，在脂肪细胞、肝细胞以及肝星状细胞的脂质代谢中发挥重要作用。*PNPLA3* rs738409 GG变异可能通过多种方式影响该酶的功能，有研究提示该SNP可导致底物结合结构域的功能改变，进而其与底物结合能力下降，导致PNPLA3的甘油三酯水解能力下降，肝细胞中脂质堆积，脂肪毒性相应增加[8]。

同样地，多项研究提示*TM6SF2*基因在rs58542926位点的SNP与酒精相关肝癌有关[4,6,8]。除上述Stickel等[8]与Trépo等[4]报道*TM6SF2*在rs58542926位点的SNP与酒精相关肝癌有关外，最近Buch等[6]纳入1214例酒精相关肝硬化并肝癌患者与1866例酒精相关肝硬化未发展至肝癌患者的病例对照GWAS，也再次明确了在*TM6SF2*的rs58542926位点的多态性与酒精相关肝癌发生的相关性。*TM6SF2*基因参与调节肝细胞内脂蛋白的分泌以及极低密度脂蛋白（very low-density lipoproteins，VLDL）的酯化，*TM6SF2*在rs58542926位点多态性导致TM6SF2蛋白功能受损，进而影响VLDL输出，从而导致细胞内脂质含量增加，这可能是该SNP影响ARLD进展的可能机制[8]。

Nahon等[9]通过Fine-Gray模型和7-SNP遗传风险评分对纳入研究的1145例酒精性肝硬化患者的多种SNP发生HCC的风险进行评估，发现AA-WNT3A-WNT9A纯合子患者的5年HCC发生率（10.3%，95%*CI*：7.2～14.1）高于至少有1个T-WNT等位基因的患者（7.8%，95%*CI*：5.6～10.5）。Trépo等[4]也报道*WNT3A-WNT9A*（rs708113；$P = 1.11 \times 10^{-8}$）是酒精相关肝癌的风险位点，*WNT3A-WNT9A* rs70811 rs708113 SNP与酒精相关HCC患者中免疫细胞数量和*CTNNB1*（catenin beta 1，CTNNB1）基因突变比例相关。而*CTNNB1*基因可编码WNT/β-连环蛋白，导致WNT/β-连环蛋白通路的激活，参与肝脏发育、代谢、再生，肝纤维生成和肝癌的发生。

多项研究表明*HSD17B13*的rs72613567位点SNP对ARLD包括酒精相关肝硬化和肝癌有一定的保护作用[10,11]。Schwantes-An等[5]分析了1128例酒精相关肝硬化患者和614例无肝病酗酒者的DNA样本，通过GWAS观察到rs4607179的C等位基因对酒精相关性肝硬化有保护作用（*OR* = 0.80，$P = 1.39 \times 10^{-8}$）。此外，Stickel等[10]对1031例酒精相关肝癌患者、1653例无HCC酒精性肝硬化患者、2588例酗酒者以及899例健康对照者进行*HSD17B13*基因分型，发现携带*HSD17B13*（rs72613567：TA）可降低HCC（*OR* = 1.77，95%*CI*：1.58～1.98）风险。

除上述位点外，Buch等[6]通过联合荟萃分析发现*TERT*中的位点rs2242652（A）也与HCC风险降低相关。Nahon等[12]发现*Ala-SOD2*中rs1799725位点与*2G-MPO*中的rs2333227位点等位基因是导致酒精性肝硬化患者HCC发病的独立危险因素[13]。

2 乙醇与乙醛的直接毒性作用

酒精相关肝癌的发生与乙醇和乙醛的直接毒性作用有关。Yu等[14]通过细胞实验表明，肝细胞暴露于酒精可导致细胞内氧自由基水平升高，并诱导肝细胞*SATB2*基因表达。*SATB2*作为一种转录因子可调控*Bcl-2*、*Nanog*、*c-Myc*、*Klf4*和*Oct4*基因表达，进而受损的肝细胞会呈现癌症干细胞的表型，表达干细胞标记物CD133、CD44、CD90、上皮细胞黏附分子（epithelial cell adhesion molecule，EpCAM）与AFP等。*SIRT7*基因的表达与HCC的转移相关，Zhang等[15]研究表明，酒精可通过上调小鼠肝细胞中的细胞色素P450 2E1（cytochrome P450 2E1，CYP2E1）水平促进氧应激从而上调*SIRT7*表达。Marié等[16]用酒精处理Huh-7肝癌细胞系6个月后发现，慢性酒精暴露可选择性激活细胞外调节蛋白激酶（extracellular signal-related kinases，ERK）1/2通路，抑制糖原合成酶激酶-3β（glycogen synthase kinase-3β，GSK3β）通路，导致Huh-7细胞系的迁移与侵袭能力明显增强，且细胞表达CD133、CD44与CD90等标记物，呈现出癌症干细胞表型。此外胆汁酸代谢在肝细胞癌变中发挥重要作用，研究提示细胞内胆汁酸代谢障碍可导致肝细胞内多种抑癌基因表达下调[17]。Chen等[17]研究表明，酒精可抑制肝细胞上的胆汁输出泵（bile salt export pump，BSEP）进而导致胆汁酸代谢障碍从而促进肝癌的发生，而体外研究也提示改善胆汁酸代谢障碍可抑制肝癌细胞活力并促进癌细胞凋亡[18]。

乙醇的代谢产物乙醛是国际癌症研究机构（International Agency for Research on Cancer，IARC）认定的与含酒精制品消耗相关的Ⅰ类致癌物[19]。乙醛可与DNA或蛋白质形成加成物。乙醛与DNA加成可形成1,N^2-丙烷-2'-脱氧鸟苷（1,N^2-propano-2'-deoxyguanosine，1,N^2-PdG）加成物结构，1,N^2-PdG以单链形式存在时具有致癌作用。乙醛还可与蛋白质分子中的赖氨酸或N端氨基酸的ε-或α-氨基结合形成加合物进而影响蛋白质的功能。如乙醛可与O^6-甲基鸟嘌呤转移酶结合，导致该酶修复DNA损伤的能力下降；乙醛还可与谷胱甘肽（glutathione，GSH）形成加合物。而GSH本身是细胞内关键的抗氧化物

质，乙醛与GSH形成加成物后GSH不能发挥抗氧化作用，从而导致细胞脂质过氧化及氧自由基损伤增加，细胞损伤与癌变风险升高[19]。

3 酒精相关肝癌与表观遗传学异常

酒精可通过作用于DNA甲基化与乙酰化等多种表观遗传学途径促进肝癌的发生。Lu等[20]通过酒精喂养大鼠9周发现大鼠肝脏甲硫氨酸腺苷转移酶1A（methionine adenosyl transferase 1A，MAT1A）表达下调，S-腺苷蛋氨酸（S-adenosylmethionine，SAMe）水平下降而甲硫氨酸腺苷转移酶2A（methionine adenosyl transferase 2A，MAT2A）表达上调。机制研究表明，过量饮酒可抑制*MAT1A*基因表达，进而导致成人肝脏SAMe表达明显降低，SAMe水平下调会导致MAT2A水平升高[21]。MAT2A有促进肝癌发生的作用，其机制在于MAT2A可通过结合于BCL-2启动子区等途径来上调*BCL-2*表达，进而抑制肝癌细胞凋亡[22]。

*ADRA1A*基因是HCC的保护性基因[23,24]。Chen等[25]研究发现酒精可通过上调*ADRA1A*启动子甲基化而抑制*ADRA1A*基因表达，从而促进HCC的发生。且*ADRA1A*启动子的甲基化水平与酒精摄入有明显的量效关系，在高酒精摄入量的HCC患者中，*ADRA1A*的甲基化水平下降至未饮酒人员的21.37%。

酒精还可通过促进组蛋白去甲基化导致肝细胞去分化，从而促进肝癌发生。Schonfeld等[26]发现在酒精喂养的雄性小鼠中，酒精可上调赖氨酸去甲基化酶5B（lysine demethylase 5B，KDM5B）和赖氨酸去甲基化酶5C（lysine demethylase 5C，KDM5C）的表达。KDM5B与KDM5C可特异性结合组蛋白H3赖氨酸K4（histone H3 lysine K4，H3K4）而抑制H3K4表达，导致肝细胞核因子4α（hepatocyte nuclear factor 4 alpha，HNF4α）表达下调与肝细胞去分化，从而促进了肝癌发生。相应地，敲低雄性小鼠的*KDM5B*和*KDM5C*基因则恢复HNF4α表达水平，减少肝脏肿瘤增殖从而抑制肝癌发展。

4 氧化应激机制

氧化应激继发于酒精代谢、炎症和铁储存增加等产生的活性氧（reactive oxygen species，ROS）[13]，其通过促进DNA突变、消耗抗氧化系统等促进肝癌发生。活性氧主要由超氧阴离子（$\cdot O_2^-$）、单线态氧（$^1O_2$）、过氧化氢（H_2O_2）、次氯酸（HClO）和羟自由基（·OH）组成[27]。CYP2E1在酒精诱导的氧化应激中起核心作用[28,29]。酒精不仅可以增加CYP2E1的活性，产生ROS[30]，还可通过诱导微粒体CYP2E1将黄嘌呤脱氢酶转化为黄嘌呤氧化酶，导致肝脏中自由基增加[31]。CYP2E1催化视黄醇和类维A酸（retinoid acid，RA）的代谢，导致RA浓度降低，与细胞分化的丧失和细胞过度再生相关。RA低水平导致RXR和RAR受体表达减少，减弱了细胞凋亡，促进细胞增殖从而促进癌变[32]。

此外，铁代谢在促进氧化应激过程中也发挥重要作用。铁调素是肝脏合成的多肽，可通过抑制十二指肠铁的摄取和巨噬细胞中铁的释放来负性调控体内铁水平，从而维持铁稳态[33]。多项研究表明，酒精可通过抑制铁调素，增加肝脏中的铁水平[33,34]。Gerjevic等[33]在小鼠ARLD模型中发现慢性酒精暴露可上调骨形态发生蛋白（bone morphogenetic protein，BMP）水平，抑制转录因子Smad4与肝脏中铁调素启动子结合，下调铁调素的转录。Harrison-Findik等[34]通过酒精喂养小鼠发现，酒精可通过下调转录因子CCAAT/增强子结合蛋白α（CCAAT/enhancer-binding protein α，C/EBPα）与铁调素启动子区域的结合活性抑制铁调素的转录。铁调素表达水平降低可上调小鼠十二指肠二价金属离子转运蛋白1（divalent metal-ion transporter 1，DMT1）的表达，促进了十二指肠对铁的吸收。乙醇还可能通过作用于转铁蛋白受体（Fe-transferrin，TfR）来诱导铁在肝脏中的积累。Suzuki等[35]用大鼠原代肝细胞进行的体外研究表明，肝细胞暴露于酒精24 h后，TfR1的表达增加了约2倍，肝细胞对转铁蛋白的摄取增加了19%。铁过载可通过Fenton反应产生ROS，其中过氧化氢在亚铁的存在下转化为羟基自由基[36]。ROS具有高度反应性活性，可通过脂质过氧化产生具有反应活性的醛分子如4-羟基壬烯醛（4-hydroxynonenal，4-HNE）和丙二醛（malondialdehyde，MDA）。4-HNE与MDA等均可与DNA碱基相互作用，形成DNA加合物如1，N^6-乙基脱氧腺苷和3，N^4-乙基脱氧胞苷，后者可通过促进DNA突变而具有致癌作用[19]。ROS还可通过诱导*Ras*原癌基因及*P53*抑癌基因等的突变促进癌症的发生[27]。

氧化应激效应可被机体的抗氧化系统中和，但长期饮酒会损害机体抗氧化系统[37]。乙醇可抑制抗氧化酶如超氧化物歧化酶1（superoxide dismutase 1，SOD1）的表达，并降低非酶类的抗氧化剂如谷胱甘肽的表达水平，从而降低肝细胞调节氧化应激的能力[38]。

5 影响抗肿瘤免疫

酒精还可通过抑制机体抗肿瘤免疫来导致肝

癌的发生。Yan等[39]通过对小鼠注射二乙基亚硝胺（diethylnitrosamine，DEN）后再对其进行酒精喂养2.5个月，与注射DEN但未进行酒精喂养的小鼠相比，酒精摄入显著减少了小鼠肝细胞中抗肿瘤$CD8^+$T细胞数量，其机制可能与酒精诱导细胞凋亡和较高水平的转化生长因子β（transforming growth factor-β，TGF-β）相关。因此酒精可通过作用于抗肿瘤免疫而促进DEN诱导的肝癌发生。此外，白细胞介素-17受体A（interleukin-17 receptor A，IL-17RA）是机体一种促癌的肿瘤免疫细胞因子，其可上调巨噬细胞中肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）的表达，通过激活核因子-κB（nuclear factor-kappaB，NF-κB）和JAK2-ATAT37信号通路等多种机制导致细胞癌变。酒精可促进肝脏表达IL-17A及其受体IL-17RA，从而促进肝癌的发生[40,41]。相应地，Ma等[40]研究表明，阻断细胞IL-17A通路可抑制酒精喂养小鼠HCC的进展。

6 肠道微生态

酒精可通过多种机制导致肠道微生态失调与肠道屏障功能受损。相应地，肠道细菌、细菌组分与脂多糖（lipopolysaccharides，LPS）等可通过门静脉血流进入肝脏，通过多种机制改善肝脏肿瘤微环境促进肝癌的发生[42-45]。Liu等[46]研究发现肠道来源的LPS通过激活Kupffer细胞上的Toll样受体4（Toll-like receptor 4，TLR4）刺激中性粒细胞外陷阱（neutrophil extracellular traps，NETs）生成，进而上调趋化因子配体2（chemokine ligand 2，CCL2）、细胞周期蛋白B1、细胞周期蛋白B2、TNF-α、白细胞介素-6（interleukin-6，IL-6）和增殖细胞核抗原（proliferating cell nuclear antigen，PCNA）等的表达，促进酒精相关肝癌发生。Dapito等[47]证实了LPS激活的TLR4可通过降低NF-κB通路的激活导致抗凋亡基因*Birc3*、*Birc5*和*Nos2*的表达降低，从而抑制肝细胞的凋亡。此外，TLR4还可诱导干细胞因子NANOG表达，上调IGF2BP3和YAP1水平，具有拮抗抑癌基因*P53*的作用[48]。

综上所述，酒精相关肝癌有其独特的遗传易感性，并与酒精的直接作用、表观遗传学修饰、氧化应激、肿瘤相关免疫异常及酒精导致的微生态紊乱等相关。此外，酒精还可通过影响细胞自噬等多种途径导致肝癌的发生[49-51]。随着酒精导致肝癌负担的不断增长，深入探讨酒精导致肝癌的可能机制有助于发现肝癌治疗的新靶点，切实改善患者预后。

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