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Shijie Huaren Xiaohua Zazhi

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文献综述 REVIEW

肠上皮化生在Barrett's食管进展为食管腺癌中作用的研究进展

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Intestinal metaplasia in progression of Barrett's esophagus to esophageal adenocarcinoma

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Abstract

The incidence of esophageal adenocarcinoma (EAC) has been increasing year by year. The prognosis of EAC is poor, and the 5-year survival rate is less than 20%. Barrett's esophagus (BE) is the only known precancerous lesion of EAC. BE with intestinal metaplasia (IM) has a higher risk of progressing to EAC. Exploring the mechanism of IM and finding targeted therapeutic targets for BE has become an important measure for tumor prevention. Bile acid reflux is considered an important factor in the occurrence of IM and promotes the progression of BE to EAC. However, the molecular regulatory mechanism of bile reflux induced IM and carcinogenesis remains unclear. This article reviews the environment, significance, and cell origin theory of IM, toxic effects of bile reflux, and molecular changes of IM progression to tumor, aiming to improve clinicians' understanding of IM in BE and provide evidence for early intervention of BE and prevention and treatment of EAC.

Key Words: Barrett's esophagus; Intestinal metaplasia; Bile acid; Esophageal adenocarcinoma; Epigenetics

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摘要

食管腺癌(esophageal adenocarcinoma, EAC)的发病率有逐年增加的趋势, EAC预后差, 5年生存率不足20%. Barrett's食管(barrett's esophagus, BE)是目前唯一已知的EAC癌前病变, 伴肠上皮化生(intestinal metaplasia, IM)的BE有更高的风险进展为EAC, 探究IM的发生机制, 寻找BE的针对性治疗靶点, 成为预防肿瘤的重要措施. 胆汁酸反流被认为是IM发生的重要因素, 并促进BE向EAC进展, 但胆汁反流诱导肠化、癌变的分子调节机制尚不清楚. 本文就IM发生的环境、意义、

细胞起源学说, 胆汁反流的毒性作用以及IM向肿瘤进展的分子改变进行综述, 旨在提高临床医师对BE中IM的认识, 为早期干预BE和防治EAC提供证据.

关键词: Barrett's食管; 肠上皮化生; 胆汁酸; 食管腺癌; 表观遗传学

核心提要: 胆汁酸长期反流造成食管黏膜化学性和免疫性损伤, 形成Barrett's食管(barrett's esophagus, BE), 伴有肠上皮化生时易进展为食管腺癌, 其机制可能与尾型同源盒转录因子2、黏蛋白2等激活有关, 测序技术亦发现基因组和表观遗传学改变, 新的生物标记物将用于临床, 成为预防和治疗BE的有用靶点.

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0 引言

食管腺癌(esophageal adenocarcinoma, EAC)作为食管癌的重要病理类型, 近年来发病率有逐年增加的趋势, 尤其在欧美等发达国家, 占食管癌的比例高达2/3, 而在我国EAC约占5%[1-3]. EAC预后差, 5年生存率不足20%, 而Barrett's食管(barrett's esophagus, BE)是目前唯一已知的EAC癌前病变[4], BE的癌变风险约为0.5%[5]. BE定义为内镜下食管鳞柱上皮交界线相对于胃食管结合部上移, 并且组织学证实复层鳞状上皮被化生的柱状上皮所取代, 化生的组织类型分胃底腺黏膜化生、贲门腺黏膜化生和肠上皮化生(intestinal metaplasia, IM)[6], 而伴有IM的BE进展为EAC风险是不伴有IM类型的3倍[5]. 胃食管反流病(gastro-oesophageal reflux disease, GERD)是BE最主要的危险因素[7,8], 随着GERD全球发病率的显著增高[9,10], BE发病率随之增高, 也是欧美等国家EAC发病率迅速增加的原因[8]. 在酸碱反流物的刺激下, 食管上皮发生炎症-修复-炎症的不断循环, 经历正常食管上皮-IM-低级别上皮内瘤变-高级别上皮内瘤变-EAC的发展过程. 目前对BE的治疗主要根据异型增生的程度选择不同的方式, 包括内镜下切除术、消融术、光动力疗法、外科手术等[11,12], 术后复发比较常见[13-16], 主要原因是未有效根除IM[17], 所以研究IM的发生机制, 有利于寻找针对性的治疗靶点, 达到根治BE的目的.

1 肠上皮化生

1.1 化生的定义 化生是一种分化成熟的组织被另一种分化成熟的组织所取代的过程, 是组织面对慢性、持续性损伤的一种适应性反应. 高酸性胃内容物长期反流进入食管下段, 食管的鳞状上皮被胃黏膜样的柱状上皮所取代, 即发生了BE, 因为正常的胃黏膜可以抵抗高酸的伤害, 食管用这种适应性反应免受胃酸和胃蛋白酶的损害.如果损伤持续存在, 化生可进展为异型增生, 甚至恶性肿瘤[18].

1.2 肠上皮化生的分类与意义 IM是指黏膜上皮细胞被肠型上皮细胞所代替的病理形态学改变, 多发生于胃和食管远端, 根据组织形态及分泌黏蛋白的不同分为Ⅰ型、Ⅱ型和Ⅲ型[19]. Ⅰ型, 又称完全小肠型: 由非分泌型的吸收细胞和分泌唾液黏蛋白的杯状细胞组成; Ⅱ型, 又称不完全小肠型, 由少量吸收细胞, 分泌中性和酸性唾液酸黏蛋白的柱状细胞和分泌唾液酸黏蛋白、硫酸黏蛋白的杯状细胞组成; Ⅲ型, 又称不完全大肠型, 由分泌硫酸黏蛋白的柱状细胞和分泌唾液酸黏蛋白或硫酸黏蛋白的杯状细胞组成. 其中, Ⅲ型肠化通常被认为更容易进展为早期癌变[20]. 一项前瞻性研究对Ⅲ型IM患者进行密切随访, 相对于进展期胃癌, 提高了早期胃癌的诊断率[21]. 另一项研究对79例IM患者进行跟踪随访9年, 发现肠化生的改变存在双向性, 明显的逆转或进展, 得出肠化分型不能预测癌症风险的结论[19]. 研究结果的不同, 考虑与活检标本的抽样误差、黏蛋白检测对肠化分型鉴定的可靠性等多种因素有关, 目前尚没有关于BE患者IM分型与EAC关系的研究报道, 所以肠化生分型能否预测癌症风险尚需更多的研究证实.

1.3 BE的细胞起源 关于BE细胞起源及IM是如何发生的一直存在争论[22-24], 主要学说有: (1)食管上皮细胞的转分化, 即在胃食管反流作用下, 成熟的食管鳞状上皮基因重编码, 获得未成熟祖细胞的分化潜能, 表达出柱状上皮的表型[25,26]; (2)具有分化潜能的干/祖细胞通过基因重编码, 改变原有的分化方向, 产生特定的肠上皮柱状细胞, 上皮干/祖细胞的来源有四种推测: a: 食管鳞状上皮基底部的干/祖细胞[27]; b: 食管黏膜下腺管或腺泡的干/祖细胞[28]; c: 循环中骨髓来源的干/祖细胞[29]; d: 食管鳞柱交界或贲门部的柱状干/祖细胞, 包括残留胚胎干细胞[30,31]. 从发病机制上来讲, 无论哪一种来源的干/祖细胞, 都需要获得或保持柱状表型, 进而发生IM. 从鳞状到柱状表型的转换或保持柱状表型可能需要下调鳞状细胞的转录因子如性别决定基因相关转录因子2(sex determining region Y-box 2, SOX2)、P63等, 激活柱状细胞的转录因子如SOX9等, 随后可能是肠道和黏蛋白相关转录因子如尾型同源盒转录因子1(caudalrelated homeobox transcription factor 1, CDX1)、CDX2、叉头转录因子A2(forkhead transcription factor A2, FOXA2)等的激

活[24]. 研究BE细胞起源将有助于开发针对BE患者的治疗干预措施, 以阻止或逆转化生或恶性进展. 以上BE细胞起源推测大都来自小鼠模型获得的实验结果, 但这些细胞群能否代表人类BE患者独特的细胞起源仍不清楚, 也不能完全解释患者的一些临床观察结果. 所以, 关于BE细胞起源的研究需要开辟新的思路, 将小鼠模型研究与临床观察相结合, 应用先进的实验技术, 进一步探究和分析.

2 胆汁酸在BE肠上皮化生发生中的作用

2.1 反流液中胆汁酸成分 胆汁酸在肝脏合成后, 大部分与甘氨酸或牛磺酸结合形成结合型胆汁酸进入胆囊中储存, 在食物的刺激下由胆道排入肠道, 在肠道细菌分泌的胆盐水解酶作用下, 水解形成次级胆汁酸, 约95%胆汁酸被肠壁重吸收, 经门静脉回流入肝, 被肝细胞再次利用, 该过程称作胆汁酸的肠肝循环. 而在GERD中胆汁反流的主要成分是十二指肠液, 没有经过胆盐水解酶的作用, 所以反流液中以结合型胆汁酸为主[32]. 一项以超高效液相色谱－三重四极杆质谱定量人胃液胆汁酸的研究证实了这一观点, 对胃液中23种胆汁酸进行检测, 结果与无胆汁反流组相比, 胆汁反流组13种结合胆汁酸定量显著增高[33]. 另一项研究, 应用改良的高效液相色谱法测定食道样品的胆汁酸含量, 正常、轻度食管炎、糜烂性食管炎、BE组胆汁酸峰值浓度中位值分别为(0、14、124、181) μmol/L, 胆汁酸成分以初级胆汁酸为主, 但在糜烂性食管炎及BE组次级胆汁酸, 如脱氧胆酸、牛黄脱氧胆酸显著增高[34]. 反流液中含有次级胆汁酸, 考虑为胆汁反流经过胃时, 胃内细菌作用的结果, 该推论尚需进一步的实验研究来证实.

2.2 胆汁酸的毒性作用 不同的pH值会影响胆汁酸的浓度, 高pH值下胆汁酸呈离子状态, 对黏膜无损伤; 低pH值下胆汁酸形成结晶; 所以pH3-6被称作危险区, 胆汁酸处于可溶解的非离子状态, 胆汁酸浓度高, 易对食管上皮超微结构造成损伤, 同时胆汁酸也能够增加H+的渗透性, 而次级胆汁酸可以在不依赖于酸的情况下对黏膜造成损伤[34,35]. 传统观念认为酸性胆盐对食管上皮以腐蚀性化学损伤为主, 主要破坏细胞间紧密连接, 造成细胞通透性增加而死亡, 从腔表面发展到组织深层, 一项体内外研究表明, 酸性胆盐通过诱导食管上皮细胞分泌白介素-8、白介素-1β等趋化因子引起免疫损伤[36]. 酸性胆盐通过直接激活上皮内炎症信号转导通路, 破坏食管黏膜上皮屏障功能[37]. 弱酸性胆盐可引起BE上皮细胞氧化性DNA损伤, 从而促进肿瘤的发生[38]. 以上研究表明, 胆汁酸在BE的发生、发展中起到非常重要的破坏作用.

2.3 胆汁酸诱导肠上皮化生相关转录因子 胆汁酸可诱导IM, 目前涉及IM的关键因子包括CDX2、黏蛋白2(mucin2, MUC2)等. CDX2是一种肠特异性的核转录因子, 能够维持肠上皮的正常增殖与分化, 一般只在肠上皮、胰腺导管和腺泡上皮中表达, 在食管和胃粘膜上皮中不表达. MUC2又称肠型黏液, 是一种分泌型黏蛋白, 主要分布在小肠腺上皮、涎腺上皮、乳腺上皮, 附着在肠道表面形成黏液层, 起到润滑及拮抗致病菌侵袭的作用. 临床研究表明, 与正常、反流性食管炎、食管腺癌患者相比, BE患者组中CDX2、MUC2表达显著增高, CDX2表达是IM的始动因素, MUC2表达是IM的晚发事件[39,40]. 有研究者用胃全切+食管十二指肠吻合术构建BE大鼠模型, 食管组织中CDX2、MUC2表达显著增高, 与其检测的临床BE患者标本结果一致[41]. 一项对BE患者来源的正常食管鳞状上皮细胞的体外实验表明, 酸和胆盐可通过核易位和NF-κB p50亚基的结合激活CDX2 mRNA的表达, 使CDX2、MUC2蛋白表达显著增高[42]. 我国一项回顾性研究分析了453例BE患者临床和病理资料, 发现伴杯状细胞比不伴杯状细胞的BE患者食管异型增生显著增高, 轻度较中度异型增生BE患者食管杯状细胞数显著增高, 从而得出结论, BE异型增生可能与杯状细胞的出现有关, 杯状细胞的减少或消失或许提示BE疾病的进展[43]. 在结直肠癌患者中, CDX2的表达缺失被认为是生存期预后不佳的生物学标志[44,45]; 在胃癌患者中, CDX2高表达者, 预后相对好, 而CDX2低表达或无表达的胃癌患者往往生存期较短[46,47]. 以上CDX2低表达考虑与异型细胞分化程度低, 不能维持肠上皮表型有关, EAC中CDX2表达减低可能与之存在相同的机制, 具体涉及的调节因子和信号转导通路尚需进一步的研究.

3 BE中肠上皮化生向肿瘤进展的分子改变

目前先进的诊断技术可以评估每个个体的遗传和表观遗传信息, 个体化医疗也将有望成为最有效的诊断和治疗方法之一[48], 越来越多的分子生物学标记物被发现用来诊断消化道肿瘤[49]. 既往BE诊断依赖于内镜检查和组织病理学检测, 2022年ACG指南推荐, 对于有反流症状或危险因素的患者, 一种可吞咽的、非内镜胶囊海绵装置, 结合一种分子生物学标记物, 可以用来替代内镜诊断BE, 可能的分子生物学标记物包括IM相关蛋白三叶因子3(trefoil factor 3, TFF3)和BE黏膜相关甲基化DNA标记(methylated DNA markers, MDMs)[12]. 研究表明BE不是简单的组织肠化生, 而是发生了频繁的基因突变, BE和EAC共同的分子改变包括基因组改变、表观遗传学的改变, 多条信号通路参与BE的发生、发展[50].

3.1 基因组改变 一项规模较大的研究对112个EAC患者进行全基因组测序和外显子组测序, 通过鉴定选择了

26个显著变化的突变基因, 然后筛选79个BE患者的109个活检组织进行检测, 包括不伴异型增生的BE(never-dysplastic barrett's esophagus, NDBE)66例和伴重度异型增生的BE(high grade dysplasia, HGD)43例, 结果显示TP53和SMAD4在BE和EAC之间的突变率存在显著差异, 且具有分期特异性, 对于TP53, 2.5%的NDBE发生突变, 70%的HGD和EAC发生突变, 对于SMAD4, 仅在13%的EAC中发现突变; 因此, 将TP53作为生物标记物, 有利于辨别HGD的BE患者, 从而进行内镜下治疗, 阻断其向EAC进展[51]. 值得注意的是, 在EAC患者中反复突变的基因, 即使在良性NDBE患者中也发生频繁的突变, 而极少数的NDBE患者才会发展成EAC, 基因突变在肿瘤发展过程中究竟如何起作用的, 需要更深入的研究[52].

另一项研究对149个EAC患者进行测序, 发现26个基因突变与EAC有关, 其中突变最多的基因是TP53和周期蛋白依赖激酶抑制因子2A(cyclin-dependent kinase inhibitor 2A, CDKN2A), 分别有72%和12%的病例发生突变, 并发现在AA二核苷酸上发生A→C转位突变[53]. 基因突变的原因尚不清楚, 有假设认为与胆汁酸暴露和诱导氧化性DNA损伤有关[54-56]. 这些研究揭示了EAC和BE中普遍存在基因突变, 究竟哪些改变在BE→EAC发展中起潜在的驱动作用, 尚需要进一步研究, 以期发现BE治疗的早期靶点.

3.2 表观遗传学改变 表观遗产学改变是指非DNA序列变化介导的基因表达中稳定的、可遗传的改变, DNA甲基化是关键的表观遗传机制之一. 在许多不同的癌症类型中, 已经证明CpG岛的高甲基化会导致肿瘤抑癌基因的沉默, 而低甲基化则与癌基因表达的增加和基因组不稳定性相关[57]. 在EAC中, 多个研究表明CpG岛甲基化程度的显著变化[58,59]. 一项来自英国的回顾性队列研究, 通过甲基化、转录组和基因组测序以及临床数据的整合分析, 确定了与患者预后和潜在治疗反应相关的4个甲基化亚型, 其中亚型1的特征是DNA高甲基化, 突变负担高, 细胞周期、受体酪氨酸信号通路中基因多重突变, 在亚型1的17例BE患者中, 15例为重度异型增生或粘膜内癌; 亚型3有包括巨噬细胞、中性粒细胞、肿瘤相关纤维母细胞等免疫细胞的浸润, 癌基因MDM2的高扩增率, 与免疫治疗的耐药性和肿瘤的快速进展相关, 决定了该肿瘤类型生存期最短[60]. DNA甲基化的研究为BE诊断和治疗提供了新靶点, 更多的生物标记物将用于临床, 造福BE患者.

微小RNA(microRNA, miRNA)是一种小的非编码RNA, 参与基因转录后的表达调控[61]. 很多研究表明, miRNA在BE和EAC的发生发展中起重要作用[62-64]. 早期的一项研究, 通过miRNA测序分析, 鉴定出与BE癌变过程相关的23个miRNA, 对BE患者随访至少5年, 结果证实, 与未进展到EAC的患者相比, 进展到EAC的BE样本中, miR-192、194、196a和196b的表达显著升高[65]. 另一项包括EAC在内的食管癌的近期研究表明, miR-196b是食管癌中上调最多的miRNA之一, miR-196b可以直接靶向作用于肿瘤抑制因子EPHA7, 保留EPHA2的活性, 而EPHA2是上皮-间质转化和MAPK/ERK通路中的关键分子, 从而介导食管癌对放化疗的耐受性[66]. 以上发现证明miR-196b是食管癌治疗的一个强有力的候选分子靶点.其他研究表明, miRNA21、miRNA375等在BE和EAC的发生发展过程中也发挥重要作用[67,68].

关于BE患者是否进展为癌症的前瞻性研究很少, 一项来自西雅图的研究显示, BE非进展者的基因组通常只有小的局部缺失, 产生很少的遗传多样性, 在长时间的随访中保持相对稳定; 而BE进展者逐渐出现染色体不稳定性、基因组多样性、体细胞染色体改变的选择和灾难性的基因组加倍[69]. 基因改变和表观遗传学改变在BE向EAC进展中的具体作用机制尚不清楚, 需要进一步研究, 以期发现BE治疗的新靶点.

3.3 相关信号通路 研究表明, 多种信号通路参与BE→EAC的进展, 主要包括转化生长因子-β(TGF-β)通路[70,71]、Hedgehog(Hh)通路[72]、Notch信号通路[73]、Wnt信号通路[74]等. 较近的一项研究表明, 脱嘌呤脱嘧啶核酸内切酶1/氧化还原因子-1(apurinic/apyrimidinic endonuclease 1/redox effector factor-1, APE-1/REF-1)在EAC中高表达, 在酸性胆盐诱导的BE中一过性高表达, 通过过表达和基因敲除技术证明, APE-1/REF-1可通过激活EGFR-STAT3信号轴, 在酸性胆盐诱导的BE→EAC发展中起重要作用[75]. 最新的一项研究, 通过体内/外实验表明, 在BE小鼠模型中, Notch信号通路可激活NF-κB, 调节贲门祖细胞分化; 在人类食道组织中, BE进展到EAC与杯状细胞密度降低和Notch表达水平升高有关, 阻断这一途径可能被临床用来预防BE患者向EAC进展[73]. 另有研究表明, 在EAC细胞中, 脱氧胆酸通过IL-6/STAT3通路上调KLF4和OCT4表达, 对食管干细胞起到恶性诱导作用[76]. 参与BE→EAC进展的信号通路繁多, 究竟哪条信号通路起主导作用, 能成为阻断BE进展的有效靶点, 需要更多的基础和临床研究.

4 结论

胆汁酸长期反流造成食管黏膜化学性和免疫性损伤, 鳞状上皮逐渐被化生的柱状上皮所代替, 即发生了BE, 伴有IM时进展为EAC的几率增加, 然而, 胆汁酸是如何诱导食管IM发生的, 目前研究发现与CDX2、MUC2等多个转录因子的激活有关, 但具体调控机制尚不清楚, 需

要更多的研究进行探讨. 随着全基因组测序技术的出现, 越来越多的研究表明, 在BE向EAC进展过程中发生了基因组和表观遗传学改变, 包括DNA甲基化和mi RNA等的改变, 随着研究的深入, 越来越多的生物标记物将用于临床, 成为预防和治疗BE的有用靶点.

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