

## EBV相关性胃癌研究进展

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### Advances in research of Epstein-Barr virus-associated gastric carcinoma

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### Abstract

Epstein-Barr virus-associated gastric carcinoma (EBVaGC) as a unique kind of gastric cancer that has been gradually recognized in recent years. It accounts for about 10% of all gastric cancers. In this review, we will focus on the relevant research on the epidemiology, histopathologic features, pathogenesis, treatment and prognosis of EBVaGC. The underlying mechanisms of EBVaGC has not been thoroughly elucidated, and there has been no consensus on the diagnosis and treatment of this unique form of gastric cancer. Therefore, further research is necessary to better understand the progression and treatment of EBVaGC.

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Key Words: Epstein-Barr virus; EBV-associated gastric cancer; Histopathologic features; Pathogenesis; Treatment; Prognosis

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### 摘要

胃癌细胞中存在Epstein-Barr病毒(Epstein-Barr virus, EBV)者被称为EBV相关性胃癌(Epstein-Barr virus-associated gastric carcinoma, EBVaGC)。近年来EBVaGC作为一种独特的分子亚型疾病逐渐被人们所认知, 全球胃癌患者中平均有10%者为

### ■背景资料

Epstein-Barr病毒(Epstein-Barr virus, EBV)与很多恶性肿瘤有关, 如Burkitt淋巴瘤、经典的Hodgkin淋巴瘤、鼻咽癌、喉癌。其属γ-疱疹病毒科, 含184 kbp双链DNA, 其基因组约有172000个碱基, 90%以上的人在青春前期潜伏感染并成为终生携带者。研究表明, EBV是引起胃癌(gastric carcinoma, GC)的重要生物学因素之一, 尤其是胃腺癌, 1993年Tokunaga等将经EBV早期RNA原位杂交证实GC细胞EBER阳性者定义为EBV相关GC。

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## ■ 研究前沿

目前有很多学者对EBV的致癌机制进行了大量的研究, 证明基因甲基化、突变、扩增、失活等可能是其致癌的重要机制. 研究表明EBV相关性胃癌(Epstein-Barr virus-associated gastric carcinoma, EBVaGC)与普通GC不同, 男性为好发人群, 贲门为好发部位, 淋巴转移率低, 预后较好等, 但其研究尚不明确, 且尚无临床诊疗规范与共识, 也带来了新的挑战 and 机遇.

EBVaGC. 本文对EBVaGC近年来在流行病学、临床病理特征、发病机制、治疗及预后等方面的研究进展作一综述. 但目前对EBVaGC的研究尚不明确, 且尚无临床诊疗规范与共识, 也带来了新的挑战 and 机遇.

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关键词: Epstein-Barr病毒; EBV相关胃癌; 病理特征; 机制; 治疗; 预后

**核心提要:** Epstein-Barr病毒(Epstein-Barr virus, EBV)是引起胃癌的重要生物学因素之一, EBV相关性胃癌(Epstein-Barr virus-associated gastric carcinoma, EBVaGC)作为一种特殊类型的胃癌, 对其研究尚不明确. 本文通过复习相关文献, 对EBVaGC近年来在流行病学、临床病理特征、发病机制、治疗及预后等方面的研究进展作一综述.

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## 0 引言

Epstein-Barr病毒(Epstein-Barr virus, EBV)是50余年前从伯基特淋巴瘤发现的<sup>[1,2]</sup>, 是第1个被发现的能够引起人类肿瘤病毒<sup>[1,3]</sup>. 它是一种由长度约170 kb双链DNA组成的γ疱疹病毒, 在感染细胞的细胞核中维持自身的附加型环状DNA而不产生病毒颗粒, 并且不会整合到宿主基因组中<sup>[4,5]</sup>, 约90%的健康人可终身携带而无症状<sup>[6]</sup>. 目前被归类为1型致癌物, 是因其与各种癌症如鼻咽癌、胃癌等有关<sup>[7]</sup>. EBV在1990年首次被发现存在于胃癌(gastric carcinoma, GC)细胞中<sup>[8]</sup>, 近年来EBV和GC之间的关系已成为研究热点.

## 1 流行病学

越来越多的研究<sup>[9-12]</sup>表明, EBV感染会增加GC的风险, 且约10%的GC患者中携带EBV. EBV相关性胃癌(Epstein-Barr virus-associated gastric carcinoma, EBVaGC)是一种独特的分子亚型疾病<sup>[13]</sup>, 在全球GC患者中不同国家的患病率从1.3%到20.1%不等<sup>[13-16]</sup>. 在我国, 北方的EBVaGC患病率为7.0%(13/185)<sup>[17]</sup>, 也有更大

的调查表明其为6.1%(102/1678)<sup>[18]</sup>, 而在胃残留瘤(手术后至少5年发生在胃残端的良性疾病如胃溃疡和十二指肠溃疡)中这一比例更高. 如在日本为(27.1% vs 6.4%)<sup>[19]</sup>, 荷兰为(35% vs 8%)<sup>[20]</sup>, 韩国为(29% vs 6%)<sup>[21]</sup>, 但我国华南地区为(30.8% vs 6.7%)<sup>[22]</sup>.

## 2 机制研究

**2.1 EBVaGC与相关基因甲基化** 据报道, EBVaGCs的主要机制是GC相关基因的启动子区CpG岛甲基化<sup>[23]</sup>, 如*p14ARF*、*p15*、*p16INK4A*、*p73*、*TFF1*、*TIMP3*、*DAPK*、*GSTP1*等基因的启动子区<sup>[24,25]</sup>. 这种CpG岛高甲基化导致与GC发生有关的许多肿瘤抑制基因表达水平下调. Matsusaka等<sup>[26]</sup>揭示了EBV对DNA甲基化的全基因组作用, 并分为EBV-和低甲基化、EBV-和高甲基化、EBV+和广泛高甲基化三组. 因此, CpG甲基化在EBVaGC并不是随机的. 这种广泛甲基化, 提供了病毒控制细胞功能的可能, 并促进病毒的持久性繁殖<sup>[27,28]</sup>, 而EBV组蛋白的翻译后修饰进一步促进甲基化, 参与EBVaGC的发展<sup>[29]</sup>. EB病毒*Zebra*基因(EBV *BZLF1*)是第1个表现出优先结合甲基化启动子以诱导基因表达的蛋白质, 他克服了转录沉默, 将受感染的细胞从病毒潜伏转变为有活性的裂解性病毒复制<sup>[30]</sup>. 已报道<sup>[31]</sup>EBV潜伏膜蛋白2A(latent membrane protein 2A, LMP2A)的表达也可能通过诱导信号转导、转录激活因子3(signal transducer and activator of transcription 3, STAT3)磷酸化及DNA甲基转移酶1[human DNA (cytosine-5)-methyltransferase 1]的转录而进一步促进DNA甲基化.

**2.2 EBVaGC与基因突变、扩增、失活** 研究发现, 在EBVaGC中存在着不同程度的基因突变, 其中最突出的是*PIK3CA*, 这种突变存在于80%的EBVaGC中<sup>[32]</sup>, 其他基因如*BCOR*、*CTNBN1*、*APC*、*p53*、*STK11*、*CDKN2A*等<sup>[33]</sup>. EBVaGC的另一个新的特征是频繁的18q损失和9p24.1的复发性扩增<sup>[34]</sup>, 这种扩增与Janus激酶2、CD274[即程序性死亡受体-1(programmed cell death-1, PD-L1)]和PDCD1LG2[即程序性死亡受体-2(programmed cell death-2, PD-L2)]的表达水平升高有关<sup>[35]</sup>, 因由CD274和PDCD1LG2编码的PD-L1和PD-L2的升高会介导肿瘤从宿主免疫应答逃逸<sup>[36]</sup>. 此外, *ARID1A*功能的缺失

可能参与了EBVaGC发生,也可能与淋巴细胞入侵、淋巴结转移、错配修复缺陷及不良预后相关<sup>[37,38]</sup>,而*p16/CDKN2A*基因的失活在几乎所有EBV相关的上皮癌中均可以检测到<sup>[35]</sup>。同时,Chen等<sup>[39]</sup>发现EBVaGC组织中SNHG8表达比EBV阴性胃癌(EBV-negative gastric carcinoma, EBVnGC)组织表达上调25倍( $P = 0.027$ ),SNHG8可能作为一个原癌基因,参与GC的发生发展,同时EB病毒感染胃黏膜可能促进SNHG8的表达。

**2.3 EBVaGC与miRNA功能** miRNA是长约22个核苷酸的小分子非编码RNA,EBV是第1个被发现能编码miRNA的人类病毒。EBV可通过编码miRNA抑制有效的宿主免疫应答或通过阻断凋亡过程而感染细胞<sup>[40]</sup>。EBV编码的miRNA主要分为两簇:即BHRF-1和BART, BHRF-1簇包含4个成熟miRNA,其仅在溶解感染的细胞或具有潜伏III型感染的细胞中表达, BART簇位于BART的非编码区,并进一步细分为亚簇1和2,其总共包括38个成熟EBV miRNA,且miRNA ebv-miR-BART2-5p和ebv-miR-BART2-3p位于这两个簇的下游。EBV miRNA在EBVaGC细胞中表达程度各异,其中ebv-miR-BART1-3p, 2-5p, 3-3p, 4-5p, 5-5p, 7-3p, 9-3p, 10-3p, 17-5p和18-5p相对高水平表达<sup>[41-44]</sup>。研究<sup>[45]</sup>还发现在EBVaGC中,miRNAs hsa-miR-200a和hsa-miR-200b两种分子均被下调,导致E-钙黏蛋白表达减少并触发上皮-间质转化。

### 3 病理特点

近期,癌症基因组谱将GC分为4种亚型:EBV阳性(即EBVaGC),微卫星不稳定型,基因组稳定性和染色体不稳定型<sup>[35]</sup>。EBVaGC作为一个特定的亚型,具有其独特的病理特点。

研究表明,EBVaGC与年龄有强相关性,大多数患者均在60岁或以下<sup>[46-49]</sup>,且具有男性优势<sup>[7,15]</sup>。根据15952例的Meta分析<sup>[50]</sup>,男性EBVaGC的发生频率高于女性患者,但也有研究<sup>[51]</sup>表明年龄和EBVaGC之间没有显著的相关性。此外,EBVaGC好发于胃的近端(胃的贲门部和胃体),而普通型GC好发于胃窦部<sup>[7,52]</sup>,常形成溃疡或茶碟样团块,其胃壁明显增厚<sup>[53]</sup>。组织学上,EBVaGC的特征在于在肿瘤内或肿瘤周围有着明显的免疫细胞浸润<sup>[54]</sup>,通常伴有大量淋巴细胞浸润<sup>[55]</sup>。

### 4 诊断

目前,胃癌诊断方法包括实验室诊断(胃蛋白酶原、胃泌素-17、GC标志物等)、放射学检测(X线检查、CT检查)、内镜检查(普通内镜、超声内镜、放大内镜、色素内镜等),EBVaGC的诊断除上述方法,还有其新的诊断指标。EBVaGC通常缺乏TP53突变,因此TP53免疫染色已作为组织病理学诊断方法之一<sup>[56]</sup>。EBV血清学标志物(即抗EBV抗体)检测是另一种诊断方法。研究<sup>[57,58]</sup>发现EBVaGC中的VCA IgG平均滴度高于EBV阴性病例和对照组病例。此外,长链非编码RNA已被确定在GC中具有重要作用,SNHG8可作为EBVaGC诊断的候选生物标志物<sup>[59]</sup>。对于免疫学诊断而言,PD-L1/PD-1似乎是EBVaGC诊断的关键<sup>[60]</sup>。

### 5 治疗

目前,针对EBVaGC尚无特异性治疗,关键在于早防早治。在早期阶段,EBVaGC倾向于在黏膜下层形成良好分界的结节性病变,与EBVnGC相比具有较少的纤维化,这有利于肿瘤的内窥镜黏膜下切除术<sup>[61]</sup>。除了传统治疗方法,应用新的抗病毒药、基因、免疫、靶向分子治疗等方法也为GC治疗提供了新的机遇。体外证据表明可以应用药物逆转去甲基化,如5-氮杂胞苷加苯基丁酸等,但其临床疗效却不佳<sup>[62]</sup>。靶向分子疗法已逐渐成为癌症治疗的潜在方案。磷酸肌醇特异性磷脂酶C $\gamma$ (phospholipase C $\gamma$ , PLC $\gamma$ )参与调节肿瘤生长和转移,体外动物实验表明通过用慢病毒介导的PLC $\gamma$ 1基因短发夹RNA(short hairpin RNA, shRNA)载体转导PLC $\gamma$ 1,可致GC生长和转移减少。此外,Akt、ERK、Bad和S6信号分子的磷酸化参与PLC $\gamma$ 1介导的肿瘤生长及GC细胞的转移。数据<sup>[63]</sup>表明,通过Akt/Bad、ERK/Bad和Akt/S6信号轴,PLC $\gamma$ 1信号通过shRNA的消除可有效抑制GC的生长和转移,这意味着PLC $\gamma$ 1是治疗GC的潜在靶点。研究<sup>[32]</sup>表明,EBV阳性癌症具有活化的骨形态发生蛋白(bone morphogenetic protein, BMP)信号,提示BMP/SMAD途径也可作为潜在的治疗靶点。此外,血管生成常被看作是一种恶性的标志,血管生成已成为常见的治疗靶点<sup>[64]</sup>,血管内皮生长因子受体(vascular endothelial growth factor receptor, VEGFR)-靶向抗体已被证实有抗GC的作用<sup>[63]</sup>。EBVaGCs

### ■ 相关报道

目前,对EBVaGC的研究主要在于发病机制的研究,重点基于基因及蛋白,可检索相关文献阅读。病理方面EBVaGC好发于胃的近端(胃的贲门部和胃体),常形成溃疡或茶碟样团块,其胃壁明显增厚有着明显的免疫细胞浸润。



# 创新盘点

本文复习近年来相关文献,从流行病学、临床病理特征、发病机制、治疗及预后等方面对EBVaGC的研究进展予以综述。

常伴有大量CD8<sup>+</sup>细胞毒性T细胞浸润,而调节性T细胞被认为是抗肿瘤免疫的关键<sup>[65]</sup>,他可通过抑制自体CD4<sup>+</sup>辅助T细胞和CD8<sup>+</sup>效应T细胞在抑制T细胞介导的抗肿瘤免疫中起重要作用<sup>[66]</sup>。PD-1/PD-L1(一种T细胞共抑制受体)在癌细胞从宿主免疫系统中逃逸中有重要作用,且在EBVaGCs中过表达,可能作为免疫治疗靶点之一<sup>[67]</sup>。到目前为止,只有两种生物疗法可改善患者的总体生存,即曲妥单抗和雷莫芦单抗,前者是一种重组DNA衍生的人源化单克隆抗体,可选择性地作用于人表皮生长因子受体-2的细胞外部位,后者是一种特异性阻断VEGFR2及下游血管生成相关通路的人源化单克隆抗体<sup>[68,69]</sup>。裂解诱导治疗是促进受感染细胞破坏的有效手段<sup>[70]</sup>,放射治疗和选择性药物诱导裂解病毒基因表达,增强外源蛋白的免疫识别力也是一种潜在的治疗方法<sup>[71,72]</sup>。目前,组蛋白脱乙酰酶抑制剂是活性病毒复制的最有效的诱导剂<sup>[73]</sup>,短链脂肪酸如丁酸盐也是良好诱导剂。

## 6 预后研究

EBVaGCs的预后目前是有争议的。一项4599例的荟萃分析显示EBVaGC患者的生存期比EBVnGC的患者长<sup>[74]</sup>,一些研究也表明与EBVnGC相比,EBVaGC的预后相对较好<sup>[75-78]</sup>,但其他研究未能观察到这种预后差异<sup>[51]</sup>。因此,有关EBVaGCs的预后问题仍需大宗数据的统计来验证。

## 7 结论

GC是世界上第四大最常见的癌症,在全球范围内其在经济和社会方面都造成重大的公共卫生负担<sup>[79]</sup>。EBVaGC作为一种特殊类型的GC,具有独特的生物学行为。目前,尽管对EBVaGC的研究很多,但大多尚在实验室研究阶段,一些新型的诊疗手段很难在临床推广应用,且尚无临床诊疗规范与共识,这也带来了新的机遇和挑战。

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#### 应用要点

目前对EBVaGC的研究尚不明确,且尚无临床诊疗规范与共识,也带来了新的挑战 and 机遇,需进一步制定临床诊疗规范与共识来应用于临床诊疗。

## ■名词解释

Epstein-Barr病毒 (EBV): 又称人类疱疹病毒4型。在性病临床上是 Epstein 和 Barr 于 1964 年首次成功地将 Burkitt 非洲儿童淋巴瘤细胞通过体外悬浮培养而建株, 并在建株细胞涂片中用电镜观察到疱疹病毒颗粒, 故名 Epstein-Barr 病毒; EBV 相关性胃癌 (EBVaGC): 指 GC 细胞中存在 EB 病毒, 癌症基因组谱将 GC 分为 4 种亚型: EBV 阳性 (即 EBVaGC)、微卫星不稳定型、基因组稳定性和染色体不稳定型。EBVaGC 作为一个特定的亚型, 具有其独特的病理特点。

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#### 同行评价

本文选题新颖, 文章脉络清晰, 对EBVaGC的流行病学、临床病理特征、发病机制、治疗及预后等方面做了详细的综述, 对加深EBVaGC的认识有很大意义, 对临床有一定参考价值。

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