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评 述 EB病毒发现60周年: 回顾与展望专题

EB病毒与鼻咽癌研究进展

王颢钧[1,2], 肖倍倍[1,2], 马骏[1,3*], 麦海强[1,2*], 唐林泉[1,2*]

1. 华南恶性肿瘤防治全国重点实验室, 广东省鼻咽癌诊治研究重点实验室, 广东省恶性肿瘤临床医学研究中心, 中山大学肿瘤防治中心, 广州 510060;
2. 中山大学肿瘤防治中心鼻咽科, 广州 510060;
3. 中山大学肿瘤防治中心放疗科, 广州 510060
* 联系人, E-mail: tanglq@sysucc.org.cn; maihq@sysucc.org.cn; majun@sysucc.org.cn

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摘要 鼻咽癌(nasopharyngeal carcinoma, NPC)是原发于鼻咽黏膜上皮的恶性肿瘤, 好发于鼻咽隐窝、侧壁和顶后壁. 其多发于东南亚和我国南方地区, 发病率较稳定. 鼻咽癌的发病危险因素包括EB病毒(Epstein-Barr virus, EBV)感染、遗传因素及环境因素等, EBV在鼻咽癌的发病中占有重要作用. 鼻咽癌早期症状不明显, 主要依靠鼻内镜病理活检与MRI, PET/CT检查等方式明确诊断与分期. 目前, 放射治疗是鼻咽癌主要的根治性治疗手段, 综合运用化疗与免疫治疗可以提高其疗效. EBV相关标志物在鼻咽癌筛查、预后评估、疗效监测与随访等方面被广泛应用. 本文综述了EBV与鼻咽癌发病机制以及临床诊治方面的密切联系, 并展望了未来鼻咽癌与EBV相关研究的机遇与挑战.

关键词 鼻咽癌, EB病毒, 发病机制, 综合治疗, 生物标志物

鼻咽癌(nasopharyngeal carcinoma, NPC)是起源于鼻咽黏膜上皮的恶性肿瘤, 其发病与EBV感染密切相关. 鼻咽癌具有明显的地区聚集性, 好发于东亚与东南亚[1]. 我国是鼻咽癌高发地区, 新发病例约占全球新增病例的47.7%, 其中, 广东省的发病率最高, 每年的平均发病率约为20~30/100000[1~3]. 鼻咽癌根据病理类型可分为三种亚型: 角化性鳞状细胞癌、非角化性癌以及基底样鳞状细胞癌[4]. 非角化性癌又根据肿瘤细胞的分化程度分为分化型和未分化癌[4], 未分化非角化型癌在流行地区占绝大多数[5]. 鼻咽癌发病的危险因素包括遗传因素、环境因素与EB病毒(Epstein-Barr virus, EBV)感染. 其中, EBV感染与未分化非角化型鼻咽癌密切相关.

EBV又称人类疱疹病毒4型(human herpesvirus 4, HHV-4), 在人群中的感染率超过95%[6]. 其最早在Burkitt淋巴瘤中被发现, 已被证实与多种恶性肿瘤的发生有关[6,7]. 与其他疱疹病毒相似, EBV有两个明显的生命周期阶段——潜伏期和裂解期. 其中, 潜伏性是EBV的一个重要特征, 病毒在人体内建立终身潜伏, 只有零星的再激活和裂解性复制. 其潜伏感染的基因产物在鼻咽癌的发生与进展过程中发挥了重要作用[8].

由于EBV在鼻咽癌的发生与发展过程发挥重要作

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用，因此本文将对EBV与鼻咽癌发病机制、诊断、治疗等方面的密切关联进行综述，并对未来鼻咽癌与EBV相关研究的机遇与挑战进行展望. EBV与鼻咽癌相关研究未来将聚焦于揭示肿瘤微环境互作机制、优化EBV相关标志物协助诊治方法、开发基于EBV的新型免疫治疗方法和肿瘤疫苗等方向，从而推动个体化精准治疗鼻咽癌的新突破.

1　鼻咽癌的危险因素与发病机制

1.1　危险因素

鼻咽癌的危险因素有遗传因素，环境因素以及EBV感染. 位于6p21染色体的Ⅰ类主要组织相容性复合体(major histocompatibility complex 1, MHC-I)区域的*HLA*基因被认为是与鼻咽癌风险关联最强的基因位点[9,10]. 此外, 全基因组关联研究和全外显子组测序鉴定出多种MHC区域外的鼻咽癌易感位点[11]. EBV感染与流行区的鼻咽癌风险尤为密切相关. Xu等人[12]鉴定了EBV高危亚型，并发现了EBV基因组中的两个非同义*BALF2*变异体与鼻咽癌的高发病风险相关, 两个变异体的累积效应占中国南方鼻咽癌总风险的83%. 在环境因素中，一些腌制食品、口腔卫生以及主动与被动吸烟都被发现与鼻咽癌发病风险升高有关[13~15].

1.2　发病机制

EBV在流行地区的鼻咽癌未分化癌的发病中起到重要作用[2,8]. EphA2被认为在EBV感染上皮细胞的过程中发挥关键作用，它可以直接结合EBV糖蛋白gB和gH/gL并促进EBV内吞和融合，而且EphA2胞外段的EBD和FNR结构域对其介导EBV感染极为关键. 除EhpA2外，既往的研究还鉴定了鼻咽上皮细胞上的另外两种受体——神经纤毛蛋白-1(neuropilin-1, NRP1)、非肌肉肌球蛋白重链IIA(non-muscle myosin heavy chain IIA, NMHC-IIA), 它们分别与EBV糖蛋白gB和EBV糖蛋白gHgL结合，促进EBV进入上皮细胞[16,17]. 此外，研究发现, EBV感染原代上皮细胞通常会导致生长停滞，而癌前鼻咽上皮细胞的遗传改变可能会逆转EBV感染的生长抑制作用，以支持鼻咽上皮细胞中稳定和潜伏的EBV感染[8,18].

目前的观点认为，癌前鼻咽上皮细胞的基因突变是EBV稳定感染建立的前提(图1). 这种感染以Ⅱ型潜伏感染为特征, 是鼻咽癌发病的重要驱动因素. 癌前基因突变主要包括染色体3p和9p上端粒酶活性的激活、

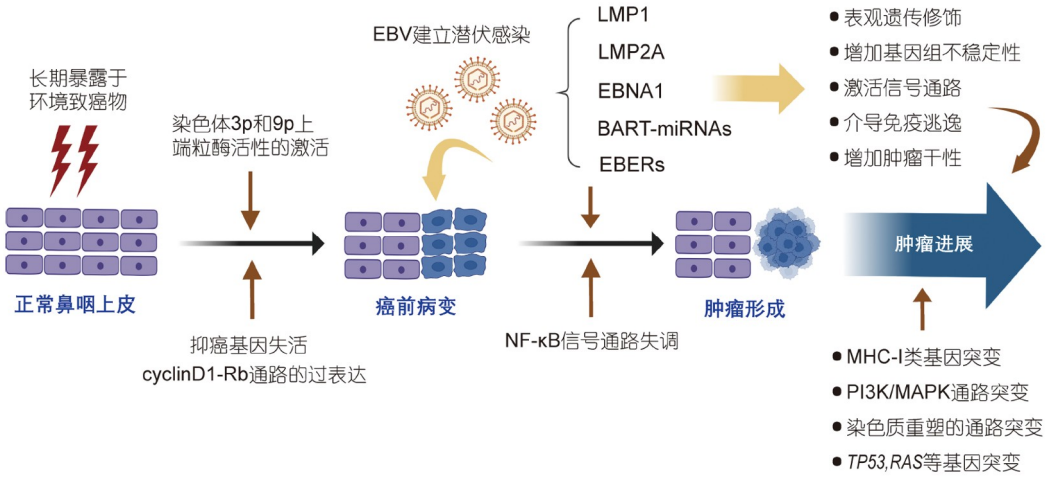

图 1　EBV感染等因素导致鼻咽癌发生与进展模式图. 抑癌基因突变与环境致癌物暴露等因素共同导致鼻咽上皮癌前病变, 为EBV在鼻咽上皮建立稳定潜伏感染创造条件. EBV持续潜伏感染的多种基因产物, 主要包括LMP1, LMP2, EBNA1, BARTs, EBERs等, 在表观遗传、基因组不稳定性、免疫逃逸等多个方面, 与NF-κB通路失调等因素共同促进肿瘤发生发展

Figure 1　Diagram of the development and progression of nasopharyngeal carcinoma caused by EBV infection and other factors. Tumor suppressor gene mutations and exposure to environmental carcinogens collectively lead to precancerous lesions of the nasopharyngeal epithelium, paving the way for EBV to establish stable latent infection in the nasopharyngeal epithelium. Various gene products from persistent EBV latent infection, including LMP1, LMP2, EBNA1, BARTs and EBERs, together with NF-κB pathway dysregulation, contribute to tumorigenesis and progression through mechanisms such as epigenetic modifications, genomic instability, and immune evasion

抑癌基因的失活(如*RASSF1A*与*CDKN2A*)与cyclinD1-Rb通路的过表达[1,19,20], 它们可能是鼻咽黏膜长期暴露于环境致癌物导致的DNA损伤不断积累的结果[1]. Ⅱ型EBV潜伏感染基因产物, 如LMP1(latent membrane protein 1), LMP2(latent membrane protein 2), EBNA1(Epstein-Barr virus nuclear antigen 1), BARTs (BamHI-A rightward transcripts), EBERs(Epstein-Barr virus encoded RNAs)等的表达, 改变了多种细胞通路, 并通过影响表观遗传修饰、促进免疫逃逸、增加基因组不稳定性等方式, 促进癌前鼻咽上皮细胞增殖与癌变[8](表1)[21~51]. 许多研究表明, EBV驱动的全基因组DNA甲基化会导致多个抑癌基因的失活, 证明了表观遗传修饰在鼻咽癌发生发展过程中具有重要作用[52~55]. 此外, 全基因组和全外显子测序发现, 由通路上游负调控因子的体细胞突变以及LMP1过表达引起的NF-κB信号通路的失调是鼻咽癌的主要致癌驱动因素, 而且基因突变与LMP1过表达具有相互排斥性[56~58]. 在肿瘤进展过程中, MHC-I类基因突变、PI3K/MAPK与染色质重塑通路的突变以及进一步的体细胞基因突变(包括*TP53*, *RAS*等)可能会驱动肿瘤细胞的亚克隆生长, 成为治疗后会出现局部复发和远处转移的来源[8].

近年来单细胞测序技术(single cell sequencing, SCS)在解析鼻咽癌肿瘤异质性与肿瘤微环境(tumor microenvironment, TME)中发挥重要作用, 并揭示了EBV+鼻咽癌通过塑造免疫抑制微环境介导肿瘤进展. Jin等人[59]对EBV+NPC单细胞转录组数据应用非负矩阵因子分解(non-negative matrix factorization, NMF)方法鉴定出一种特殊的肿瘤细胞特异的"上皮-免疫"双重特征, 并发现其对$CD8^+$ T细胞具有抑制作用, 从而抑制抗肿瘤免疫. Gong等人[60]发现, EBV通过诱导表观遗传修饰上调NF-κB转录, 进而上调CD70表达, 并通过CD70-CD27互作增强调节性T细胞(regulatory T cell, Treg)的抑制功能. 另一项研究通过单细胞转录组测序鉴定出一类具有免疫抑制功能的LAMP3+树突状细胞(dendritic cell, DC), 它是由EBV+NPC细胞从外周血募集树突状细胞到肿瘤微环境后分化的高度成熟形态, 并与耗竭性$CD8^+$ T细胞以及Treg细胞互作导致肿瘤进展[61].

2 鼻咽癌的诊断

2.1 影像学诊断

鼻咽癌的常用影像学检查手段有MRI, CT和PET/CT. MRI具有出色的软组织分辨率以及多方位多参数成像, 在评估原发肿瘤浸润范围、咽后淋巴结转移以及颅底骨质侵犯方面优于CT, 在检测颈部淋巴结转移方面与CT具有相似的准确性[62,63], 目前已取代CT成为鼻咽癌诊断、分期、疗效评价及随访监测的首选检查手段. ^{18}F-脱氧葡萄糖(fluorodeoxyglucose, FDG) PET/CT在诊断远处转移方面优于常规检查(胸片、腹部超声、骨扫描), 在发现颈部小淋巴结转移和局部残留、复发或两者兼有方面也相对更敏感和准确[1]. Tang等人[64]发现, $N_{2\text{-}3}$分期和EBV-DNA≥4000拷贝/mL的亚组患者能从PET/CT检测中获益最大. 一项临床试验评估了^{18}F-FDG PET/MRI具有比PET/CT与头颈部MRI更高

表 1 EBV相关成分的致病机制及临床意义

Table 1 Pathogenic mechanisms and clinical implications of EBV-related components

成分	分子	致病机制/临床意义
EBNAs	EBNA1	增加基因组不稳定性[21,22], 介导免疫逃逸与调节肿瘤微环境[23]
LMPs	LMP1	诱导宿主基因甲基化[24,25], 增加基因组不稳定性[26], 激活促增殖通路[25,27~30,57], 诱导肿瘤干性[31,32], 介导免疫逃逸与调节肿瘤微环境[33,34]
	LMP2	激活促增殖通路[30], 诱导肿瘤干性[35], 介导免疫逃逸与调节肿瘤微环境[36]
非编码RNA	EBERs	介导免疫逃逸与调节肿瘤微环境[37], 促肿瘤血管生成[38] 原位杂交协助病理诊断
	BARTs	抑制细胞凋亡[39], 介导免疫逃逸与调节肿瘤微环境[40~42]
EBV-DNA		早期筛查与诊断[43]、风险分层与预后预测[44,45]、疗效评估[46,47]、复发转移监测[48,49]
EBV抗体	EBNA1-IgA	早期筛查与诊断[50]
	VCA-IgA	早期筛查与诊断[50]
	P85-Ab	早期筛查与诊断[51]

的准确性, 可作为单步分期方式[65]. 其能否取代PET/CT与头颈部MRI作为治疗前分期评估手段还在探索中.

2.2 病理学诊断

鼻内镜下病理活检是鼻咽癌诊断的金标准. 鼻咽癌的病理类型主要分为角化性鳞状细胞癌, 非角化性癌(包括分化型和未分化型癌)以及基底样鳞状细胞癌[4]. 对于病理形态不能明确诊断为鼻咽癌的病例, 须加做免疫组织化学或原位杂交检测, 协助病理诊断. 其中, EBERs是鼻咽癌最常用的原位杂交标志物.

2.3 临床分期

目前临床采用的鼻咽癌TNM分期系统是第8版AJCC/UICC TNM分期系统(表2). 针对第8版分期T_2与T_3预后区分度欠佳等问题, Du等人[66]改进了第8版分期, 将轻度颅底骨质受侵降为T_2, 将严重颈部淋巴结包膜外侵升级为N_3, 并重新构建了具有更好风险分层效果的新版分期模型. 此外, 多项研究表明, 将血浆EBV-DNA纳入TNM分期系统可以提高对鼻咽癌患者预后的预测效能[67~70].

表 2 鼻咽癌第8版AJCC/UICC分期系统[a)]

Table 2 Eighth version of the AJCC and UICC nasopharyngeal carcinoma staging classification[a)]

	T分期	N分期	M分期
0期	Tis	N_0	M_0
I期	T_1	N_0	M_0
Ⅱ期	$T_{0\text{-}1}$	N_1	M_0
	T_2	$N_{0\text{-}1}$	M_0
Ⅲ期	$T_{0\text{-}2}$	N_2	M_0
	T_3	$N_{0\text{-}2}$	M_0
ⅣA期	T_4	$N_{0\text{-}2}$	M_0
	任何T	N_3	M_0
ⅣB期	任何T	任何N	M_1

a) T分期——T_X: 原发肿瘤无法评估; T_0: 未发现肿瘤, 但EB病毒阳性且有颈转移淋巴结; T_1: 肿瘤局限于鼻咽, 或侵犯口咽和(或)鼻腔, 无咽旁间隙受累; T_2: 肿瘤侵犯咽旁间隙, 和(或)邻近软组织受累(翼内肌、翼外肌、椎前肌); T_3: 肿瘤侵犯颅底骨质结构, 颈椎、翼状结构, 和(或)鼻旁窦; T_4: 肿瘤侵犯至颅内, 有颅神经、下咽、眼眶、腮腺受累, 和(或)有超过翼外肌的外侧缘的广泛软组织侵犯. N分期——N_X: 无法评估区域淋巴结; N_0: 无区域淋巴结转移; N_1: 单侧颈部和(或)咽后淋巴结转移(不论侧数), 最大径≤6 cm, 且位于环状软骨下缘以上区域; N_2: 双侧颈淋巴结转移, 最大径≤6 cm, 位于且环状软骨下缘以上区域; N_3: 颈淋巴结转移(不论侧数): 最大径>6 cm和(或)位于环状软骨下缘以下区域. M分期——M_0: 无远处转移; M_1: 有远处转移

3 鼻咽癌的治疗

3.1 早期鼻咽癌的治疗

由于鼻咽癌对电离辐射非常敏感, 加上鼻咽部解剖结构复杂及可及性差等原因, 放射治疗是鼻咽癌最主要的根治性治疗手段. 早期鼻咽癌, 通常指I期和Ⅱ期鼻咽癌, 通过单纯放疗即可治愈. 下文对鼻咽癌的放疗技术、靶区范围与剂量进行简要总结.

(1) 放疗技术与射线类型. 调强放疗(intensity modulated radiotherapy, IMRT)目前是鼻咽癌放疗的主要技术类型. 与传统的二维或三维放疗相比, IMRT可以在保护临近重要结构的同时对鼻咽癌进行高剂量照射. 多项随机对照试验证实, IMRT不仅能降低放疗毒性, 还提高了鼻咽癌疾病控制率与生存率[71~74]. 关于射线类型, 目前鼻咽癌放疗推荐使用光子线(X线), 必要时有条件可考虑质子或重离子射线(如肿瘤累及或距离重要危及器官过近或复发鼻咽癌).

(2) 靶区范围和照射剂量. 鼻咽癌的大体肿瘤靶区(gross tumor volume, GTV)包括原发灶和颈部淋巴结, 目前推荐的GTV照射剂量是70 Gy(分割次数32~35次, 单次剂量2.0~2.2 Gy). 鼻咽癌靶区中原发灶的临床肿瘤靶区(clinical target volume, CTV)范围主要基于鼻咽癌的局部进展规律[75,76], 可分为高、中、低风险区; 颈部淋巴结的CTV范围主要基于淋巴结的转移规律[77], 即通常从上到下同侧循序转移, 跳跃转移少. 多项研究探索了缩小颈部淋巴结CTV靶区从而减少放疗相关毒性的可行性. Tang等人[78]的一项Ⅲ期临床研究证实, 对于$N_{0\text{-}1}$期的鼻咽癌患者, 淋巴结阴性侧上半颈部照射(upper-neck irradiation, UNI)与全颈部照射(whole-neck irradiation, WNI)的3年无淋巴结复发率相当, 但前者的晚期毒性发生率更低. 另一项研究发现, 对于没有内侧咽后淋巴结(medial retropharyngeal lymph nodes, MRLN)受累的患者, MRLN豁免放疗相比于标准放疗具有非劣效性, 且放射相关毒性更小[79].

3.2 局部晚期鼻咽癌的治疗

局部晚期鼻咽癌(locally advanced nasopharyngeal carcinoma, LA-NPC)通常包括Ⅲ期和ⅣA期. 此阶段的

肿瘤已扩展至周围组织或区域淋巴结，但尚未出现远处转移，因此需通过以放化疗为核心的综合治疗，提高肿瘤的局部控制率，减少远处转移风险，并延长患者的生存期. 对于局部晚期鼻咽癌, 目前NCCN指南推荐诱导化疗联合同期放化疗为1类证据, 同期放化疗后辅助治疗为2A类证据, 单纯同期放化疗为2B级证据.

(1) 同期放化疗. 同期放化疗(concurrent chemoradiotherapy, CCRT)是局部晚期鼻咽癌治疗的支柱[2]. 同期化疗通常采用顺铂方案, 推荐剂量为100 mg/m^{2}每3周一次或40 mg/m^{2}每周一次. 多项研究证实, 相较于单纯放疗, 同期放化疗联合或不联合辅助化疗在局部晚期鼻咽癌患者中具有生存获益[80~87]. 随着IMRT的广泛使用, 多项临床研究探索低危鼻咽癌患者免除化疗或降阶梯治疗的非劣效性. 一项纳入341名患者的三期临床试验显示, 低危Ⅱ期/T3N0M0患者单独使用IMRT治疗的3年无失败生存期(failure-free survival, FFS)不劣于顺铂同期放化疗, 且单独IMRT组的不良反应率显著低于同期放化疗组[88]. 在一项二期随机对照试验中, Li等人[89]定义治疗前EBV-DNA水平<4000拷贝/mL为低风险局部晚期鼻咽癌患者, 他们接受两周期顺铂(100 mg/m^2, 每3周一次)同期放化疗的预后不劣于标准的三周期顺铂同期放化疗. 此外, 由于顺铂化疗的副作用较大, 而且顺铂化疗前后需要水化保护肾脏, 因此需要探索低毒且疗效相当的药物替代顺铂. Tang等人[90]报道了一项对比第二代铂类药物奈达铂与顺铂同期放化疗疗效与安全性的Ⅲ期临床试验, 结果显示, 奈达铂与顺铂疗效相当, 但毒副反应更低并且能带来更好的生活质量. 另一项Ⅲ期临床试验发现, 含第三代铂类药物洛铂的诱导化疗序贯同期放化疗方案的生存不劣于含顺铂的方案, 且洛铂方案的不良事件更少[91].

(2) 诱导化疗. 诱导化疗(induction chemotherapy, IC)是指在同期放化疗之前进行的化疗, 其主要目的有: 缩小肿瘤体积、降低肿瘤负荷, 为后续放疗创造更好条件; 早期控制可能存在的微小转移灶, 降低远处转移风险; 筛选化疗敏感性, 根据诱导化疗反应调整后续治疗方案. 两项前瞻性三期临床试验分别证实, 多西他赛、顺铂和氟尿嘧啶(TPF)联合化疗方案[92]和吉西他滨+顺铂(GP)方案[93]诱导化疗可以显著提高Ⅲ~ⅣB期患者(排除N0期患者)的无复发生存期(recurrence-free survival, RFS)和总生存期(overall survival, OS), 其中患者对GP方案的耐受性相对较好. 两种方案均被NCCN指南采纳作为证据级别最高的诱导化疗方案.

(3) 辅助化疗. 辅助化疗(adjuvant chemotherapy, AC)是指在同期放化疗后进行的化疗, 目的是进一步降低肿瘤复发或转移的风险. 然而, 同期放化疗加用辅助化疗能否带来额外的生存获益一直存在争议. 尽管荟萃分析显示, 在同期放化疗中加入辅助化疗或诱导化疗相比单纯同期放化疗提升了OS[94], 但Chen等人[95]和Chan等人[96]的两项三期随机对照研究显示, 局部晚期鼻咽癌患者同期放化疗后辅助治疗并未改善患者的生存结局. 常规化疗方案的耐受性与依从性差可能是辅助治疗效果不佳的原因之一. 节拍化疗(metronomic chemotherapy)是较长时间内以较低的毒性剂量密切、规律地给予化疗药物, 具有顺应性好、毒性低和方便的优点[1]. 在一项三期临床试验中[97], 高危局部区域晚期鼻咽癌患者放化疗后接受卡培他滨节拍化疗可显著改善预后, 同时安全性较好. 此外, 一项头对头三期临床试验证实, GP辅助化疗方案相比于顺铂+氟尿嘧啶(PF)辅助化疗方案对$N_{2\text{-}3}$期鼻咽癌效果更好[98].

(4) 免疫治疗. 免疫治疗是近年来肿瘤治疗领域一项重要的进展, 在多种实体瘤中显著改变了患者的临床结局, 并且能带来持久的临床获益. 鼻咽癌是免疫治疗的理想瘤种: 鼻咽癌是典型的“热肿瘤”, 肿瘤组织存在大量淋巴细胞; 鼻咽癌中程序性死亡配体(programmed death ligand-1, PD-L1)阳性表达高达85%~95%[33]; 在流行区鼻咽癌与EBV感染密切相关, 鼻咽癌细胞表达EBV抗原, 可作为T淋巴细胞的靶抗原. 以上因素都提示免疫治疗在鼻咽癌中具有巨大的潜力. 近年来, 免疫检查点抑制剂(immune checkpoint inhibitors, ICIs), 尤其是程序性死亡受体-1(programmed death-1, PD-1)抑制剂治疗在复发或转移性鼻咽癌(recurrence and/or metastatic NPC, R/M NPC)中已取得了显著的进展. 而在局部晚期鼻咽癌中, 多项前瞻性的Ⅱ期或Ⅲ期临床试验正在进行中. 一项代号为CONTINUUM的多中心三期随机对照试验证实, 在局部晚期鼻咽癌患者诱导化疗与同期放化疗的基础上, 治疗全程(诱导、同期、辅助)加入免疫治疗能够显著提升患者的无事件生存期(event-free survival, EFS)和无远处转移生存期(distant metastasis-free survival, DMFS), 但OS暂未显示差异, 该研究提示免疫治疗

可能给局部晚期鼻咽癌带来生存获益，但仍需进一步延长随访时间确认结果[99]. 免疫治疗的最佳使用时机目前仍在探索中. 一项代号为DIPPER的Ⅲ期临床试验[100]证实, 在辅助治疗阶段加入免疫治疗能够显著提高3年EFS, 且OS存在获益趋势; 另一项Ⅱ期临床试验研究发现[101], 在同期放化疗基础上在诱导阶段和辅助阶段“三明治式”联用免疫治疗，可显著降低60%的疾病进展或死亡风险, 同时安全性良好. 此外, 免疫治疗的联用策略的探索也十分重要. Liang等人[102]发现, 免疫治疗及抗血管生成治疗(anti-angiogenic therapy, AAT)联合诱导化疗及同期放化疗可有效提升N_3期局部晚期鼻咽癌患者的无远处转移率与客观缓解率，且安全性良好.

3.3 复发转移性鼻咽癌的治疗

(1) 局部区域复发鼻咽癌的治疗. 约有5%~15%的患者在根治性治疗后发生局部区域复发[103]. 对于仅有颈部复发的患者，颈淋巴结清扫术(neck dissection, ND)是重要的根治手段. 对于原发灶局部或区域复发的患者, 手术或再程放疗(reirradiation therapy, re-RT)是主要的治疗方式. 对于不可手术的患者, 再放疗一般采用IMRT、立体定向体部放疗(stereotactic body radiotherapy, SBRT)或调强质子放疗(intensity modulated proton therapy, IMPT), 60 Gy(普通分割)被认为是实现最佳局部控制所需的最小剂量. Chen团队[104]证实, 超分割调强放疗(hyperfractionated intensity-modulated radiotherapy, HF-IMRT)可显著降低局部晚期复发性鼻咽癌患者的严重晚期并发症发生率，提高总生存期. 全身化疗适用于不能切除肿瘤或不适合再放疗的高风险患者.

(2) 转移性鼻咽癌的治疗. 对于单个转移灶或寡转移灶的患者, 局部治疗, 如SBRT、转移灶切除术和射频消融术(radiofrequency ablation, RFA)可用于治疗转移病灶[105,106]. 对于复发/转移鼻咽癌的全身性化疗, Zhang等人[107]的三期临床试验确立了GP方案作为复发/转移性鼻咽癌的一线标准化疗方案. 近期的一项研究表明, 白蛋白紫杉醇、顺铂联合卡培他滨(nab-TPC)方案相较于GP方案具有更好的抗肿瘤疗效与安全性, 但仍需长时间随访来确定对总生存期是否有提升[108]. 近年来, 免疫检查点抑制剂疗法改变了复发/转移鼻咽癌的临床实践, JUPITER-02[109], RATIONALE-309[110], CAPTAIN-1st[111]三项三期随机对照试验均报道了抗PD-1抑制剂联合GP方案一线治疗复发/转移鼻咽癌具有更好的PFS以及可控的安全性.

对于一线含铂方案治疗失败的患者，通常选择一线未使用的药物进行单药化疗，但PD-1单抗也显示了一定的治疗价值[112,113]. 此外，Ding等人[114]和Yuan等人[115]的两项Ⅱ期临床探索了免疫治疗联合抗血管生成治疗作为复发转移鼻咽癌患者的二线治疗方案，显示出较好的疗效.

4 EBV标志物在鼻咽癌诊治中的作用

4.1 早期筛查与诊断

由于鼻咽癌早期症状不典型，大多数鼻咽癌被发现时已是晚期. 早期鼻咽癌是高度可治愈的，因此在流行地区进行鼻咽癌筛查可以降低鼻咽癌死亡率. 由于在流行地区EBV与鼻咽癌的密切联系，分别以EBV抗体[50]和EBV-DNA[43]为筛查指标的人群筛查临床试验均显示了较好的结果. 目前鼻咽癌的初筛方法主要为EBNA1-IgA和VCA-IgA联合检测(表1)，但是其较低的阳性预测值(positive predictive value, PPV)[50]不仅降低了鼻咽癌筛查的成本效益和能力，还导致受试者长期焦虑和依从性低. Li等人[51]鉴定了P85-Ab作为筛选生物标志物，其敏感性和特异性均优于标准的双抗体筛选方法，显著提升了阳性预测值(10.0% *vs*. 4.3%), 而且P85-Ab联合双抗体法可进一步提高阳性预测值(44.6%). 该研究表明, P85-Ab有望成为鼻咽癌新的标准筛查方法.

4.2 风险分层与预后预测

血浆EBV-DNA拷贝数与肿瘤负荷之间的相关性[116]表明，EBV-DNA水平具有反映患者预后的潜力. 许多研究表明，基线EBV升高与不良的临床结局相关[117~121]，而且血浆EBV-DNA水平是鼻咽癌的独立预后生物标志物[45,117,122]. 基于基线EBV-DNA的重要预后价值, 将基线EBV-DNA与当前的预后分期系统结合有助于提升预后预测能力. Tang等人[44]结合EBV-DNA与T、N分期以及其他临床因素构建了列线图模型，并验证了其预测复发的能力高于未结合EBV-DNA的列线图模型. 此外，多项研究表明，通过递归分割分析(recursive partitioning analysis, RPA)将血浆EBV-DNA

纳入TNM分期系统可以显著提高对鼻咽癌患者预后的预测效能[67~70]. 在治疗方面, 基于基线EBV-DNA可以将局部晚期鼻咽癌患者分层为高危与低危, 实现精准分层治疗. 对于基线EBV较高的高危患者, 可以联用免疫治疗等手段增强治疗效果[101]; 对于基线EBV较低的低危患者, 可以减少治疗剂量从而降低治疗相关毒副反应[89].

4.3 疗效评估

由于其肿瘤源性, 治疗过程中EBV-DNA的变化可以反映治疗过程中肿瘤的退缩情况, 即鼻咽癌对放化疗的敏感性, 评估治疗疗效, 进而指导后续治疗方案. Lo等人[123]研究发现, 根治性放疗后EBV-DNA降至阈值以下提示临床完全缓解, 而EBV-DNA持续阳性则提示肿瘤残留可能性大. Chan等人[96]将104例放疗后血浆EBV-DNA阳性的鼻咽癌患者评估为高危鼻咽癌患者, 并随机分配至观察组或GP辅助化疗组, 结果显示辅助化疗无法显著提高PFS与OS. 该研究是第一个基于治疗中EBV-DNA驱动的随机对照试验. Guo等人[124]将诱导化疗后CR/PR且EBV-DNA降为0的患者评估为化疗敏感患者, 并给予60 Gy的放疗照射剂量, 结果显示, 该部分患者接受降剂量放疗后预后良好, 且毒副反应发生率低. 基于该研究的良好结果, 一项探索降低放疗剂量的Ⅲ期随机对照试验正在开展(NCT05304468). EBV-DNA的重要意义不仅体现在静态节点的检出情况, 还体现在整个过程中的动态变化. Lv等人[46]基于局部晚期鼻咽癌患者治疗过程中EBV-DNA清除率对患者进行预后分层: 早反应A型、早反应B型、中等反应型、迟反应A型、迟反应B型和治疗抵抗型, 并在前瞻性临床试验中探索对不同预后表型分别进行不同强度的化疗或免疫治疗. 此外, Xu等人[47]通过监测接受抗PD-1治疗的复发性或转移性鼻咽癌患者EBV-DNA, 发现基线低水平EBV-DNA组、第4周EBV-DNA滴度下降≥50%组及前8周EBV-DNA滴度下降趋势组的患者更有可能获得持久临床获益.

4.4 随访监测复发转移

鼻咽癌常规随访方法主要有影像学、鼻内镜和血清学指标. 血清学指标中, 在鼻咽癌达到根治后, EBV相关抗体转阴存在相当长时间的滞后性, 但血浆EBV-DNA的清除非常迅速[123,125]. 因此EBV-DNA的持续存在或再次升高很可能预示着疾病进展, 可以动态监测鼻咽癌的复发转移. Ngan等人[48]对19例患者根治性治疗后的EBNA-1 EBV-DNA进行连续监测, 发现62%的患者EBV-DNA阳性比临床诊断复发提早17.4周. Wang等人[49]的研究也证实, 血浆EBV-DNA检测随访对监测鼻咽癌复发转移具有较高的准确性, 而且EBV-DNA提示远处转移方面的价值高于局部区域复发[49,126,127], 可能是由于局部区域复发的患者通常比远处转移的患者具有更低的肿瘤负荷, 以及放疗后局部区域间质纤维化和血管减少等因素可能会阻碍EBV-DNA进入血液循环[128]. 因此, 血浆EBV-DNA检测联合鼻咽部及头颈部MRI检查可作为鼻咽癌患者有效的随访策略, 能够同时有效监测局部区域复发与远处转移.

总之, 血浆EBV-DNA检测作为一种简单、有效、经济的方法, 在鼻咽癌的筛查、风险分层、疗效监测等方面具有广阔的应用前景(表1). 但目前关于EBV-DNA检测缺乏标准化, 阻碍了不同机构检测结果的比较和互换. 因此, 标准化检测的建立对于基于EBV-DNA的临床个体化治疗至关重要.

5 总结与展望

EBV与鼻咽癌发病机制与临床诊治等方面存在密切联系. 在遗传与环境因素导致的癌前基因突变的背景下, EBV感染鼻咽上皮细胞并诱导潜伏性感染, 进而通过多种潜伏期基因表达产物, 激活NF-κB等信号通路, 改变宿主细胞的基因表达, 抑制抗肿瘤免疫反应, 促进肿瘤进展. 在鼻咽癌的临床诊治中, EBV的DNA、RNA及其抗体已成为鼻咽癌早期诊断和预后评估的重要标志物, 特别是EBV-DNA的水平变化可以用于评估治疗反应与监测复发转移风险.

尽管在EBV与鼻咽癌的研究取得了显著进展, 但未来仍面临许多挑战. 在鼻咽癌进入免疫治疗时代的背景下, 未来的研究应当聚焦于深入解析EBV感染与鼻咽癌独特的免疫微环境的互作机制, 以及EBV感染促进免疫逃逸与免疫治疗耐药的机制, 从而寻找合适的免疫治疗人群与发现新的靶点, 增强免疫治疗的疗效. 在诊断与治疗层面, 在鼻咽癌精准治疗时代, 发掘EBV更多有效的生物标志物并进一步挖掘已有标志物

的意义有助于鼻咽癌早诊早治, 并实时精准预测病人的预后与疗效, 从而实现高效低毒的个体化治疗. 最后, 针对EBV的新型免疫治疗方式, 如EBV抗原特异性的细胞毒性T淋巴细胞(cytotoxic T lymphocyte, CTL)疗法、T细胞受体工程化T细胞(T cell receptor-engineered T, TCR-T)疗法, 以及鼻咽癌肿瘤疫苗正在进行临床试验, 未来与传统治疗方法联用有望降低传统治疗的不良反应, 提升免疫反应的特异性和有效性.

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Research progress of Epstein-Barr virus and nasopharyngeal carcinoma

WANG HaoJun[1,2], XIAO BeiBei[1,2], MA Jun[1,3], MAI HaiQiang[1,2] & TANG LinQuan[1,2]

1 State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou 510060, China;
2 Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou 510060, China;
3 Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou 510060, China

Nasopharyngeal carcinoma (NPC) is a malignant tumor originating from the epithelium of the nasopharyngeal mucosa, with a predilection for the nasopharyngeal recess, lateral wall, and posterior wall of nasopharynx. NPC is endemic to Southeast Asia and southern China, where its incidence rate has remained relatively stable. The risk factors of NPC include Epstein-Barr virus (EBV) infection, genetic factors, and environmental factors, with EBV playing a pivotal role in the pathogenesis of undifferentiated NPC. The early symptoms of NPC are often subtle, making early detection challenging. Magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT), and nasal endoscopic biopsy remain the most commonly employed modalities for diagnosis and staging. Radiation therapy is the cornerstone of NPC treatment, often complemented by chemotherapy and immunotherapy to enhance therapeutic outcomes. EBV-related biomarkers have found broad applications in screening, prognostic assessment, treatment evaluation, and long-term follow-up of NPC patients. This article reviews the close association between EBV and NPC in terms of pathogenesis and clinical diagnosis and treatment. It also discusses the opportunities and challenges for future research on NPC and its connection with EBV.

nasopharyngeal carcinoma, **Epstein-Barr virus**, **pathogenesis**, **combined treatment**, **biomarker**

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