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评 述 EB病毒发现60周年: 回顾与展望专题

EB病毒与相关疾病的流行病学研究

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摘要 EB病毒(Epstein-Barr virus, EBV)是一种全球各人种普遍感染且终生携带的一类γ疱疹病毒. 一般情况不引发疾病, 但越来越多证据表明, 其感染与多种严重疾病密切相关. 了解EBV感染的流行病学特征对于预防和治疗EBV相关疾病至关重要. 本文对EBV的自然感染史及其特征进行综述, 包括感染途径、潜伏状态和裂解复制过程; 进一步分析影响EBV感染的环境和遗传因素; 此外, 本文还对EBV相关疾病的流行病学特征进行概述, 包括传染性单核细胞增多症、多发性硬化症、系统性红斑狼疮, 以及恶性肿瘤如淋巴瘤、鼻咽癌、胃癌等, 特别强调*HLA*等免疫相关遗传基因在病毒致癌中的关键作用. 基于EBV血清学、游离核酸及甲基化等新型标志物, 探讨这些标志物在疾病诊断中的重要作用. 本文旨在为深入理解EBV相关疾病的病因、发病机制和预防措施提供详实的流行病学依据.

关键词 EBV感染, EBV相关疾病, 流行病学

EB病毒(Epstein-Barr virus, EBV)作为人类首个被发现的致瘤病毒, 在全球范围内广泛传播, 对人类健康产生重大危害. 自1964年被发现以来, 科学家们相继证实多种疾病与EB病毒感染密切关联, 包括传染性单核细胞增多症、自身免疫性疾病和恶性肿瘤等. 尽管EBV感染在全球普遍存在, 但EBV相关疾病发病率存在显著差异. 例如, 鼻咽癌(nasopharyngeal carcinoma, NPC)在中国华南地区高发, 广东和广西最为显著, 而在其他地区则较为罕见. 近年来, 随着遗传学和免疫学等领域的不断发展, 越来越多的研究开始关注遗传因素与EBV感染相关疾病之间的关系, 这些发现为人们理解疾病的显著地域差异提供了重要线索. 此外, 随着生物技术的迅速发展, 基于EBV抗体水平和血浆游离EBV DNA载量的研究正在广泛进行. 一些新的标志物, 如BNLF2b抗体, 被认为是EBV相关疾病的潜在生物标志物. 深入了解不同地区的EBV感染流行病学特征对于制定针对性的预防和治疗策略至关重要, 进一步寻找更有效的诊断标志物和监测指标对于提高EBV相关疾病的早期诊断率和治疗效果至关重要. 本文旨在系统探讨EBV及全球范围内相关疾病的流行病

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学研究进展, 分别从EBV感染史及感染特征、EBV感染及相关疾病的流行病学特征及影响因素、EBV相关标志物在疾病早期诊断和筛查中的应用等方面进行评述. 通过全面了解EBV及其相关疾病的流行病学特征, 为预防和治疗EBV相关疾病提供更深入的理论基础和临床依据.

1 EBV自然感染史及感染特征

EBV是第一个被国际癌症研究机构(International Agency for Research on Cancer, IARC)列为Ⅰ类致癌物的人类疱疹病毒[1], 最早在非洲地方性伯基特淋巴瘤(Burkitt lymphoma, BL)中被发现[2,3]. 全球范围内, EBV感染非常普遍, 成人感染率在95%以上. 病毒感染率随着年龄增加而上升, 不同国家和地区间儿童的感染率存在差异. 美国6~19岁儿童及青少年感染率约为50%~69%, 成年人感染率则高达89%[4,5]; 相较于西方国家, 中国3岁前儿童感染率大于50%, 8~9岁感染率已超过90%, 成人感染率达95.4%[6~8]. 影响EBV原发感染年龄差异的因素较为复杂, 如人种差异、家庭规模、家庭经济及父母教育程度等[9,10].

EBV通常经唾液传播, 也可以通过性接触、输血、脐带血及器官移植时的血液和精液传播[11~16]. 也有报道EBV可通过母乳或子宫分泌物感染初生婴儿[17,18]. EBV感染后在宿主体内可分为三种不同状态: 原发感染、潜伏和裂解复制感染[19]. 一般认为病毒在原发感染新宿主的口咽黏膜上皮后出现裂解复制, 新产生的EBV可通过Waldeyer环进入淋巴组织, 感染扁桃体内的naive B细胞, 形成潜伏Ⅲ期并表达所有潜伏期蛋白. 大部分EBV感染的naive B细胞被NK细胞及T细胞杀灭后, 小部分仅表达部分病毒蛋白的naive B细胞进入生发中心(germinal center, GC), 形成潜伏Ⅱ型感染状态[20,21]. 在GC分化成熟后, 受感染的B细胞分化成静息记忆B细胞和浆细胞, EBV几乎不表达病毒基因(潜伏0期)并保持终身潜伏. EBV感染的静息记忆B细胞在外周血中再循环, 最终分化成为浆细胞进入口咽黏膜下层, 经过外界刺激后激活病毒裂解复制并通过唾液感染新宿主. 大多数EBV感染的细胞被宿主的NK细胞及T细胞识别并清除, 从而防止EBV诱导B细胞及上皮细胞癌变[22]. 当机体免疫细胞对感染EBV的细胞清除能力减弱, 在化学物刺激及外界环境因素影响下, EBV可发生异常的裂解复制, 病毒子代可感染上皮细胞、NK细胞、T细胞、平滑肌细胞、滤泡树突状细胞甚至神经细胞, 导致相关感染性疾病发生[23~25].

2 EBV感染相关疾病的流行病学负担及流行特征

据估计EBV感染每年导致超过20万例恶性肿瘤的发生, 占所有癌症的1.8%[1,26,27]. 同时EBV感染也与多种良性疾病和自身免疫疾病密切相关, 如传染性单核细胞增多症(infectious mononucleosis, IM)[28]、多发性硬化症(multiple sclerosis, MS)[29]和系统性红斑狼疮(systemic lupus erythematosus, SLE)[30,31].

在儿童期EBV的原发感染多无症状, 从感染到发病的潜伏期长达6周[32]. 如果在青少年或青年中发生EBV原发感染时, 呈现为传染性单核细胞增多症(infectious mononucleosis, IM)的比例明显上升, 患者常伴有明显的临床综合征, 表现为发烧、咽炎和淋巴结肿大的“三联征”, 并伴有外周血淋巴细胞增多和异质淋巴细胞出现[33]. IM在不同地区的高发年龄差异较大. 在西方国家, 社区IM发病率约为45/10万例, 而青少年发病率则高达320~370/10万例[34]. 美国18~22岁的大学生EBV原发感染后有74%可形成IM[35]; IM在发展中国家发病年龄较小. 流行病学研究表明, 中国学龄前儿童的IM发病率相对较高, IM发病入院儿童占所有入院儿童的0.42%, 其中4~6岁的儿童发病率最高, 男女比例为1.48:1[36]. IM发病的机制尚未完全阐明, 目前普遍认为$CD8^+$ T细胞对EBV的异常反应是导致IM急性症状的原因.

多发性硬化症是中枢神经系统最常见的慢性炎症和神经退行性疾病, 全球大约有280万(35.9/100000)患者, 女性发病率约为男性的2倍[37]. 发展中国家各年龄段的MS发病率均在增加[38,39]. 目前认为, 该病与EBV感染导致的自身免疫紊乱有关, EBV感染是MS发病的必要条件. 基于多个大型人群的血清学流行病学研究证实, 感染EBV后发生MS的风险增加32倍[40]. 基于MS的脑脊液中的BCR多态性研究表明, 被感染EBV的MS患者的脑脊液中存在大量识别EBNA1 AA386-405表位的抗体, 这些抗体可结合具有相似表位的神经细胞的免疫球蛋白样细胞黏附分子(immunoglobulin-like cell adhesion molecule, GlialCAM), 直接损伤神经细胞,

诱发MS. 此外, 在MS患者的脑脊液中检测到对EBV裂解蛋白有反应的细胞毒性T淋巴细胞(cytotoxic T lymphocytes, CTL), CTL激活产生的细胞因子, 如IFN-γ可加重MS的症状[41,42].

系统性红斑狼疮是一种自身免疫性疾病, 患者多为女性和非白人群体[43,44], 全球成年人SLE患病率大约为30~150/100000, 年发病率在2.2~23.1/100000[45]. SLE曾被认为是一种进展迅速且致命的疾病, 但随着治疗方式的发展, 发达国家SLE患者的5年生存率已从50%提高至95%[46]. 多项病例对照研究发现, SLE患者的EBV抗体水平和EBV DNA载量均高于健康人[47~50], 并且SLE的临床症状和病程也与EBV裂解感染相关[51], 提示EBV参与SLE的发病过程. EBV感染可能会激活非特异性免疫系统和B细胞分化, 刺激产生针对宿主SmB[52]、SmD[53]、SSA[54]、补体C1q[55]等蛋白和双链DNA[56,57]的自身抗体, 这些抗体与EBV编码的EBNA1蛋白存在分子拟态(molecular mimicry), 提示EBV感染后可能通过诱发自身免疫反应而引发SLE[58,59].

EBV感染相关的伯基特淋巴瘤(BL)及霍奇金淋巴瘤(Hodgkin lymphoma, HL)是目前已知EBV致病机理最为明确的淋巴瘤. 2018年, 全球约有6600例新发BL病例与EBV相关, 占全部病例的55%. 与恶性疟原虫流行区重叠的流行性BL中EBV阳性率高达81%~100%; 流行性BL通常发生在非洲和大洋洲部分国家的儿童中, 在14岁以下儿童中的发病率约为3~6/10万例[60~62]. 恶性疟原虫感染通过激活B细胞中TLR-9和诱导胞苷脱氨酶使*MYC*基因易位至免疫球蛋白编码基因内, 生发中心内的B细胞在EBV感染后大量表达*MYC*基因编码的c-myc蛋白, 通过抵抗凋亡从而进展为BL[63]. 而散发性BL中, EBV的感染率为10%~20%. BL中EBV多为潜伏Ⅰ期感染状态.

HL是另一种与EBV感染相关的B细胞淋巴瘤, 2020年, 全世界有78800~87600例HL新发病例和20100~27000例HL死亡病例[64]. 根据浸润的性质可将HL分为四种组织学亚型, 即结节硬化型(nodular sclerosing, ns-cHL)、混合细胞结构型(mixed cellularity, mc-cHL)、较罕见的富含淋巴细胞型(rarer lymphocyte rich, lr-cHL)和淋巴细胞耗尽型(lymphocyte-depleted, ld-cHL)[65]. 不同组织类型的肿瘤中, EBV感染率不同. 其中, mc-cHL显示出最强的EBV关联性, 80%~90%的肿瘤细胞呈EBV阳性感染. 不同地区患者EBV的感染率也不同, 非洲为74%, 拉丁美洲为60%, 亚洲为56%, 欧洲为36%, 北美洲为32%, 大洋洲为29%[61,66]. EBV感染引起的IM及存在免疫系统损伤会增加HL的发病风险[67]. B细胞在生发中心中需要表达高抗原亲和性的BCR才能抵抗正向选择的凋亡而存活, 由于EBV感染B细胞缺少高抗原亲和力的BCR, EBV的潜伏蛋白LMP1及LMP2A可替代B细胞低表达的BCR的功能, 激活BCR下游途径以抵抗凋亡, 促进HL的形成[68,69]. HL患者中EBV通常处于潜伏Ⅱ期, 可以表达潜伏蛋白EBNA1, LMP1, LMP2A/B, EBERs及BART microRNA[65].

EBV感染相关的上皮性肿瘤包括鼻咽癌、胃癌(gastric carcinoma, GC)及淋巴上皮瘤样肺癌(lymphoepithelioma-like carcinoma of the lung, LELC of the lung). EBV上皮性肿瘤具有许多类似的共同点, 例如都伴有大量淋巴样基质浸润, 病毒在肿瘤细胞中处于潜伏Ⅰ或Ⅱ型感染, 并且为单克隆状态. 宿主基因及EBV基因呈高度甲基化状态, 肿瘤细胞具备CDKN2A/PI3K类似的体细胞突变. 预后相对较好, 但对免疫检查点抑制剂响应度较差[70,71]. 这些特征提示, EBV对上皮性肿瘤具有相似的癌变途径, 能引起相似的体细胞突变及免疫微环境的改变. 但EBV与这些上皮性肿瘤之间的病因流行病学特征有所不同. 首先, EBV与鼻咽癌的关系具有明显的地域聚集性特点. 在高发区, EBV感染被认为是鼻咽癌发生的必要因素, 几乎在100%的肿瘤组织中可检测到EBV感染. 而EBV相关的胃癌和肺癌不具备类似鼻咽癌的地域性聚集特点. 其次, EBV与鼻咽癌发生之间的病因学证据已经获得较充分的前瞻性流行病学证据支持. 多个鼻咽癌高发区基于人群的前瞻性队列研究已证实, EBV在鼻咽癌发病前3~5年EBV处于活跃的复制状态, 表现为EBV的相关蛋白的IgA类(如VCA-IgA, EA-IgA, Dnase)抗体明显增高, 发病风险(hazard ratio, HR)增加达10倍以上, 并呈明显的剂量-反应关系[72~74]. 而基于人群的EBV相关胃癌及肺癌的前瞻性流行病学研究则相对缺乏, 仍需明确EBV感染与这些上皮性肿瘤间的病因流行病学关系.

2020年, 估计全球有124700~142500例鼻咽癌新发病例及72800~87800例死亡病例[75]. 鼻咽癌具有明显的地方聚集性, 高发地区主要集中在中国华南地区, 其病例约占全球的50%, 男性发病率为女性的2倍以上[75]. 世界卫生组织(World Health Organization,

WHO)将鼻咽癌分为2种主要组织学类型——角化鳞状细胞癌和非角化鳞状细胞癌. 高发区(中国华南地区)患者的病理类型以未分化型非角化鳞状细胞癌为主, 该类型的病例与EBV感染密切相关[76,77], 而高分化的角化型鳞状细胞癌仅占全球病例的20%, 在高发区相对罕见[78,79]. 一般认为, 鼻咽癌的发生是由遗传、EBV和环境因素交互作用导致. 其中, EBV感染是最主要致病因素. 鼻咽癌独特的地理分布特征促进EBV分型的研究, 包括EBNA1, EBER2, Rta, LMP1和BALF2的基因变异被发现与鼻咽癌的发病风险相关[80~84]. EBV在鼻咽癌中表现为潜伏Ⅱ型感染, C启动子处于高甲基化水平, 并表达LMP1, LMP2A/B, EBNA1和MicroRNA病毒潜伏期蛋白. 而且, 病毒主要以环状附加体的形式存在于肿瘤细胞中, 而很少在淋巴细胞中. 在所有肿瘤细胞EBV均为单克隆存在, 提示EBV在癌变的早期起到关键的作用.

EBV相关胃癌(Epstein-Barr virus-associated gastric cancer, EBVaGC)占所有新发胃癌的8%~10%, 每年约75000例[85]. EBVaGC好发于胃的近端区域, 包括贲门、胃底和胃体, 组织亚型包括淋巴上皮瘤样癌(lymphoepithelioma-like carcinoma, LELC)型和常规型腺癌; 超过80%的LELC型胃癌感染EBV, 而只有约15%的常规型腺癌感染EBV[86]. EBV在肿瘤中被分为潜伏Ⅰ或Ⅱ型感染, 并表达潜伏期蛋白LMP1, LMP2A/B, EBNA1[83~87], EBVaGC还具有DNA高甲基化的特点, 提示EBV调控CpG甲基化在癌变过程中发挥重要作用[86,87].

肺淋巴上皮瘤样癌(pulmonary lymphoepithelioma-like carcinoma, PLELC)作为非小型肺癌(non-small cell lung cancer, NSCLC)的亚型, 与EBV感染相关. 组织特征表现为未分化癌伴有大量淋巴细胞浸润, 类似于鼻咽癌病理特征[88]. 目前针对EBV相关的LELC型肺癌在不同地区的发病率, 尚缺乏全面的流行病学评估. 不过, LELC型肺癌在中国华南地区的EBV感染率较高, 且其体细胞突变特征与EBV感染相关的NPC具有相似性[89~91].

3　影响EBV感染的流行病学因素

3.1　环境因素

EBV对于鼻咽癌、淋巴瘤及多发性硬化症等自身免疫性疾病具有病因作用[92~95]. 因此, 识别与EBV再激活相关的环境危险因素对于EBV相关疾病的一级预防具有重要意义. 中国学者在广东[96~100]、香港[101]、台湾[102]等地区开展多项流行病学研究发现, 吸烟是影响EBV激活的主要因素, 分子生物学实验证明香烟提取物能够促进EBV复制并增强裂解期基因的表达水平[100]. 台湾人群的中介效应分析显示, 吸烟对鼻咽癌发病风险的影响约90%是通过EBV VCA-IgA抗体介导的, 即吸烟主要通过激活EBV进而增加鼻咽癌的发病风险[102]. 此外, 已有综述讨论使用固体燃料、食用咸鱼、阳光照射、精神压力、发生某些疾病、口腔致病菌感染, 以及携带某些特定易感基因对增加EBV裂解激活风险的可能性[100,101,103~106]. 一些化合物及细胞因子均被证明在体外可刺激PI3激酶、p38激酶、ERK激酶和蛋白激酶C信号通路, 激活EBV进入裂解复制状态, 如佛波酯、巴豆醇-12-十四烷酸酯-13-乙酸酯(TPA)、丁酸钠及TGF-β[107~109]. 未来需要在全球多个国家开展更为广泛的多中心研究, 以探讨全球范围内不同人群的环境暴露, 更好地了解EBV激活的多样性和影响机制, 为EBV相关疾病的一级预防提供潜在理论依据.

3.2　遗传因素

遗传因素在宿主对EBV感染的反应以及相关疾病的发生中发挥着重要作用. EBV感染后, 宿主的免疫系统起着控制病毒复制和清除感染细胞的关键作用. 然而, 个体的遗传背景可能影响其对EBV感染的易感性, 以及感染后发展成为相关疾病的可能性. EBV感染后, 宿主免疫系统会启动一系列复杂的免疫应答, 包括细胞免疫和体液免疫等. 细胞免疫通过活化T细胞和自然杀伤细胞(NK细胞)等效应细胞清除感染细胞, 而体液免疫则通过产生抗体来中和病毒颗粒和抑制病毒复制. 这些免疫应答协同作用, 使宿主能够有效地控制EBV感染后的免疫反应, 并防止相关疾病的发展.

人类白细胞抗原(human leukocyte antigen, HLA)分子在宿主免疫系统中扮演着重要角色, 其通过呈递抗原片段来激活T细胞和调节免疫反应[110~112]. 特定的*HLA*基因型可能影响HLA分子的抗原结合特异性和亲和性, 从而影响T细胞的免疫应答. 一些*HLA*基因型能够更有效地呈递EBV抗原片段, 激活EBV特异性T细胞应答, 从而有助于控制病毒复制和清除感染细

胞[113~115]. 而某些HLA基因型与较高的EBV载量和持续感染相关, 增加了该个体发展为EBV相关疾病的风险.

多项研究发现, *HLA*型别可影响血浆EBV抗体水平及EBV抗体表位选择, 在EBV相关疾病中发挥重要作用. 2013年一项包括1367名美国人的全基因组关联研究(genome-wide association study, GWAS)发现, HLA II类基因*DRB1*和*DQB1*是影响血浆EBNA1/IgG抗体水平的重要遗传易感基因. 有趣的是, 这些遗传易感位点同时也是多种EBV相关疾病的风险位点, 包括鼻咽癌、霍奇金淋巴瘤、系统性红斑狼疮、多发性硬化症等[116]. 随后在基于更大样本量的英国生物样本库(UK Biobank)人群和法国家系队列人群的GWAS研究中也得到类似的发现, 进一步证实*HLA*区域遗传变异与VCA/IgG, EBNA1/IgG, ZEBRA/IgG等多种EBV抗体水平显著相关[117,118]. 这些研究结果显示, *HLA*基因在宿主对抗EBV免疫反应中的核心作用. 近期, 基于TwinsUK双胞胎队列的研究在系统分析宿主对EB病毒抗体免疫反应的遗传特征方面取得新的进展. 研究者们利用噬菌体免疫沉淀测序(phage immunoprecipitation sequencing, PhIP-Seq)和人类病毒组检测技术(VirScan), 对494名双胞胎人群进行全面分析. 在涉及两百多种病毒的研究中, EBV表现出最多的活性肽. 进一步的GWAS分析显示, *HLA-DRA*, *HLA-DRB1*等HLA II类基因对于EBV抗体的表位选择发挥关键作用, 而*HLA-A, HLA-B*等HLA I类基因则显著影响外周血EBV载量[119].

值得注意的是, 宿主遗传变异与EBV感染可能存在复杂的交互作用, 例如2015年的一项meta分析发现, *HLA-DRB1*1501*等位基因与EBV感染对多发性硬化症存在显著的协同相加的交互作用[120]. 最近在中国华南地区进行的研究也发现宿主遗传因素(包括*HLA*区域遗传易感位点)与EBV VCA-IgA抗体/EBV病毒型别在鼻咽癌发生中的加性交互作用[121,122]. 这些发现强调在理解宿主遗传对EBV相关疾病影响的过程中, 需要考虑宿主与病原体之间的复杂相互关系. 未来的研究应更全面地阐明遗传与EBV感染之间的复杂关系, 以及它们在不同人群中的表现差异, 这将有助于全面理解宿主遗传因素在EBV相关疾病中的作用机制, 为个体化治疗和预防策略的制定提供更为精准的科学依据.

4 EBV相关疾病的流行病学因素

4.1 环境因素

EBV在多种疾病的发生中起着关键作用, 但除EBV的直接作用外, 环境因素也在这些疾病中发挥着重要作用. 研究表明, 吸烟、饮食习惯和紫外线辐射等环境因素与EBV感染及其相关疾病密切相关. 尤其是某些环境因素, 如吸烟, 与EBV之间可能存在相互作用, 共同推动疾病的发生. 因此, 本部分将对EBV相关疾病的环境因素进行综述, 探讨这些因素如何共同影响EBV相关疾病的发生.

4.1.1 吸烟

吸烟是已知的致癌因素, 与多种EBV相关恶性肿瘤的发生显著相关. 在我国华南地区、美国及马来西亚等地区的队列及病例对照研究表明, 吸烟与鼻咽癌的发生风险密切相关[123,124]. Meta分析结果显示, 吸烟者患鼻咽癌的风险增加60%, 且吸烟剂量与鼻咽癌的发生风险呈剂量-反应关系. 吸烟被认为是影响EBV激活的重要环境因素, 通过促进EBV的复制及增强病毒裂解期基因的表达, 进一步增加鼻咽癌的发生风险. 此外, 吸烟与多种类型的淋巴瘤显著相关, 包括非霍奇金淋巴瘤[125]和霍奇金淋巴瘤[126]等. 基于2020年全球数据的生态学研究表明, 霍奇金淋巴瘤的发病率和死亡率均与人群吸烟率呈显著正相关[127]. 香烟中的多环芳香烃是一种明确的致癌物, 能够诱导抑癌基因*p53*突变, 这一机制可能是吸烟促进淋巴瘤等恶性肿瘤发生的关键因素.

除恶性肿瘤外, 吸烟还与多种自身免疫性疾病相关. 在美国[128,129]和欧洲部分国家[130]开展的多项流行病学研究显示, 吸烟者罹患系统性红斑狼疮或出现相关症状的风险高于非吸烟者, 而戒烟者则无此现象. 吸烟对多发性硬化症的严重程度和预后也具有显著影响, 吸烟者的MS严重程度评分显著高于非吸烟者[131], 且继续吸烟会加速其转为继发进展型MS的进度, 而戒烟则有助于减缓疾病进展[132]. 香烟燃烧时产生的多种复杂有毒化合物质可能通过与宿主遗传因素互作、参与氧化应激、改变免疫细胞功能等机制, 促进SLE及MS的发生[133].

4.1.2 饮食习惯

在鼻咽癌高发区的华南地区, 特定的饮食习惯被

认为是鼻咽癌的危险因素. 例如, 食用咸鱼和腌制蔬菜与鼻咽癌的发生密切相关[134~136]. 研究显示, 食用咸鱼者与未食用咸鱼者相比, 鼻咽癌的风险显著增加. 此外, 腌制蔬菜的摄入也与鼻咽癌发生风险增高相关[137]. 反之, 食用新鲜蔬菜和水果则被认为是鼻咽癌的保护因素[137]. 对于淋巴瘤, 相关的饮食因素与鼻咽癌有所不同. 欧洲癌症与营养关系的前瞻性研究(The European Prospective Investigation into Cancer and Nutrition, EPIC)未发现蔬菜水果的摄入与淋巴瘤相关. 瑞典的研究则提示海洋性脂肪酸的摄入可能是非霍奇金淋巴瘤的保护因素[138]. 而膳食中缺乏硒和镁可能增加伯基特淋巴瘤的发病风险[139]. 在美国黑人妇女中开展的前瞻性研究提示, 不饱和脂肪酸及反式脂肪酸的摄入可能是系统性红斑狼疮的保护因素[140]. 尽管这些饮食因素显示出一定的保护作用, 但相关证据仍较为单一, 因此膳食因素与淋巴瘤、SLE和MS等自身免疫性疾病的关联需要进一步验证.

4.1.3 体育锻炼

体育锻炼被认为是非霍奇金淋巴瘤的保护因素, 特别是在女性群体中. 来自欧洲、美国及澳大利亚的8项大型队列联合分析表明, 每周进行7.5~15代谢当量小时(MET-hours)的体育锻炼是NHL的保护因素, 可降低女性发病率的11%~18%[141]. 然而, 鼻咽癌和其他类型淋巴瘤与体育锻炼的相关研究较为有限. 美国护士健康队列(Nurses' Health Study, NHS)研究则表明, 健康生活方式(包含了充足的体育锻炼、非吸烟等因素)与SLE的低风险相关[142], 提示体育锻炼对SLE可能具有保护作用.

4.1.4 紫外线辐射

紫外线辐射(UV radiation)对EBV相关疾病的影响呈现不同的作用. 紫外线暴露与多发性硬化症的发病风险降低相关[143], 可能通过促进机体维生素D3水平的升高起作用[144]. 然而, 紫外线辐射则被认为会加重系统性红斑狼疮患者的症状, 尽管其对SLE发病风险的具体影响尚不明确[145]. 一项病例对照研究发现, 职业性日晒可使携带谷胱甘肽S-转移酶Mu型同工酶(glutathione-S-transferase Mu, GSTM1)无效基因的个体患SLE的风险增高3倍[146]. 虽然紫外线暴露可能引起SLE风险的提高, 但紫外线照射也是体内维生素D3形成的必要条件, 经紫外线辐射后皮肤合成的维生素D可能会降低SLE的风险[147]. 适度的紫外线暴露历史, 如日光浴, 可能将非霍奇金淋巴瘤(non-Hodgkin lymphoma, NHL)发病风险降低30%~40%, 且随着暴露水平的增加, 这一负相关关系的强度也有所增强[148].

4.1.5 其他因素

除上述环境因素外, 还有许多其他因素可能与EBV相关疾病的发生有关. 例如, 肥胖与MS的发病率相关[144]; 职业性粉尘、大气污染物和环境有机污染物则可能是SLE和NPC的危险因素[149~154]. 接触农药或除草剂则可能提高SLE和淋巴瘤的发病风险[155,156].

4.2 EBV高危亚型

EBV虽然在全球感染普遍, 但其病毒亚型存在着地域分布的差异[157~162]. 目前普遍接受的EBV分型是基于其*EBNA2*和*EBNA3A/B/C*基因的多态性划分, 病毒被分为1型和2型. 1型EB病毒在世界大多数地区流行, 2型则主要在非洲部分地区流行. 此外, 基于*LMP1*和*EBNA1*等基因多态性也可对EBV进行亚型的划分. 但目前基于全球病毒序列的进化分析并未发现这些病毒亚型和特定的人类疾病具有显著的关联, 一般认为, 宿主和病毒在长期的互作中共同进化, 形成具有地域差异性的病毒亚型[163]. 近年来, 在我国开展的一些研究提示特定EBV亚型和鼻咽癌的发生具有显著关联, 如基于*BRLF1*启动子变异的V1型在中国鼻咽癌高发区的频率显著高于其低发区(52.4% *vs*. 18.2%), 且与口腔EBV DNA高拷贝数相关(OR=1.64, 95% CI:1.21~2.24), 该研究提示和鼻咽癌低发区相比, 高发区的V1亚型具有更强的EBV激活能力[82], 提示其可能与鼻咽癌地域分布差异相关. 我国华南地区开展的一项基于EBV全基因组测序的研究整合对比分析215个鼻咽癌及其他EBV相关癌症患者的肿瘤组织、唾液及血浆样本中的病毒序列, 发现位于病毒*BALF2*基因的两个突变与鼻咽癌高风险显著相关(162476T>C, OR=8.69, 95% CI: 5.79~13.03; 163364C>T, OR=6.14, 95% CI: 4.59~8.22)[84], 上述EBV亚型在中国华南地区对鼻咽癌的人群归因危险度为83%(PARF=82.8%, 95% CI=75.6%~90.0%)[84], 并与其他EBV相关肿瘤的发病风险无显著关联[84]. 另一项研究利用全球范围628个EBV基因组全长和792条蛋白氨基酸序列, 对22个关

键病毒蛋白进行进化分析，发现中国鼻咽癌患者中高度富集4种EBV特异氨基酸突变(BALF2 V317M, BNRF1 G696R, V1222I和RPMS1 D51E)[164]和携带原始病毒株者相比, 携带同时含4个变异的病毒株者罹患鼻咽癌风险增加31倍. 此外, 来自中国的研究团队基于鼻咽癌病例对照研究构建一个纳入661个EBV变异的鼻咽癌风险评分模型，该模型在区分鼻咽癌患者和健康人方面表现出良好的鉴别能力[165]. 上述研究提示, 特定的EBV变异可能和鼻咽癌的发生存在着关联，但其分子机制还有待进一步探索.

4.3 遗传因素

*HLA*基因是EBV相关疾病作为显著的遗传易感基因, 其关联性被多项流行病学研究反复验证, 足以证明其在相关疾病发生发展中的重要作用. *HLA*区域的易感关联信号在霍奇金淋巴瘤和多种非霍奇金淋巴瘤的亚型中均被报道[166]. 包括EBV感染相关的霍奇金淋巴瘤[167~170]，伯基特淋巴瘤[171]、自然杀伤性T细胞淋巴瘤(NK/T-cell lymphoma, NKTCL)[172,173]等. 其中, 位于HLA II类基因的关联信号报道最多, 例如, 多态性位点rs2040406所代表的等位基因*HLA-DQA1*04:01*以及该基因抗原结合口袋氨基酸变异53Q与BL的发病风险增加显著相关；位于*HLA-DRB1*基因抗原结合口袋P7的氨基酸变异47Y-67L与NKTCL的发病风险增加显著相关. 提示*HLA*分子可能通过参与病毒及肿瘤来源的抗原肽呈递，参与疾病的发生发展. 越来越多研究发现, 除*HLA*区域多态性位点，*HLA*等位基因的杂合性与多种淋巴瘤的发病降低显著相关[174~176]，其保护作用可能的解释是，*HLA*的杂合性优势有利于识别更为广谱的病原体及肿瘤抗原.

与EBV感染相关淋巴瘤相似，鼻咽癌的遗传易感信号也集中在HLA区域, 包括经典HLA I类基因(*HLA-A*，*-B*，*-C*)和HLA II类基因(*HLA-DQB1*，*-DRB1*，*-DPB1*)[177~184]，最新全转录组研究[185]以及*HLA*捕获测序研究[186]还发现该区域的非*HLA*基因*GABBR1*, *HCG9*, *TRIM*基因家族, *MIC*基因等. 此外, *HLA*捕获测序联合EBV全肽组学关联研究进一步揭示*HLA*与EBV的互作关系，发现携带鼻咽癌危险基因型*HLA-A02*超型的个体对包含EBV高危突变(如*BNRF1 V1222I*)的抗原肽结合能力显著降低，提示*HLA*等位基因遗传多态性通过影响个体EB病毒抗原肽的结合能力，参与鼻咽癌发生发展[115].

*HLA*基因多态性还与多发性硬化症、系统性红斑狼疮等多种EBV相关免疫疾病关联. MS是一种自身免疫性疾病，其特征是中枢神经系统中的炎症和脱髓鞘. 大量研究表明, *HLA*基因多态性是MS易感性的主要因素之一. *HLA-DRB1*基因*DRB1*15:01*，*DRB1*03:01*等位基因与MS的发病风险增加显著相关[187~189].

SLE是一种慢性自身免疫性疾病，其特征是多系统器官的炎症和损害. 遗传因素被认为在其发病中起着重要作用，其中HLA II类基因被报道得最多，例如*DQA1*，*DQB1*，*DRB1*等与SLE的发病风险显著相关[190~195]. 这些*HLA*基因型可能通过影响自身免疫反应和自身耐受性等机制参与MS，SLE等疾病的发病过程.

综上，这些研究为研究者更全面地理解宿主*HLA*对EBV感染的反应以及相关疾病的影响提供大量线索，有望促进对EBV相关疾病免疫机制的更深入理解. 需要注意的是，虽然目前对于*HLA*与EBV相关疾病发病风险相关性的研究日益增多，但不同研究的结果可能受到样本规模、人种差异、研究设计和方法等因素的影响. 因此, 需要进一步地大规模、多中心的研究来验证这些发现，并深入探究HLA遗传易感与EBV相关疾病之间的关系.

除*HLA*基因型外，其他免疫相关位点的变异也与EBV感染相关疾病的发病风险密切相关. 这些位点包括细胞因子基因和免疫调节基因等. 它们在调节宿主免疫反应中发挥着重要作用，影响着个体对EBV感染的抵抗能力以及相关疾病的发展. 既往研究表明，一些细胞因子基因的变异与宿主免疫反应的调节密切相关. 这些基因编码的细胞因子在调节炎症反应、细胞信号传导和免疫细胞活性等方面起着关键作用. 某些细胞因子基因的变异可能影响宿主免疫细胞对EBV感染的识别和清除能力，从而影响相关疾病的发展. 例如，IL-10，TNF-α和IFN-γ等细胞因子基因的单核苷酸多态性(single nucleotide polymorphism, SNP)已被发现与EBV相关疾病的易感性相关[196~202]. 此外，*CTLA-4*, *PD-1*和*PD-L1*等免疫检查点基因的变异已被发现与EBV相关疾病的发病风险相关[203~207]. 免疫调节基因编码的蛋白质在免疫细胞的发育、分化和功能调节中发挥着重要作用[208]. 这些基因的变异可能影响免疫细胞的功能和数量, 进而影响个体对EBV感染的反应. 综

上，免疫相关位点的变异在调节宿主免疫反应和影响对EBV感染的抵抗能力方面发挥着重要作用. 深入研究这些位点的功能和影响机制，有助于更好地理解个体对EBV感染的反应以及相关疾病的发展.

综上，EBV感染及其相关疾病受到多种因素的影响, 其中包括环境因素和遗传因素等. 环境因素, 诸如吸烟、饮食习惯等，被认为与EBV的激活及相关疾病的发生发展密切相关. 遗传因素，尤其是*HLA*相关基因，在宿主对EBV感染的免疫反应和相关疾病的发展中扮演着重要角色. 此外，免疫相关基因的变异也可能影响宿主对EBV感染的抵抗能力和相关疾病的发展. 未来, 通过进一步探究环境、遗传等多种因素之间的相互作用，我们将能够更深入地理解和应对EBV相关疾病. 这有望为个体化预防、诊断等提供更为精准的策略，为预防和控制EBV相关疾病提供更有效的手段.

5 EBV血清流行病学

5.1 血清EBV抗体在EBV初次感染或再激活期中的流行病学特征

在EBV感染的早期阶段，血清中特定的抗体表现出不同的动态变化，反映宿主免疫系统对病毒的复杂反应. 具体而言, IgM, IgG和IgA抗体在感染初期和感染后的不同时间点表现出不同的模式. IgM抗体是在感染的早期阶段产生的，通常在初次感染期间最早出现. 反映宿主免疫系统对病毒初次侵入的迅速应答, 主要作用在于阻止病毒扩散和启动宿主免疫系统的响应. 随着感染持续时间延长，IgM抗体水平逐渐下降[209,210]. IgG和IgA抗体通常在感染初期稍后出现，可持续存在较长时间, 甚至维持终身. 它们的产生反映了宿主免疫系统对病毒的持续性应答[209,210]. 这些抗体的水平在感染初期也会上升, 但相对于IgM抗体, 持续时间更长. 它们的存在有助于宿主免疫系统在感染后控制病毒复制和维持免疫记忆，提供对后续感染的保护. 在某些情况下, EBV可能发生再次激活, 激发宿主免疫系统对病毒的反应，从而引起抗体水平的变化[211]. 与初次感染相比，再激活期间的抗体水平变化可能更为迅速，因为宿主免疫系统已经具有对病毒的记忆反应. 这些抗体的动态变化反映了宿主免疫系统对病毒再次活跃的调节，并且可能在限制再次感染以及某些疾病的发生和发展中发挥作用.

5.2 血清EBV抗体在疾病诊断中的作用

EBV血清学检测是诊断传染性单核细胞增多症的基础，其中包括检测VCA-IgM抗体、VCA-IgG抗体、EBNA-IgG抗体以及血清中的EBV DNA载量等指标. 在IM患者中, VCA-IgM抗体通常是最早出现的标志物之一，其阳性检测提示当前处于EBV感染的活跃阶段[209,210,212,213]. 而在感染后的恢复期, VCA-IgG抗体和EBNA抗体通常会检测为阳性，表明宿主已经建立了对病毒的免疫记忆[214]. 此外，血清中的EBV DNA载量在诊断IM时也是一个重要的指标. 在感染初期，尤其是在临床症状明显的病例中, 血清中的EBV DNA载量通常会较高[215,216]. 一项纳入166名中国儿童的回顾性队列研究利用EBV特异性抗体与EBV DNA作为诊断IM的实验室检查方案，发现联合EBV DNA, VCA-IgM, VCA-IgG检测的诊断效能最佳，AUC高达0.999 (95% CI: 0.986~1.000), 敏感度达到100%, 特异性为89.8%[215]. 通过检测这些EBV血清标志物, 可以帮助确定EBV感染的活跃程度和病情的严重程度，为治疗和监测疾病进展提供指导[215,216].

在多发性硬化症患者中，研究发现EBV抗体水平通常显著增高，这可能反映免疫系统对EBV的过度激活或持续性感染. 具体而言，与健康人群相比，MS患者血浆中往往存在更高水平的EBV抗体，包括VCA-IgG, EBNA-IgG以及EA-IgG等. 尤其在MS发作期间, 这些抗体水平可能随着疾病的进展进一步增加[217,218]. EBNA-IgG与疾病活动有显著关联，特别是与复发严重程度和病变位置相关[218,219]. EA-IgG抗体则是在EBV的活跃感染或再激活时产生的，因此其水平可能在MS发作期间升高[217]. 除多发性硬化症, 系统性红斑狼疮、类风湿性关节炎(rheumatoid arthritis, RA)和干燥综合征(Sjogren syndrome, SS)等免疫相关疾病也与EBV感染密切相关. 研究表明, 这些免疫相关疾病患者中EBV感染率较高，血清中抗EBV抗体滴度和EBV病毒载量也相对较高[220]. 这些关联性的研究为进一步探索EBV与免疫相关疾病之间的关系提供了重要线索, 有望为相关疾病的诊疗提供一定的方向和策略.

EBV血清学检测在鼻咽癌筛查和辅助诊断中的应用是最为广泛和成功的(表1). 基于多项在鼻咽癌高发地区如广东省中山市和四会市以及广西壮族自治区梧

表 1 三项鼻咽癌筛查研究比较

Table 1 The comparison of three nasopharyngeal carcinoma screeningstudies

研究	检测方法	研究设计	主要纳入样本	筛检策略[a)]	灵敏度	特异度	阳性预测值	筛检阳性者中Ⅰ/Ⅱ鼻咽癌病例占比
Ji等人[221], Liu等人[222]	EBV-IgA血清学检测(VCA和EBNA1)	整群随机对照试验	28680名30~59岁男性和女性	A	93%(随访1年) 75%(随访8年)	97%(随访1年) 95%(随访8年)	4.4%(随访1年) 5.1%(随访8年)	68%(随访1年) 55%(随访8年)
Chan等人[223]	PCR检测血浆EBV载量	包含历史对照样本的前瞻性队列研究	20174名40~62岁男性	B	97%(随访1年)	99%(随访1年)	11.0% (随访1年)	70%(随访1年)
Li等人[224]	EBV-IgA血清学检测(P85-Ab)	病例-对照研究 前瞻性队列研究	24852名30~69岁男性和女性	C	97.9% (随访1.5年)	98.3% (随访1.5年)	10.0%(单独应用P85-Ab) 44.6%(P85-Ab与VCA-IgA, EBNA1-IgA联用)	79%(随访1年)

a) A: 对人群进行血浆EBV抗体检测, 根据VCA-IgA和EBNA1-IgA结合的Logistic模型得分, 将参与者分为高、中、低风险组. 高风险组被定义为筛查阳性, 并进一步进行临床检查确诊; 中风险组每年重新筛查1次; 低风险组在5年后重新筛查; B: 两时点检测方案: 进入队列时对各样本进行血浆EBV DNA检测, 结果阳性者在4周后重新检测. 两次检测均为阳性者被定义为筛查阳性, 并进一步进行临床检查确诊; C: 人群进行血浆EBV抗体检测, 血浆P85-Ab阳性者被定义为筛查阳性, 并进一步进行临床检查确诊

州市等地区进行的前瞻性队列研究发现, VCA-IgA, EA-IgA, EBNA1-IgA抗体阳性者的鼻咽癌发病风险明显升高, 且抗体水平升高现象最早可在发病前10年出现, 平均在发病前3年即可观察到[72,74,221,225~227]. 在多种抗体中, VCA-IgA及EBNA1-IgA的双抗体组合显示较好的诊断效能[228]. 基于此双抗体作为初筛手段, 在30~69岁的广东省中山市和四会市社区居民中开展一项随机对照试验(PRO-NPC-001)[222]. 其中, 中山市29413名社区居民参与筛查, 50636名居民作为对照, 经过近4.5年的随访, 显示鼻咽癌筛查敏感性和特异性分别为90.3%和96.2%, 阳性预测值为4.8%[221]. 在定期复查和随访12年后, 结果显示筛查地区的鼻咽癌死亡率相较于未筛查地区显著性下降达30%(P<0.05)[229]. 该研究首次证实EBV病毒抗体筛查降低死亡率的效果, 该方案已被国家卫健委纳入《癌症早诊早治项目技术方案》. 近期, 中国学者[224,230]发现一种新型EBV血清学标志物——BNLF2b, 使用该指标在高发区24852的队列人群中进行验证, 其灵敏度、特异度分别达到97.9%和98.3%, 阳性预测值达到10.0%, 有望在未来进一步提升高发区鼻咽癌的筛查效果, 提高筛查效率.

血浆EBV抗体或EBV DNA载量可能是EBV相关胃癌的生物标志物[231,232], 但是, 目前对于EBV与胃癌的研究仍较为有限, 缺乏高级别流行病学证据. 一项巢式病例对照研究纳入54名胃腺癌的日籍美国男性和108名健康对照, 认为血浆EBV抗体与胃腺癌的发病风险无显著关联[233]. 另一项由中国学者开展的巢式病例对照研究, 纳入185名胃癌病例和200名对照, 发现了类似的结果[234]. 在韩国人群开展的基于100名胃癌病例与200名对照的巢式病例对照研究同样发现血浆EBV抗体水平与胃癌的发病风险无关[235]. 因此, 受限于研究设计和样本量, 目前尚缺乏高质量大样本的前瞻性队列研究进一步明确评估EBV血清学标记物和EB-VaGC[236]之间的相关性, 未来需要加强对EBV感染情况与其他类型肿瘤关联的研究.

6 EBV DNA分子标志物在相关疾病早期诊断及疗效监测中的应用

除EBV抗体外, 其他EBV标志物也在鼻咽癌的诊断和预后中得到广泛的应用. 血浆游离EBV DNA载量已成功用于鼻咽癌筛查和早期诊断. 一项基于20174名中国香港男性人群的前瞻性队列研究显示, 基于血浆EBV DNA筛查的阳性预测值约为11%, 敏感性为97.1%, 特异性为98.6%, 可有效筛查出早期鼻咽

癌患者[223]. 该队列随访信息显示, 与初始研究时血浆EBV DNA 检测阴性的参与者相比, 初始EBV DNA短暂阳性和持续阳性参与者在后续随访中发生鼻咽癌的风险显著增加, 相对风险值分别为4.4和16.8[237]. 另外, 血浆EBV DNA载量对鼻咽癌的预后评估和复发监测具有重要的临床价值, 可以作为诊断和疾病监测的生物标志物之一. 多项研究表明, 鼻咽癌患者血浆中的EBV DNA载量与患者的临床病理特征和预后密切相关, 较高水平的EBV DNA载量通常与较差的治疗反应、短期生存率和总体生存率相关联[238~241].

除EBV特异性抗体水平和DNA载量外, 一些探索性研究发现新型分子标志物在鼻咽癌的筛查和诊断方面也展现出了较大的潜力. 2018年的一项研究基于全基因组测序的血浆DNA片段长度研究, 观察到鼻咽癌患者的EBV DNA片段长度主要分布于166 bp和150 bp左右, 而健康人的EBV DNA片段较短. 根据这些结果, 结合血浆中EBV DNA载量和特定长度EBV DNA在血浆DNA中的占比, 用于鼻咽癌的诊断, 研究结果显示该方法具有良好的诊断性能(灵敏度=97.1%, 特异度=99.3%), 并将阳性预测值从11%提高至19.6%[242]. 此外, 血浆游离EBV DNA甲基化对鼻咽癌的早期诊断也展示良好的性能. 中国香港同一团队于2019年应用血浆DNA全基因组甲基化分析15名鼻咽癌患者, 9名EBV相关淋巴瘤患者、5名传染性单核细胞增多症患者的血浆EBV DNA的甲基化谱, 确认不同EBV相关疾病间存在不同的血浆EBV DNA甲基化模式, 并定义158个鼻咽癌特异性差异甲基化区域(differentially methylated regions, DMRs). 进一步将EBV DNA甲基化评分结合EBV DNA载量及片段比值进行分析, 发现与后者相比, 该筛查队列的阳性预测值从16.6% 提高至35.1%(灵敏度=97.1%, 特异度=99.7%)[243].

由于抽血检测的参与度和依从性问题, 自采样(非临床人员指导的采样)的筛检手段逐渐受到重视. 唾液EBV DNA甲基化检测因其无创和便捷性, 在提供有创血液检测外的多模式检测中具有一定潜力. 在一项纳入477例鼻咽癌病例和432例对照的研究中, 基于唾液CpG位点甲基化检测的灵敏度和特异度分别为75.8%和99.7%[244]. 另外, 通过鼻内镜引导的鼻咽拭子采样, EBV DNA载量检测的灵敏度和特异度分别为92.9%和95.8%, EBV DNA甲基化检测的灵敏度和特异度分别为95.9%和91.7%[245]. 此外, 研究者对无内镜引导的鼻咽刷采样(盲刷采样)法也进行探索, 一项纳入164例鼻咽癌病例和141例对照的研究发现, 利用盲刷采样的EBV DNA甲基化率检测的诊断性能受取样方式的影响不大: 内镜引导下刷样AUC=0.923, 无内镜引导盲刷采样训练集AUC=0.928, 验证集AUC=0.902[245]. 然而, 上述两种探索性研究的样本量较小, 还需在更大的人群中进一步评估才能广泛应用实施. 此外, 有报道探究鼻咽拭子EBV DNA载量检测对鼻咽癌筛查阳性人群的分流效果, 研究结果显示鼻咽拭子EBV DNA载量检测可以减少约40%的双抗体阳性人群的非必要临床检查[246], 提高阳性预测值(PPV)达10%; 而鼻咽拭子EBV DNA甲基化具有更高的特异性, 也是一个极具潜力的分流指标[247].

7 总结与展望

EBV无处不在, EBV与人类疾病的关系可能远比人们已知的更为广泛和复杂, 其造成的疾病负担也远比目前的估计更为严重. 未来, 需要更多研究投入到该领域中, 包括发现EBV与疾病的更为广泛的流行病学证据、基于更多检测方法如多组学的EBV相关疾病病因学研究等. 更为重要的是, 基于对EBV致病机制的深入了解, 研究者应致力于探索EBV相关疾病的预防手段, 包括研发EBV疫苗以及实施针对其他病因因素的一级预防策略. 同时, 建立基于更准确、便捷的早期诊断技术的二级预防策略, 也是未来努力的方向. 全球相关领域科学家需要通过广泛的合作与交流, 共同应对EBV感染带来的挑战, 以期为保障人类健康作出更大的贡献.

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Epidemiological studies of Epstein-Barr virus and associated diseases

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Epstein-Barr virus (EBV), a member of the γ-herpes virus family, is commonly found in almost all humans worldwide and establishes a lifelong infection. Although most individuals remain asymptomatic after infection, mounting evidence suggests a significant association between EBV and various serious diseases. This review provides a comprehensive examination of the natural history and characteristics of EBV infection, including its transmission routes, latent phases, and lytic replication processes. Additionally, we summarize the effects of environmental and genetic factors on EBV infection and EBV-associated diseases, including autoimmune conditions such as infectious mononucleosis, multiple sclerosis, and systemic lupus erythematosus, as well as malignancies like lymphoma, nasopharyngeal carcinoma, and gastric cancer. We particularly emphasize the crucial role of immune-related genetic factors, such as *HLA* genes, in the carcinogenicity of the virus. Furthermore, we discuss the crucial role of emerging biomarkers, including EBV serologic markers (such as VCA-IgA, EBNA1-IgA, BNLF2b) and cell-free nucleic acids (such as EBV DNA load and EBV DNA methylation), in clinical applications. Understanding the epidemiological characteristics of EBV infection is important for the prevention and management of EBV-associated diseases. In conclusion, this review provides robust epidemiological evidence to deepen the understanding of the etiology, pathogenesis, prevention and management strategies related to EBV-associated diseases.

EBV infection, **EBV-associated diseases**, **epidemiology**

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