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EB病毒在体内传播机制的研究进展

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[摘 要] 爱泼斯坦-巴尔病毒(Epstein-Barr virus，EBV)是一种常见的疱疹病毒，与多种淋巴瘤和上皮恶性肿瘤的发生发展有关。已知EBV在体内感染主要存在原发感染、潜伏感染和裂解性感染等一系列生物循环。EBV通过细胞膜上CD21独立/非独立途径入侵宿主细胞，环化的病毒末端重复序列与核小体结合成游离基因，修饰导致特定DNA序列甲基化和去甲基化，调节病毒从潜伏感染到裂解的转换；通过病毒DNA滚环复制模型形成单独的EBV基因组，在外泌体介导下EBV感染细胞转移mRNA到靶细胞，产生体内传播。深入研究EBV入侵宿主细胞及其体内复制、表达、释放、感染周围细胞的机制可为阻止EBV体内传播，抑制感染提供新线索。

[关键词] 爱泼斯坦-巴尔病毒；感染；体内传播

Advances on the mechanism of Epstein-Barr virus transmission in vivo

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Abstract Epstein-Barr virus (EBV) is a common herpesvirus that is associated with a variety of lymphoid and epithelial malignancies. It is known that EBV infection in the body mainly includes a series of biological cycles such as primary infection, latent infection, and lytic infection. EBV invades the host cell through the CD21 independent/independent pathway on the cell membrane. The circularized virus terminal repeat sequence combines with the nucleosome to form a free gene. The modification results in the methylation and demethylation of specific DNA sequences, regulating the virus from latent infection to The conversion of lysis; a separate EBV genome is formed by the viral DNA rolling circle replication model, and EBV-infected cells transfer mRNA to target cells under the exosomes, resulting in in vivo transmission. In-depth study of the mechanism by which EBV invades host cells and their replication, expression, release, and infection of surrounding cells can provide new clues to prevent EBV from spreading in vivo and inhibit infection.

Keywords Epstein-Barr virus; infection; transmission in vivo

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EB病毒(Epstein-Barr virus，EBV)是一种只感染人类的γ-疱疹病毒，1964年首次由Epstein团队在伯基特淋巴瘤(Burkittlymphoma，BL)中发现，由184 kb大小的双链DNA组成，主要通过唾液传播[1]。全球95%的人曾感染过EBV[2]，它能在体内潜伏感染，也能导致多种疾病及肿瘤的发生，目前已知与EBV感染相关的肿瘤包括上皮性肿瘤如鼻咽癌(nasopharyngealcarcinoma，NPC)，胃癌(gastric carcinomas，GC)，淋巴造血恶性肿瘤如霍奇金淋巴瘤(Hodgkin's lymphoma，HL)和非霍奇金淋巴瘤(non-Hodgkin lymphoma，NHL)、BL、脓胸相关淋巴瘤(pyothorax-associated lymphoma，PAL)和NK/T细胞淋巴瘤及其他少见的肿瘤(如EBV相关性平滑肌瘤、神经内分泌癌)等[3-5]。EBV对人类的威胁远不止于此。因此，了解EBV如何感染宿主并在体内进行传播发展过程显得尤为重要。

1 EBV 侵入宿主细胞的机制

1.1 EBV 侵入 B 淋巴细胞

EBV是一种通过唾液传播的病毒，口咽黏膜上皮细胞是其入侵宿主细胞的第一道门槛，EBV的原发感染被认为是由穿过口咽上皮的病毒引发的，感染存在于Waldeyer's扁桃体环中的幼稚B细胞。EBV对B淋巴细胞显示出明显的趋向性，容易感染B细胞并将初始B细胞转化为增殖的类淋巴母细胞。病毒糖蛋白包括gp350，gHgL，gB和gp42等通过与B细胞表面补体受体CR2(CD21)相互作用介导EBV与B细胞优先结合，随后包膜糖蛋白gp42与gp85/gp25形成融合蛋白三分子复合物，复合物中的gp42与HLA II类分子结合，在gp85/gp25及gp110糖蛋白的参与下引发病毒细胞融合[6]。Haverkos等[7]认为EBV糖蛋白gHgL/gB和gp42共同介导，通过胞吞作用及病毒与胞膜融合作用共同参与EBV入侵B细胞。B细胞是EBV的天然宿主[8-9]。

1.2 EBV 侵入 T/NK 淋巴细胞

EBV也可感染T/NK淋巴细胞，但EBV附着及侵入T/NK淋巴细胞的机制尚未阐明[8]。T/NK淋巴细胞既不表达CD21也不表达HLA II类，但T/NK淋巴细胞表达一些整合素(integrins)，在受到刺激时整合素表达增加，可作为T/NK淋巴细胞的受体。研究[10]显示原始T淋巴细胞和淋巴祖细胞均可表达CD21，EBV也可通过CD21附着于T淋巴细胞上感染原始T细胞和淋巴祖细胞。文献[11-13]报道慢性活动性EBV感染患者(chronic active EBV infection，CAEBV)T淋巴细胞和NK细胞双重感染，进一步支持EBV可能感染T细胞和NK细胞共同的祖细胞。

EBV也可通过细胞–细胞间感染，即从EBV感染的B细胞或上皮细胞传播给T/NK淋巴细胞[14]。EBV感染的B细胞可以激活NK细胞，通过突触转移(synaptic transfer)的方式使其获得CD21分子，异位的受体导致EBV与NK细胞结合[15]。研究[16-18]表明感染了EBV的T/NK淋巴细胞通常表达细胞毒性分子，如穿孔素、粒酶B和T细胞胞质内抗原(T cell intracytoplasmic antigen，TIA-1)。EBV相关性T/NK淋巴细胞肿瘤中观察到NK细胞、$CD8^+$ T细胞和γδT细胞是典型的EBV感染细胞，属于杀伤细胞类型，这些试图杀死EBV感染的B细胞或上皮细胞的T/NK淋巴细胞可能通过免疫突触密切接触而感染EBV[19]。

1.3 EBV 侵入鳞状上皮细胞

EBV最初通过口咽黏膜进入体内，通过病毒包膜蛋白gp350与B细胞表面CD21结合而感染B细胞。上皮细胞不表达CR2，EBV如何侵入上皮细胞及从上皮细胞释放机制尚未明确。有研究显示EBV可通过3个独立于CD21(CR2)的途径进入舌、咽上皮细胞：1)通过顶端细胞膜与EBV感染的淋巴细胞直接的细胞-细胞间接触；2)通过β1或α5β1整合素与EBV BMRF-2蛋白之间的相互作用介导EBV游离病毒颗粒进入基底膜；3)初次感染后，EBV直接穿过外侧膜扩散到邻近上皮细胞[20]。

抗EBV抗原的聚合物IgA可通过内吞途径介导EBV侵入咽上皮细胞，结合IgA的EBV可通过分泌小体(secretory corpuscle，SC)介导内吞作用侵入咽上皮细胞[21]。在鼻咽癌患者的黏膜分泌物中发现抗EBV特异性抗原IgA水平升高，这种EBV-IgA-SC介导的内吞作用可能代表EBV在体内侵入鼻咽上皮细胞的生理途径[22]。Wang等[23]研究发现神经毡蛋白1(neuropilin 1，NRP1)是上皮细胞感染EBV的受体，EBV通过NRP1与EBV包膜蛋白gB相互作用、促进EBV内化及融合，巨噬细胞增多及脂筏依赖性内吞作用侵入鼻咽上皮细胞。NRP1部分介导EBV活化的EGFR/RAS/ERK信号转导，NRP1依赖性受体酪氨酸激酶(receptor tyrosine kinase，RTK)信号转导促进鼻咽上皮细胞EBV感染[23]。

1.4 EBV 侵入腺上皮细胞

EBV感染腺上皮细胞可引发胃癌及胆管癌，机制不清。目前推测至少有3种模型作为EBV附着于腺上皮细胞的机制，与EBV侵入鳞状上皮细胞的

机制或有重叠：1)已证明带有对gp350/220特异的IgA的EBV病毒粒子可以有效地与聚合的IgA受体结合[24]。聚合的IgA通常存在于人唾液中，并与极化上皮细胞基底外侧表面表达的跨膜蛋白结合。EBV-IgA-SC复合体通过内吞途径内化到腺上皮细胞，与通过上皮细胞基底外侧表面的感染机制有关，可能类似于病毒在体内的生理性感染[25]。2)已证明在CD21(CR2)缺乏的情况下，gH和gL复合体可作为上皮的配体，来源于B细胞的EBV能高亲和力地与CD21(CR2)阴性的上皮细胞结合，但缺乏gH/gL复合体的EBV丢失结合的能力[26-27]，提示EBV表面存在的gH/gL复合体可与上皮细胞特异性受体(如整合素αVβ6和αVβ8)直接结合而触发EBV与上皮细胞质膜的融合[28]。3)EBV编码的膜蛋白BMRF2与极化上皮细胞上的整合素相互作用是EBV附着到细胞表面的另一模型[29]。BMRF2分子中的三肽Arg-Gly-Asp(RGD)基序作为rβ1，α5，α3和αV整合素的配体呈现[30]。然而，BMRF2不是细胞-细胞融合所必需的膜蛋白[31]，并且病毒粒子中存在的BMRF2分子很少[32]。目前尚不清楚BMRF2与整合素的相互作用是否主要负责附着和/或后附着事件。

新近研究[33]提示EphA2是EBV感染上皮细胞的关键受体，能直接特异性结合EBV糖蛋白gB和gH/gL，这种相互作用是通过EphA2细胞外结构域(EphA2 extracellular domain，EphA2-ECD)完成的，进而促进EBV的内吞和融合。

2 EBVDNA在细胞内的整合与复制机制

2.1 EBV DNA在B淋巴细胞内的整合与复制机制

EBV侵入B细胞后，线性病毒DNA通过连接病毒末端重复序列(terminal repeat，TR)进行环化，该过程将EBV编码的膜蛋白1(LMP1)-2A基因的杂乱编码区组合成转录功能单位并同时生成一个独特的短DNA序列排列到核小体上，通过募集细胞蛋白，如组蛋白和染色质重塑复合物，将其包装成复杂的微小染色体结构，即游离基因。随后EBV游离基因作为表观遗传修饰的有效诱导剂，通过对抑制表观遗传标记的作用修饰病毒基因组中特定DNA序列的甲基化和去甲基化，调节病毒从潜伏感染到裂解的转换[34]。研究[35-36]表明通过组蛋白去乙酰化酶(histone deacetylase，HDAC)抑制剂和去甲基化剂在体外和体内激活细胞中EBV早期基因BZLF1(也称为ZEBRA)启动子区域(Zta)。潜伏期的重新激活取决于病毒BZLF1蛋白的表达。通过表达病毒编码的两种立即早期(IE)转录因子启动病毒复制：BamH1片段Z左阅读框1(BZLF1)和BamH1片段R左阅读框1(BRLF1)[37]，激活一系列参与复制病毒DNA的基因[38]。

EBV感染细胞的细胞核中具有潜伏状态和溶解复制周期[39]。文献[40-41]报道：在EBV潜伏感染期间，EBV基因组维持为环状质粒分子，在S期通过细胞DNA复制机制扩增1次。当早期蛋白BZLF1表达引发感染细胞从潜伏期转变为裂解周期时，产生子代病毒。在诱导有效的病毒复制后，EBV基因组通过由BALF5 DNA聚合酶(Pol)、BMRF1聚合酶持续合成因子、BALF2单链DNA结合蛋白和BBLF4-BSLF1-组成的病毒复制机制扩增100~1 000倍。

EBV普遍存在原发感染、潜伏感染和裂解性激活一系列生物循环，每种潜伏感染类型(0，I，II或III)均有其特定的EBV转录程序。研究[8]表明B细胞潜伏感染期间表达的全部潜伏EBV基因包括6种核抗原[EBNA 1，2，3A，3B，3C和前导蛋白(LP)]，3种潜伏膜蛋白(LMP1，2A和2B)，2个小的EBV编码RNAs(EBER1和EBER2)和3个微小RNA群(miRs)。而在裂解循环期间，表达大多数病毒编码的基因。裂解基因的产物介导病毒基因组的扩增、病毒结构蛋白的合成和病毒衣壳的形成[42]。

2.2 EBVDNA在NK/T细胞内的复制与表达机制

基于EBV在B细胞中的感染模式，EBV潜伏期分为0，I，II或III 4种类型。除潜伏期0型外，所有潜伏期类型均表达EBNA1蛋白、EBER1和EBER2及不同类型和水平的miRNA。潜伏膜蛋白(LMP1，LMP2A/2B)在潜伏期II和III型中表达，其他EBNAs(EBNA2， EBNA3和EBNA-LP)在潜伏期III型中表达[43]。与霍奇金淋巴瘤和鼻咽癌相似，EBV感染的T/NK细胞属于潜伏期II型，仅表达EBNA1，LMP1和LMP2A 3种病毒蛋白[44-46]。非编码RNA(例如EBER和BART)也以此潜伏类型表达。在潜伏期II型中，免疫显性抗原、EBNA2和EBNA3s未表达。因此，感染EBV的T/NK细胞不表达针对细胞毒性T淋巴细胞的主要抗原，逃避宿主免疫反应。

许多研究[42-43,47]显示：感染EBV的T/NK细胞中也存在裂解性复制，EBV编码裂解DNA复制所必需的蛋白质，而不依赖于细胞DNA复制。两个核心oriLyt复制元素(裂解复制的起源)在裂解感染期间能介导病毒DNA复制，在复制室的核内位点上遵循滚环复制模型产生指数级的基因组扩增。核心复制元素包括原始结合蛋白(ZEBRA)，单链DNA结合蛋白(BALF2)和5种复制酶和辅酶，即解

旋酶(BBLF4)，引物酶(BSLF1)，引物酶相关因子(BBLF2/3)，DNA聚合酶(BALF5)和DNA聚合酶持续合成因子(BMRF1)。复制的第一步是原始结合蛋白(ZEBRA)与oriLyt中反应元件结合募集其他复制蛋白[42-43,47]。

2.3 EBV DNA 在鳞状上皮细胞内的复制与表达

研究[42]发现原发感染中EBV病毒侵入口腔上皮细胞，经历裂解性复制，产生新的病毒。释放的病毒颗粒扩散到口腔黏膜下层感染循环B淋巴细胞建立原发感染[42]。在潜伏感染期间，EBV基因组附加体环状染色质样DNA结构使用宿主DNA复制机制在潜伏感染的细胞内以S期复制一次[48-49]。在裂解感染期间，病毒基因组在复制区内扩增100~1 000倍[50]。通过病毒DNA滚环复制模型，巨大的串联DNA分子最终被切割成单独的EBV基因组，并被包装成传染性病毒体释放到细胞外而发生传播[50-51]。

EBV相关性NPC中，p53家族蛋白p63同种型的ΔNp63通常过度表达，可能有助于维持EBV潜伏感染[52]。p16沉默对上皮细胞持续EBV感染至关重要[53]，EBV感染不会诱导原代或永生化鼻咽上皮细胞的增殖[54]，EBV感染的细胞停滞或进入衰老，p16和p21表达增加[53]。p16失活和/或cyclin D1过表达超过EBV感染的生长抑制作用，导致受感染细胞稳定表达II型潜伏基因。癌前期鼻咽上皮普遍存在p16失活和cyclin D1过表达[55]。多囊复合蛋白Bmi-1过表达可使鼻咽原始上皮细胞永生化并支持EBV潜伏感染[56]。宿主细胞因子和病毒基因表达的复杂关系可能涉及EBV感染的上皮细胞增殖与转化的调节。

2.4 EBV DNA 在腺上皮细胞内的复制与表达

全基因组测序证实病毒DNA全部整合到宿主基因组的情况极为罕见[57-58]，EBV相关性胃癌(EBV-associated gastric cancer，EBVaGC)的EBV-DNA拷贝数(<100个)不等。相同数量的拷贝数能传递给子细胞，以维持克隆生长期EBV基因组的数量。病毒核蛋白EBNA1将病毒游离基因连接到宿主染色体，招募细胞起源识别复合体到病毒DNA复制起点(oriP)[59]，病毒的复制分离与宿主细胞复制和有丝分裂同步[60]，维持了宿主细胞的持续感染。

腺上皮细胞感染EBV后，除了病毒潜在基因表达外，还进行了病毒基因组环化和染色质化，包括病毒染色质的组装、组蛋白翻译后修饰、DNA甲基化以及高阶染色体构象的形成[60]。

与BL相似，EBVaGCs也表现为潜伏I型，表达病毒基因，包括EBNA1，EBER和Bam HI-A转录物(BART)，EBNA启动子(Cp和Wp)高度甲基化，以及EBNA启动子Qp的使用，表明EBV基因组甲基化能调节EBV阳性肿瘤细胞潜在基因的表达模式[5,61]。

3 EBV 在已感染细胞中的释放与传播机制

EBV是一种唾液传播的病毒，容易穿过口腔鳞状上皮细胞的顶端膜至基底外侧膜的双向转运，潜在地促使初始EBV渗透并导致全身感染，同时通过受感染个体的唾液得以群体传播[9]。感染EBV的B淋巴细胞在病毒复制后，释放病毒粒子感染口咽上皮细胞。记忆B细胞分化成浆细胞会引发裂解性感染，释放EBV颗粒感染口鼻上皮细胞[62]。

环化EBV基因组复制产生一个长线性DNA聚合体，该聚合体进一步被切割成单个EBV基因组，并包装入病毒衣壳[43]。 在病毒DNA复制后，合成病毒结构蛋白，如包膜糖蛋白gp350/220，称为晚期抗原，引导病毒粒子的组装和释放[42]。

研究[63-64]表明：外泌体介导从感染EBV的细胞转移mRNA被认为是病毒进入B淋巴细胞以外细胞类型的可能机制。外泌体是正常细胞或肿瘤细胞释放的微囊泡，含有各种功能性RNA，包括mRNA和miRNA[65-67]。功能性mRNAs可以转移到靶细胞，并被翻译成细胞调节信号和功能蛋白质，包括转录因子、蛋白激酶和代谢酶[68]。研究[69]表明EBV阳性细胞或LMP阳性细胞外泌体分泌的膜蛋白1(LMP1)可促进肿瘤的进展和癌变。LMP 1装载到外泌体的过程可能与泛素C末端水解酶L1(Ubiquitin C-terminal hydrolase L1，UCH-L1)的多功能分子相关。EBV编码的小RNA(EBER)存在于EBV转化细胞释放的外泌体中，通过外泌体La蛋白EBER-1得到释放分泌[70-73]。Kimura等[19]发现EBERs可由EBV感染的细胞通过外泌体分泌，并发现外泌体中含有大量EBV编码的miRNA，各种mRNA已被确认为宿主细胞中EBV-miRNA调控的靶点，因此EBER和EBV-miRNA可能通过外泌体的转移发挥作用。

4 结语

EBV入侵宿主细胞及其在体内复制、表达、释放、感染周围细胞的深入研究有望阐明EBV体内

长期感染及引发多种疾病的机制，为通过裂解EBV结合蛋白、抑制DNA体内复制、抑制病毒释放以及感染周围细胞等方式来阻止EBV体内传播，抑制EBV感染的临床研究提供新的线索。

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