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• 特约专稿 •

人乳头瘤病毒与肿瘤

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摘要:人乳头瘤病毒(human papillomavirus, HPV)感染是全球最常见的性传播感染之一。根据致癌潜力,该病毒被分为高危型和低危型两种。HPV16 和 18 是最常见的高危型,也是引起宫颈癌(uterus cervical carcinoma, UCC)的病原体。近来报道的头颈部鳞状细胞癌(head and neck squamous cell carcinoma, HNSCC),包括鼻咽癌、口咽癌、喉癌,尤其是口咽部的扁桃体鳞状细胞癌的发生也与高危型 HPV 有一定的关联。由 HPV 引起的癌症尚无特殊的治疗方法,青春期男、女孩可接种 HPV 疫苗以预防相关的肿瘤发生。

关键词:人乳头瘤病毒;宫颈癌;头颈部鳞状上皮癌;疫苗

Human papillomavirus and cancer

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Abstract: Human papillomavirus (HPV) infection is one of the most common sexually transmitted infections worldwide. Based on the potential on carcinogenesis, HPV is classified into high- and low-risk types. The most common high-risk types are HPV16 and HPV18 that are the causative agents for uterus cervical carcinoma. Recent studies have shown that HPV is associated with squamous cell carcinomas of the head and neck (nasal pharynx, oropharynx, and larynx), especially the tonsillar squamous cell carcinoma in oropharynx. However, the role of HPV infection in head and neck carcinogenesis is not fully established. Currently there is no specific therapeutic for HPV-induced cancer. Therefore, it is necessary to immunize adolescent girls and boys in order to prevent HPV infection and HPV-associated cancers.

Keywords: Human papillomavirus; Uterus cervical carcinoma; Head and neck squamous cell carcinoma; Vaccine

人乳头瘤病毒(human papillomavirus, HPV)是性病传播感染最常见的病原体之一。HPV 有 170 多种基因型,根据致癌潜力,该病毒被分为高危型和低危型两种。低危型 HPV 为常引起生殖器疣和喉乳头状瘤的病原体^[1]。高危型 HPV16 和 18 的感染与 95% 的宫颈鳞状细胞癌有关^[2],也与头颈部肿瘤有密切关系^[3-4]。肛门生殖器、口咽部癌与 HPV 的因果关系已得到很好确立,抗病毒研究已逐

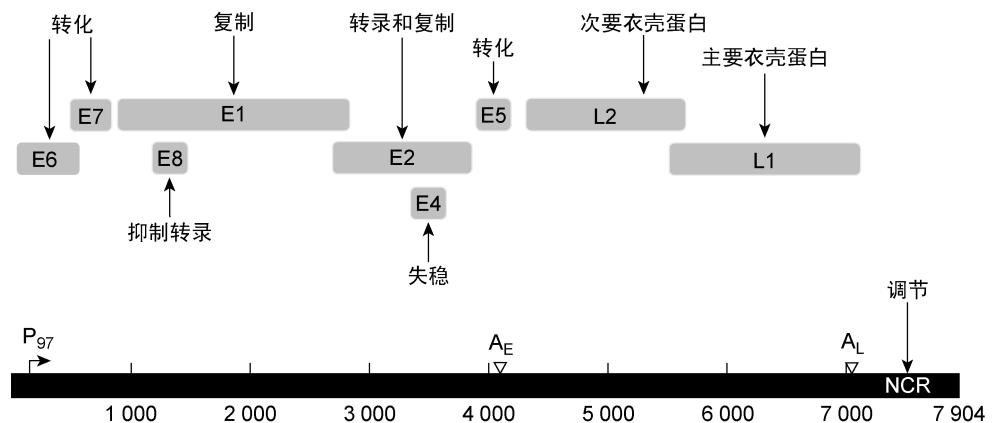
步成为国际热点。

1 HPV

HPV 属乳头瘤病毒科微小乳头瘤病毒,为无包膜的二十面体 DNA 病毒。病毒颗粒直径为 55~60 nm,由共价单链双分子组成封闭的约 7 900 bp 的环状 DNA 基因组(图 1)。所有的编码序列位于一条 DNA 链上,含有至少 6 个早期开放读码框

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ORFs deduced from the DNA sequence are designated E1 to E8, L1, and L2, indicated in grey boxes. A non-coding region (NCR) is indicated by a black box. Main functions of genes are listed.

图 1 HPV16 的基因组组成及其主要功能

Fig. 1 Genomic organization of HPV16

(open reading frame, ORF)、2个晚期 ORF、控制区 (LCR)、上游调控区 (URR) 或非编码区域 (NCR)。

1.1 分类

1.1.1 基因型 HPV 基因分型基于其主要衣壳蛋白 L1 ORF 内部的同源性^[5-6]。根据 1995 年魁北克国际乳头状瘤病毒研讨会的商定^[7]，如新分离株的 L1 ORF 的 DNA 序列与最接近的已知类型相差超过 10%，定为新型；如相差介于 2%~10%，可称为亚型；若<2% 则为变异株。目前，170 多种 HPV 基因型已全部被测序，各自有其不同的生命周期特征和致癌潜力^[8-11]。

1.1.2 黏膜和皮肤型 据被 HPV 感染后先出现病变的位置，分为皮肤型和黏膜型。皮肤疣与皮肤型 HPV 相关，主要由 HPV1、2、4 引起；但也可能由 HPV5、8、9、23、47 引起，被紫外线照射后可转为恶性肿瘤^[12-13]。黏膜型 HPV 存在于呼吸道和生殖器官黏膜表面。目前已知有 40 多种 HPV 被确定，最常见的为 HPV6、11、16、18、33 等^[5]。

1.1.3 高危和低危型 以病毒不同的致癌潜力区分病毒类型。Munoz 等认为，高危型有 15 种，包括 HPV16、18、31、33、35、39、45、51、52、56、58、59、68、73 和 82；此外，HPV26、53、66 被分为可能高危型；低危型包括 HPV6、11、40、42、43、44、54、61、70、72、81 和 CP6108^[2]。

1.2 传播途径

HPV 的传播途径包括水平传播和垂直传播。在水平传播模式中以性传播途径最为常见^[14]，也有

报道在无性生活史的成人和儿童中可通过自、异体接种或污染物传播^[15-17]。垂直传播途径指被 HPV 感染的母亲可能在生产过程中及产后的密切接触中将病毒感染婴儿^[18]。Chen 等报道约有 5% 学龄前幼儿及 10% 学生的扁桃体上皮组织中被检出 HPV16 DNA，进一步支持 HPV 可通过垂直型传播^[19]。

1.3 致癌机制

1995 年，国际癌症研究机构 (International Agency for Research on Cancer, IARC) 将 HPV16 和 18 定性为人类致癌物，是宫颈癌的主要病因^[20-22]。高危型 HPV 有 2 个主要的肿瘤蛋白 E6 和 E7。E6 蛋白通过与细胞 E6 相关蛋白 (E6AP) 及肿瘤抑制蛋白 P53 相结合，导致 P53 泛素化蛋白酶体降解及抗细胞凋亡，使细胞周期停滞或无限增殖。E6 蛋白也可与细胞 PDZ 蛋白结合，导致细胞极性和信号传导的破坏。此外，E6 蛋白还可以激活细胞端粒酶 (hTERT)，引起细胞无限增殖^[24-25]（图 2A）。E7 蛋白可使抗视网膜母细胞瘤的肿瘤抑制蛋白 pRb 磷酸化和泛素化，从而促进细胞分裂。同时，E7 蛋白可激活细胞转录因子 E2F，通过细胞肿瘤抑制蛋白 p16 途径，促进细胞分裂，诱导异常中心体复制，使多倍体和基因组不稳定^[23-24]（图 2B）。

1.4 辅因子

高危型 HPV 感染是癌症发生的必要但非充分条件。永生化细胞为正常原代细胞被 HPV16 的 DNA 转染后建立的，该细胞植入裸鼠体内未能致癌，表明由 HPV16 转化的永生化细胞是非恶性

的^[26-29]。在被高危型 HPV 感染的妇女中,长期口服避孕药、吸烟及与其他性传播因素的共同作用是影响其进展为宫颈癌的辅助风险因素^[26-29]。

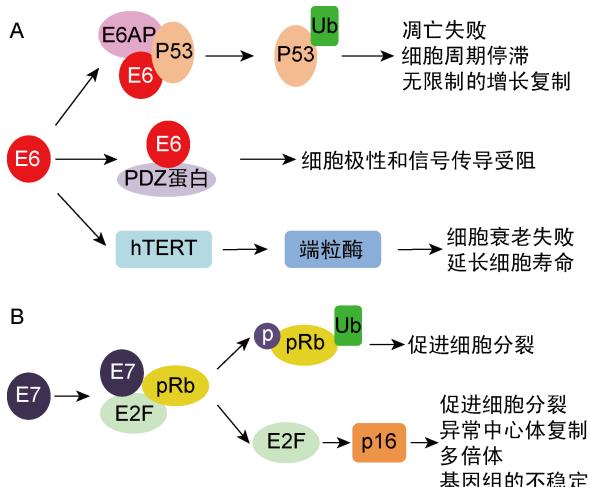


图 2 高危型 HPV E6 和 E7 肿瘤蛋白与细胞蛋白相互作用的致癌机制

Fig. 2 Molecular mechanisms of carcinogenesis by high-risk HPV E6 and E7 oncoproteins interacting with cellular proteins

2 高危型 HPV 与肿瘤关系

全球约 5% 的癌症病例由高危型 HPV 感染引起^[30]。在美国,高危型 HPV 导致女性癌症病例占 3%,男性癌症病例占 2%^[31]。几乎所有的宫颈癌均由 HPV 导致,其中 HPV16 和 18 占 70%,其余为 45、31、33、52、58、35 等^[2,32]。约 80% 的肛门癌,65% 的阴道癌,50% 的外阴癌和 35% 的阴茎癌由 HPV 引起,以 16 型最为常见^[33-34]。

约 70% 的口咽癌(包括软腭、舌根和扁桃体)由 HPV 引起,其中有一半以上与 HPV16 相关^[3-4]。越来越多的报道证实头颈部鳞状细胞癌(head and neck squamous cell carcinoma, HNSCC)中存在 HPV,总体检测率为 9%~60%^[35-37]。原位杂交法显示 HPV DNA 只存在于肿瘤细胞中,不位于周围基质或非发育不良表面上皮中^[38-39]。HPV DNA 阳性的 HNSCC 中,约有 50% 患者表达 E6/E7 mRNA^[40-41],伴有高表达 p16、野生型 P53 和低表达 pRb;相反,缺乏 E6/E7 mRNA 表达的肿瘤通常与低表达 p16、突变型 P53 及正常 pRb 相关^[40]。研究证实高危型 HPV 与 HNSCC 间存在的因果关系。值得注意的是 HPV 导致的头颈部肿瘤与肛门生殖器癌症有所不同,在 HNSCC 中 HPV DNA 和 P53

突变共存,E6 转录物表达与基底样形态(细胞拥挤、形态小、色度过高、细胞质稀少、细胞核显示活跃的有丝分裂和无角质化特征)相关^[42-44]。相反,肛门生殖器癌症的 HPV 阳性与 P53 突变之间呈负相关,且通常无明显的基底样形态组织学特征^[7]。

扁桃体鳞状细胞癌亦为头颈部肿瘤。使用不同的检测方法,约有 42%~100% 的扁桃体癌中可检测出 HPV DNA^[35]。HPV 阳性的扁桃体鳞状细胞癌被认为具有独特的生物学特征,如通常见于不吸烟饮酒的中年男性,以 HPV16 最为常见,伴有癌基因 E6/E7 表达,p16 表达增高,而 pRb 表达降低,P53 低表达野生型^[40-41]。HPV 阳性扁桃体癌的预后通常比 HPV 阴性扁桃体癌患者好^[35]。流行病学数据显示,与 HPV 相关的肛门生殖器癌症患者患扁桃体鳞癌风险增加 4.3 倍,而与 HPV 非相关癌症(结肠癌、胃癌和乳腺癌)患者不增加发生扁桃体鳞状细胞癌的风险,提示 HPV 可能是关联扁桃体与肛门生殖器之间发生鳞状细胞癌的常见因素^[45]。

3 治疗

HPV 感染的个体根据发展为肿瘤的类型和阶段,通常接受与非 HPV 感染的癌症患者相同的治疗。用于治疗宫颈癌前病变的方法通常包括冷冻破坏手术、环形电外科切除术等。宫颈癌的治疗方案根据临床症状而定,一般为手术、化疗、放疗、免疫治疗以及临床试用期的治疗性疫苗。

另外,抗 HPV 研究逐步成为国际热点。Jiang 实验室已证实,经化学修饰的牛乳清蛋白可以高效阻断 HPV 感染,对高危型 HPV 持续性感染的阻断有显著效果,且具有很好的临床安全性^[46-48]。此外,干扰素也具有调节免疫力、抗病毒增殖的作用。肛门生殖器疣的消融治疗后,全身施用干扰素可增加病毒清除率并降低复发率,但与文献报道的疗效不一致^[49]。

4 预防

HPV 疫苗的出现是肿瘤预防科研取得的重大成果。疫苗可预防 HPV 感染,从而预防全球 2/3 以上的浸润性宫颈癌和一半的高度鳞状上皮内病变^[50]。HPV 疫苗是由通过重组 DNA 技术表达的具有与 HPV 相同的主要外壳蛋白质 L1 产生的病毒样颗粒(virus-like particle, VLP)组成,没有

HPV 的遗传物质。VLP 作为抗原可诱导人体产生强烈的保护性免疫应答(抗 L1 蛋白的抗体),以便在再次接触 HPV 时,抑制其遗传物质的释放^[51]。至今,美国食品和药品管理局(Food and Drug Administration,FDA)已经批准了 3 种预防 HPV 感染的疫苗。2006 年,4 价 HPV 疫苗获得许可,其包含由 HPV 6、11、16 和 18 L1 蛋白制备的 4 种特异性 VLP。2007 年 2 价疫苗开始销售,其包含由 16 和 18 的 2 种病毒 L1 制备的 VLP^[52]。2014 年 12 月,美国 FDA 批准了 9 价疫苗上市,可保护 9 种 HPV 的感染(6、11、16、18、31、33、45、52 和 58)。疫苗以 2 个或 3 个剂量系列给药,世界卫生组织建议让 9~13 岁的青少年在有性行为之前接种^[53],降低由疫苗靶向的 HPV 感染的风险,但不能治疗由 HPV 感染所致的疾病^[54-55]。HPV 疫苗的接种被引入可作为预防宫颈癌的措施,但不能替代宫颈癌的筛查^[56]。尽管信息有限,但已报道 HPV 疫苗在预防病毒感染方面具有免疫原性、安全性和有效性,目前尚无严重的不良反应^[57-58]。各国政府在大量科研证据的基础上,应推广 HPV 疫苗接种以达到有效的预防目的。同时需要更多研究开发针对 HPV 相关癌症的治疗性疫苗,以提高治疗 HPV 相关癌症的效果。

5 结语

HPV 是一种常见的性传播疾病病原体,可导致肛门、生殖器和头颈部癌症。通过对该病毒结构生物学的研究,人们已部分掌握了 HPV 的重要细节,研发出用于预防和控制 HPV 相关癌症的高免疫原性和有效的疫苗。组合疗法的优化和计算机辅助设计将进一步提供研发和治疗方案。

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