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REVIEW ARTICLE

Physiopathology and effectiveness of therapeutic vaccines against human papillomavirus

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Abstract

Human papillomavirus (HPV) is a well-known sexually transmitted disorder globally. Human papillomavirus (HPV) is the 3rd most common cancer that causes cervical carcinoma, and globally it accounts for 275,000 deaths every year. The load of HPV-associated abrasions can be lessened through vaccination. At present, three forms of prophylactic vaccines, Cervarix, Gadrasil, and Gardasil 9, are commercially accessible but all these prophylactic vaccines have not the ability to manage and control developed abrasions or infections. Therefore, a considerable amount of the population is not secured from HPV infectivity. Consequently, the development of therapeutic HPV vaccines is a crucial requirement of this era, for the treatment of persisting infections, and to stop the progression of HPV-associated cancers. Therapeutic vaccines are a developing trial approach. Because of the constitutive expression of E6 and E7 early genes in cancerous and pre-cancerous tissues, and their involvement in disturbance of the cell cycle, these are best targets for this therapeutic vaccine treatment. For the synthesis and development of therapeutic vaccines, various approaches have been examined comprising cell-based vaccines, peptide/protein-based vaccines, nucleic acid–based vaccines, and live-vector vaccines all proceeding towards clinical trials. This review emphasizes the development, progress, current status, and future perspective of several vaccines for the cure of HPV-related abrasions and cancers. This review also provides an insight to assess the effectiveness, safety, efficacy, and immunogenicity of therapeutic vaccines in the cure of patients infected with HPV-associated cervical cancer.

Keywords Papillomavirus · Pathogenesis · HLA polymorphism · Cervical cancer · Vaccines

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Introduction

Cancer is the main cause of death worldwide (Chabeda et al. 2018) and cervical cancer is the 3rd most widely known cancer (Mousavi et al. 2020). Human papillomavirus (HPV) is a recognized causative factor of cervical cancer, the 4th well-known female cancer globally. Human papillomavirus is a typical well known sexually transmitted disorder globally (Harper and DeMars 2017). HPV is a small double-stranded DNA virus, having a genome of nearly 8kbp that encodes for six non-structural proteins (E1, E2, E4, E5, E6, and E7) and a major and a minor structural protein (L1 and L2). Genital intraepithelial neoplasia can also be caused by HPV infection or abrasion, which often proceed towards cancer (Mousavi et al. 2020). Human papillomavirus is accountable for causing 93% of the anus, 63% of the oropharynx, 51% of the vulva, 40% of the vagina, and 40% of the penis, and all cases of cervical cancers (Panahi et al. 2020).

Propagation of infected cells is thought to be responsible for HPV abrasion. All sexually active people are expected to develop HPV at some stage in their lifetime because it is the typical sexually transmitted disease (H. J. Kim and Kim 2017). A total of 527,624 females are identified with cervical cancer globally and 265,672 females are directed towards death from this disease yearly (Bruni et al. 2016). It is assumed that 275,000 people die from cervical cancer and new 530,000 cases of HPV occur every year globally, thus making it a big problem worldwide and causing loss of life, especially in developing countries (Liu et al. 2019). Various investigations have revealed that genetic factors and lifestyle aspects can considerably increase the chance of acquiring continued HPV infection. For example, several researchers have discovered that both smoking and alcohol can be crucial risk factors for long-term oral and genital HPV abrasion. It has been suggested that the carcinogens in cigarette smoke raise viral load as well as increase the probability of causing cancerous transformation of epithelial cells upon infection of these cells with HPV.

The prevalence of HPV-related diseases can be decreased through vaccination (Bogani et al. 2018). Preliminary prevention through vaccination is efficacious in controlling cervical cancer. For control and cure of HPV abrasions, several forms of vaccines have been developed. In the management and prevention of about 3 million deaths yearly, prophylactic and therapeutic vaccines perform a vital function. Cervarix, Gardasil, and Gardasil 9, three prophylactic vaccines, were approved in 2006, 2007, and 2014, correspondingly (Mousavi et al. 2020). However, all these prophylactic HPV vaccines do not have a curative effect; i.e., before vaccination, these vaccines do not control the growth of neoplasia in all those persons affected with HPV. Furthermore, these prophylactic vaccines are only targeted at the production point of virus-neutralizing antibodies. Therapeutic vaccines, however, accelerate cellular immune response leading to the removal of infected and malignant cells that express viral proteins (Vonsky et al. 2019). Research is therefore focused on discovering substitutive non-invasive curative strategies for the treatment of HPV-associated cervical infection and dysplasia (Barra et al. 2020).

The development of therapeutic vaccines emphasizes the efficacy of precise immunological responses against antigens to eradicate the developed disease or to ward off the patient from being reinfected or to neutralize consequent infections by the same virus. Due to this feature, therapeutic vaccines differ considerably from the existing prophylactic vaccines (Gonçalves et al. 2019). Therapeutic vaccination could be one of the most efficacious cures for HPV-related cancer. The first victory of therapeutic anticancer vaccines has been attained particularly in the cure of precancerous disorders that are caused by infection with HPV types 16 and 18 (Vonsky et al. 2019). The main aim of this descriptive review is to provide an insight into the function of therapeutic vaccines in the cure of pre-invasive abrasions and cervical infections caused by HPV. However, this requires huge attempts to create and launch therapeutic vaccines against HPV and HPV-related neoplasia.

Types of HPV

So far, more than 200 various forms of HPV have been reported, almost one-third of that infect epithelial cell lining the genital tract. Depending on their ability to cause malignancy, the types of HPV that infect the genital tract are categorized as either high-risk or low-risk [12, 13]. HPV forms 6 and 11 have very little oncogenes capacity and are hardly associated with cancer. These kinds of HPV infection can trigger the production of low-grade cervical cells or benign anomalies, genital warts, and laryngeal papilloma (Valentino and Poronsky 2016). HPV types 6 and 11 have been found in 99% of genital wart infections and are categorized as low-risk (Mousavi et al. 2020), whereas 70% of cervical cancers have been described to be not with high-risk categories, such as 16, 18, 33, and 45 (Landy et al. 2018). The subtypes of HPV, i.e., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 73, and 82, are taken into consideration as high risk. These subtypes can cause several oropharyngeal, anal, vulvar, vaginal, and penile cancers (Valentino and Poronsky 2016).

Pathogenesis of human papillomavirus

HPV is a double-stranded non-enveloped circular DNA virus, having a genome of ~8 kb in size, consisting of three parts: 6 early genes (E1, E2, E4, E5, E6, and E7) encoding open reading frame (ORF), open reading frame (ORF) of 2 late genes

(major L1 and minor L2 capsid proteins), and long control region (LCR). The icosahedral capsid of the HPV virus is comprised of seventy-two L1 pentamers (total360) accompanied by varying numbers of L2 submerged within the surface of the capsid (Liu et al. 2019).

Although E1 is a replication factor, E2 is a transcription manager of all HPV viral proteins, able to control DNA replication and RNA transcription of the virus. E4 governs the cytoskeleton structure of epithelial cells infected with HPV. E5, E6, and E7 facilitate and help in cellular transformation. E6 and E7 are particularly significant, as they are oncoproteins that suppress tumor repressors p53 and pRb, correspondingly, thus inhibiting the stimulation of apoptotic pathways. Furthermore, E6 and E7 promote cell propagation, eventually leading to the development of HPV-related malignancies. During the expression of HPV-related cervical cancer, incorporation of the virus into the genome of host cells usually results in the constitutive upregulation of oncogenes E6 and E7 and deletion of viral proteins E2, E4, E5, L1, and L2 (Cheng et al. 2018).

Basal epithelial cells are the main target of HPV infection and L1 and L2 capsid proteins bind to the receptors present on epithelial cells. Once the process of entrance initiates, it results in uncoating of the virus in the cytoplasm and viral genome then enters the infected host cell nucleus, where it is first replicated and then transcribed. The genome replication and pathogenesis of the host cell are controlled by early proteins because they are expressed foremost. Late proteinsL1 and L2 expression in a cell differentiation–dependent mode are controlled by early proteins. Developed squamous cells are the late protein expression sites. After terminal epithelial cell differentiation virions, development and maturation occur and viral discharge overlaps with the senescent cells' normal shedding. The immune system can eradicate the majority of infectious agents, but some cervical benign abrasions develop into cancer (Chabeda et al. 2018).

The clinical phases of cervical premalignancy stem from increasing dysplasia severities: cervical intraepithelial neoplasia (CIN) grades 1, 2, and 3 (CIN1, CIN2, and CIN3, correspondingly). CIN1 is termed as low-grade intraepithelial squamous abrasions, while CIN2/3 is known as high-grade intraepithelial squamous abrasions (Cheng et al. 2018). The persistent infection leads to low-grade CIN 1 abrasions or lacerations. The development to high-grade CIN 2/3 is triggered by high-risk (HR) HPV abrasions leading towards invasive cervical cancer (ICC). In a typical high-risk HPV carcinogenesis, the viral genome is incorporated into the chromosome of the host's DNA, and during the genomic linearization, the early protein E2 sequence is disturbed.

The early protein E2 is the transcriptional repressor of E6 and E7, and thus, upon E2 disruption, expression from these genes E6 and E7 turn out to be constitutive. Consequently, host-apoptotic regulator protein p53 undergoes degradation by protein E6. The protein E6 further triggers telomerase activity which leads to prolonged cell life. Tumor repressor retinoblastoma protein (pRb) is destroyed by E7 protein after targeting it, and as a result, genomic replication of host cell is triggered when the cell life cycle is shifted to the S-phase (Fig. 1). The proteins E6 and E7 are responsible for disturbing the regulation of the cell cycle and stimulate the end of ruing life of the host cell, preceding the instability of the genome and ultimately cancer (Chabeda et al. 2018).

Genetic polymorphism and HPV infection

HLA-G polymorphism and HPV infection

Human papillomavirus (HPV) infections are very common in the world, and they are the main causative agents of CIN and cancer [18, 19]. However, HPV infection is a necessary but insufficient cause for the development of cervical cancer (Tota et al. 2011) because recent studies show that most high-risk HPV infections of the cervix are transient, and only a small percentage of infected women can develop invasive cancer (Bowden et al. 2021).

Extensive studies have shown that HPV interacts with other co-factors, including human leukocyte antigen (HLA) class II alleles (Mahmud et al. 2007), which affect the persistence of HPV and the risk of developing cervical cancer. Indeed, HLA gene polymorphism is related to the risk of developing HPV and the risk of HPV-related cervical neoplasia (Chan et al. 2007). These genes appear to be important determinants of the risk of persistent HPV infection and disease progression (Paaso et al. 2019)

Associations between HLA and cervical cancer have been associated with precursor lesions and HPV infection in several populations (Maciag et al. 2000). Recent data show that individuals with certain alleles (HLA-DQB1 * 0602 and HLA-DRB1 * 1501) are also more susceptible to persistent HPV infection and are at increased risk for cervical cancer (Leo et al. 2017).

Several strategies are used by the virus to evade immune surveillance, hence the relevance of studying the relationship between HLA-G and HPV in tumor growth and progression (Fahim et al. 2018) because of the fundamental function of HLA proteins in T cell–mediated adaptive immune responses as they are essential for antigen presentation. HLA genes play a crucial role in the viral presentation; these molecules are involved in mediating susceptibility to HPV-related diseases (de Araujo Souza et al. 2009).

Numerous studies have investigated the associations between HLA class I and HLA class II alleles as well as HLA G and HPV-associated diseases [29, 30,31]. Associations between HLA-G polymorphisms and HPV infection and squamous intraepithelial lesions in women in northern Quebec

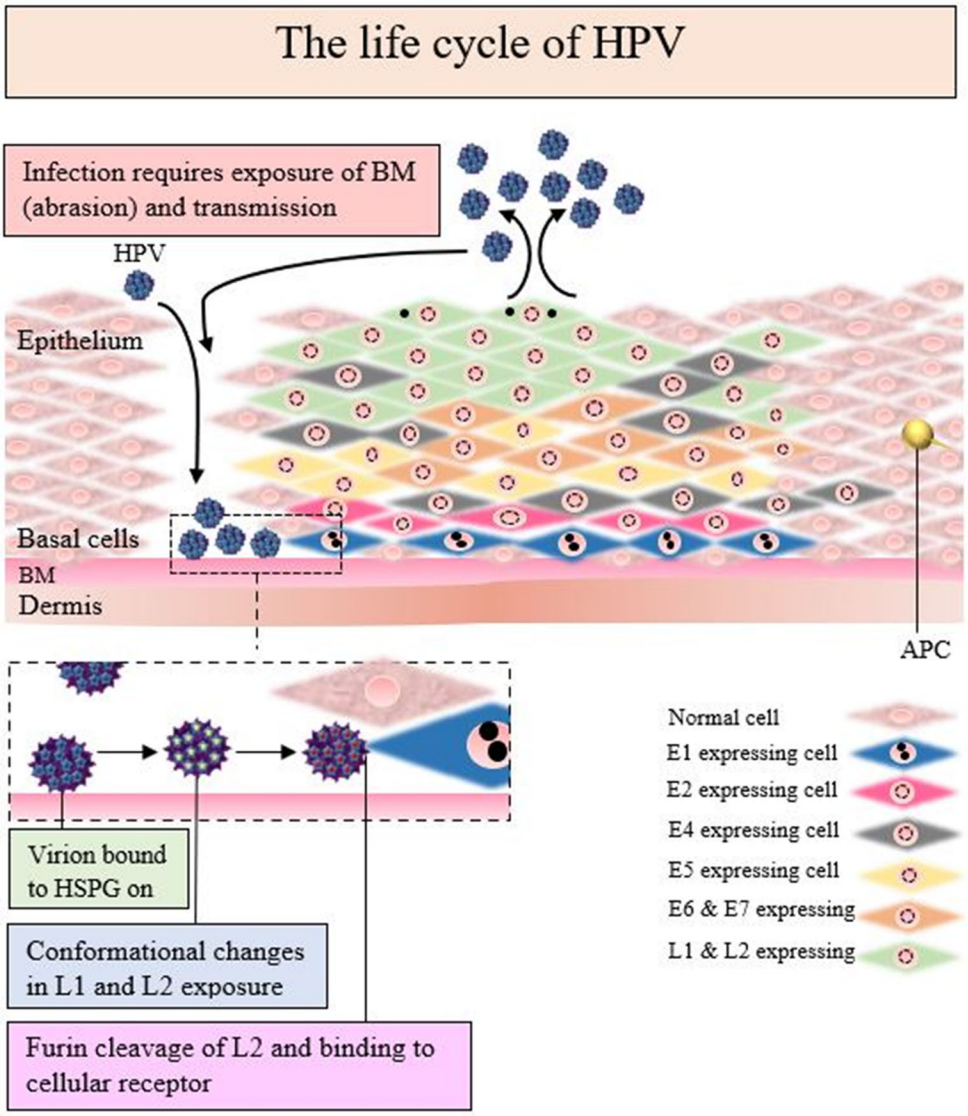

Fig. 1 The life cycle of HPV. Approach to the basal keratinocytes is provided by lesions, which proceed towards denudation of the basement membrane (BM) from epithelial cells. The virus attaches to heparin sulfate proteoglycans (HSPGs) and laminin 5 on the BM through the major capsid protein L1during human papillomavirus (HPV) infection. This activates conformational changes in the capsid that later on leads to the exposure of L2minor capsid protein, containing a conserved site on the N terminus of protein L2 that is vulnerable to breakdown by extracellular furin. Various preserved protective epitopes of L2 are exposed after furin breakage of L2, containing 17–36 residues, on the surface of viral capsid and is crucial to any infectivity. This is preceded by viral uptake into the target basal keratinocyte. Various paths have been concerned for the uptake of the virus, but not any pathway is effectively communally absolute. The viral genome undergoes replication in the basal cells infected with HPV and creates ~50 copies of HPV episomes, which then separate into the daughter lineage as the cells experience cell division (Roden and Stern 2018). Essential early E proteins proliferate and multiply in the middle layers upon the initiation of genome amplification (Liu et al. 2019). Activation of persistent propagation and E1- and E2-directed asexual replication of viral genome to a very high copy number is triggered by early viral proteins E6 and E7. Stimulation of early protein E4 expression and then late proteins L1 and L2 to package the very high copy numbers of the viral genome is accompanied by infected cells' terminal differentiation in the upper layers of the epithelial cells (Roden and Stern 2018). This is for the reason that E4, L1, and L2 are frequently exposed in the upper layers of epithelial cells where wrapping of viral DNA and assemblage of perpetual virions occur leading towards genome amplification. The virus is finally discharged in the stratified epithelium superficial layers together with the flaking of senescent cells (Liu et al. 2019). As E4 breaks the cytokeratin filaments, the virions are discharged, and the keratinocyte remains are sloughed off the epithelial surface. Hence, without exactly triggering cell death the viral life cycle is finished (Roden and Stern 2018). *Abbreviations.* BM, basement membrane; HSPGs, heparin sulfate proteoglycans; HPV, human papillomavirus

showed that HLA-G*01:01:01 was associated with an increased risk of period prevalence in the group with HPV 1, 8, 10, and 13 and the group including HPV 3 and 15 (Metcalfe et al. 2013). A Canadian population–based study showed that the HLA-G∗ 01:01:02 and HLA-G∗ 01:03 genes are associated with persistent HPV 16 infection risk and persistent HPV

2, 3, 4, and 15 infections in the Canadian population (Ferguson et al. 2011). The HLA-G∗ 01:01:03 and HLA-G∗ 01: 01:05 were determined to be a significant predictor of cumulative co-infection during follow-up (Smith et al. 2014). The same cohort showed that HLA-G * 01: 01: 02, HLA-G * 01: 04: 01, and HLA-G * 01: 06 alleles were associated with high-grade HG-CIN (Metcalfe et al. 2013). However, Metcalfe S et al. reported an association between homozygous HLA-G*01:04:01 and a decreased risk of infection period in the HPV 3 and 15 groups (Metcalfe et al. 2013). The same study suggests that the HLA-G allele is not significantly associated with HPV persistence. HLAG*01:01:02, G*01:04:01, and G* 01:06 were associated with high-grade squamous intraepithelial lesions (SIL), but the association was not statistically significant (Metcalfe et al. 2013). Studies conducted in Brazil did not observe an association between specific HLA-G alleles and HPV infection but found a protective effect of the G: 01:01:02 allele against the development of intraepithelial lesions (Alves et al. 2015).

The impact of HLA-G genotype on mother-to-child HPV transmission was studied by Louvanto et al. (2018) and indicates that an HLA-G genotype match of G∗01:01:01/01:04:01 increases the risk of high-risk HPV genotype positivity (HR) in cord blood and infant oral mucosa. The homozygous HLA-G*01:01:02/01:01:02 allele between mother-infant pairs showed an increased risk of oral HPV infection; in contrast, HLAG*01:04:01 and HLAG*01:06 have a low risk for HPV at birth (Louvanto et al. 2018).

In Brazilian population patients with HLA-G, *0104 haplotypes, and HPV-16 and HPV-18 co-infection are particularly associated with high-grade SIL, a protective effect of the HLA-G∗ 01:03 allele was observed against HPV-related cervical lesions (Simoes et al. 2009). Another study conducted also in Brazil concerning HPV-positive pregnant women showed a protective effect of the HLA-G∗01:01:02 allele against the occurrence of CIN in a cohort of HPV/HIV co-infected pregnant women (Alves et al. 2015). HLA-G expression was also significantly higher in patients with CIN and cancer with HPV 16/18 than in patients with CIN without HPV (Dong et al. 2010).

No spontaneous demethylation event in CIN2/3 cases was found in an analysis of the methylation of seven CpGs in the HLA-G promoter (Gillio-Tos et al. 2012). On the other hand, 93.7% of the patients with cervical lesions were detected as HPV positive; however, a low expression of HLA-G5 subtypes was observed in all HPV-related cases (Guimarães et al. 2010).

In benign and premalignant lesions, HLA-G expression increases, and in invasive cancer and corresponding cervical draining lymph nodes, HLA-G expression gradually decreases. On the contrary, HLA-E expression increases with the extent of disease, including increased expression of the molecules in lymph nodes (Fig. 2) (Silva et al. 2011).

HLA class II polymorphism and HPV infection

Regarding the association between HLA class II alleles and HPV, several studies have analyzed this correlation. Kunle Odunsi et al. suggested that HLA alleles DQB 1 *03, DRB 1 *04, and DRB 1* 1 1 are strongly associated with susceptibility to CIN, especially that the haplotypes DRB1*040, 1 -DQB 1*030 1, and DRB 1 * 1 10 1 -DQB 1 *030 1 were significant and indicated susceptibility (Odunsi et al. 1996). The DRB 1 *0101 -DQB 1 *050 1 haplotype showed a weak protective effect (Odunsi et al. 1996). Another previous study found similar results for HLA DQB1 * 0301 alone and in combination with the HLA DRB1 * 0401 allele which is associated with cervical cancer. This association is more pronounced in cancers positive for HPV types other than HPV16 and also a protective effect on DQB1 * 0501 was found to be slightly significant. This study shows that HLA-DRB1*1501 with HLA-DQB1*0602 is not significantly associated with cancer, but this allele is higher in cervical cancer patients with HPV type 16 positive but the protective effect on DRB1 * 1301 was not observed (Cuzick et al. 2000).

Other individual class II risk alleles that have increased the risk of cervical cancer in recent studies: DQB1*0402 and DQB1*05(X. Zhang et al. 2015), DQB1*0601(Hu et al. 2017), DQB1*0602 (Ivansson et al. 2008), DRB1*04, DRB1*0401, and DRB*15 (Leo et al. 2017), DRB1*11 (Ivansson et al. 2008), DRB1*1101(Madeleine et al. 2008), and DQA1*0102,*03, *0301, and DQB*0602 (Leo et al. 2017).

Associations between HLA class II polymorphism and HPV type 16 have been performed by several previous studies; the HLA-DQA1*0102 allele is weakly related to cervical neoplasia in HPV 16–positive patients. HLA-DQB1 *0602 was very low in all (CIN) patients but was strongly increased in HPV-16 seropositive (CIN) patients compared to HPV 16 seropositive controls (Sanjeevi et al. 1996).

The association between HLA-DR 15 and disease (CIN) was particularly strong in HPV-16 seropositive subjects. The DQA1 *0102- DQB1*0602 (DQ6) haplotype is associated with an increased risk of cervical neoplasia in HPVI6-positive subjects and DQA 1*0501 -DQB 1 *030 1 (DQ7) is associated with an increased risk of cervical neoplasia in HPV-16-positive subjects (Sanjeevi et al. 1996). Consistent associations across other studies in HPV16-infected women with cervical cancer were observed for HLA-DRB1*15 and DRB1*15 DQB1*0602 haplotype compared with control women (Hernández-Hernández et al. 2009).

Regarding HLA polymorphism and cervical squamous cell cancer risk, inconsistent results are often observed between different populations or even within the same population (Hildesheim and Wang 2002). The higher risk of cervical squamous cell cancer associated with several HLA alleles has been described, mainly for the DQB1∗03 alleles and the

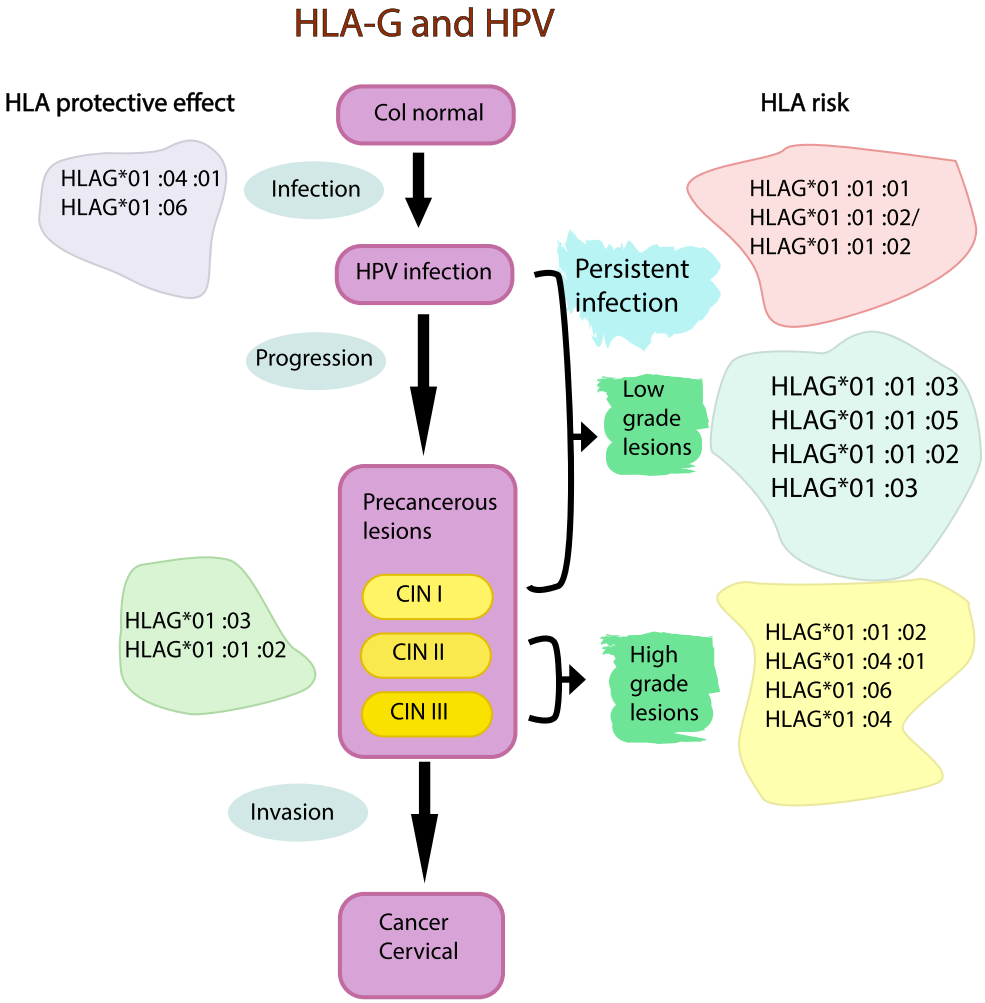

Fig. 2 The different HLA-G alleles that are associated with HPV infection or progression to cervical cancer. *Abbreviations.* HLA-G, human leukocyte antigen G; HPA, human papillomavirus

DRB1∗1501-DQB1∗0602 haplotype. Some studies have suggested strong associations of tumors containing a specific HPV type. However other studies found no associations with the DQB1∗03 haplotype and an inverse association was shown for the DRB1∗1501-DQB1∗0602 haplotype (de Araujo Souza and Villa 2003).

Many studies in different populations have shown that the risk of cervical squamous cell cancer associated with the DRB1 * 01 and DRB1 * 13 alleles or haplotypes is low. Despite these consistent results, it is not known which DRB1 * 13 allele is important, whether only the DRB1 * 13 alleles, only the DQB1 * 0603 allele is associated with a reduced risk of disease, or whether it is linked to other disease-related genes for the major histocompatibility complex (MHC) found in linkage disequilibrium with these HLA alleles are important (Fig. 3) (Goodman et al. 2001).

HLA class I polymorphism and HPV infection

The association between HLA class I polymorphism and HPV was also studied (Fig. 4); HLA-A, B alleles, and persistent HPV-16 infection and cervical cancer in South India HLA-B * 44 were significantly related to cervical cancer and persistent HPV-16 infection. The HLA-B * 15 genes are negatively related to cervical cancer (Bhaskaran et al. 2019); indeed, HLA-B15 is a protective factor for the prevention of cervical intraepithelial neoplasia grade III (CIN III) or invasive cervical cancer overall (ICC), and CIN III / ICC HPV52 positive. However, none of the HLA-B alleles was found to confer an increased risk of CIN. HLA-B15 is common in Asians for whom HPV52, an uncommon type of HPV worldwide, also exists in a relatively high prevalence (Chan et al. 2006). Leo et al. 2017 recently showed that HLA-B * 07 increases the risk of cervical squamous lesions. A significant association with persistent HPV infection and the development of cervical cancer: HLA-A*02 and HLA-A*0201 (Gokhale et al. 2014), HLAA*0301 (Madeleine et al. 2002), HLA-A*3101 and HLA-A*3303 (S. S. Wang et al. 2002), HLAB*3501, HLA-B*37, and B*3701 (Gokhale et al. 2014), HLA-B*3901 (S. S. Wang et al. 2002), HLA-B*4402 (Madeleine et al. 2002), HLA-B*58 and B*5801 (Gokhale et al. 2014), HLACw*0501 (Madeleine et al. 2002), HLA-C*0702 (Leo et al. 2017), and HLA-Cw*0704 (Madeleine et al. 2002).

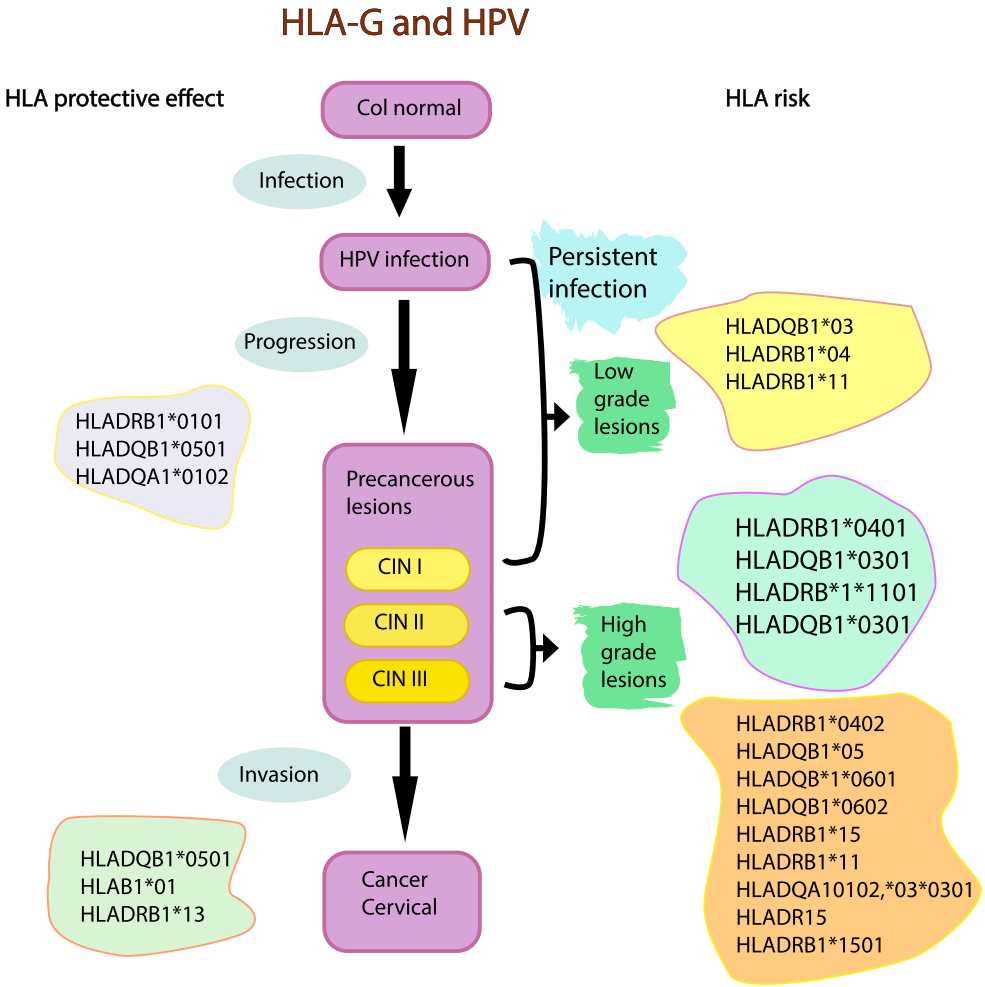

Fig. 3 The different HLA class II alleles that are associated with HPV infection or progression to cervical cancer. *Abbreviations.* HLA, human leukocyte antigen alleles; HPA, human papillomavirus; CIN, cervical intraepithelial neoplasia

HLA polymorphism and HPV E6 and E7 variants

Many studies have shown an association between HLA polymorphism and E6 and E7 variants. Indeed, an association between HLA class II and E6 variants in Japanese women with HPV16-positive cervical cancer compared to controls. Among patients with the HPV16 E6 prototype, the frequency of DRB1 * 1501 and DQB1 * 0602 was significantly higher (Matsumoto et al. 2003). Similar results regarding the association between HPV16 E6 variants and HLA class II polymorphism in a Chinese population, a significant positive correlation between the DQB1 * 060101 allele and HPV16-positive cervical cancer as a variant. A significant positive association was found in the DQB1 * 060101 allele regarding HPV16 E6 prototype–positive cervical cancers with close results indicated for DQB1 * 030201 and DPB1 * 1301 (Wu et al. 2007).

The association between HPV16 E6 variants and HLA-DRB1 and DQB1 alleles in young women with cervical cancer in China showed a low frequency of the DQB1*0501 allele in young patients compared with that in older patients (Hu et al. 2017).

HPV E6 overlapping peptide-specific T cell immune responses have been shown to predict survival in cervical cancer patients (Cai et al. 2021). A recent study was performed on the association between HLA-A alleles as a predictor of prognosis in patients with cervical squamous cell carcinoma (CSCC) and T cell response to HPV16 E6 and E7. This study shows that the level of HPV16 E6 HLA * A02: 07-specific T cell response is related to the prognosis of patients with advanced CSCC (Cai et al. 2021).

Therapeutic HPV vaccines

There is a vital requirement to create efficient therapies for developed HPV infections and HPV-related disorders, due to the predominance of HPV abrasions globally. One effective therapeutic strategy includes the use of therapeutic vaccines (Yang et al. 2017). This is because HPV late genes L1 and L2 are lost when HPV incorporates into the genome of host infected with HPV high-grade abrasions or HPV-linked malignancies. Consequently, late proteins L1 and L2 specific

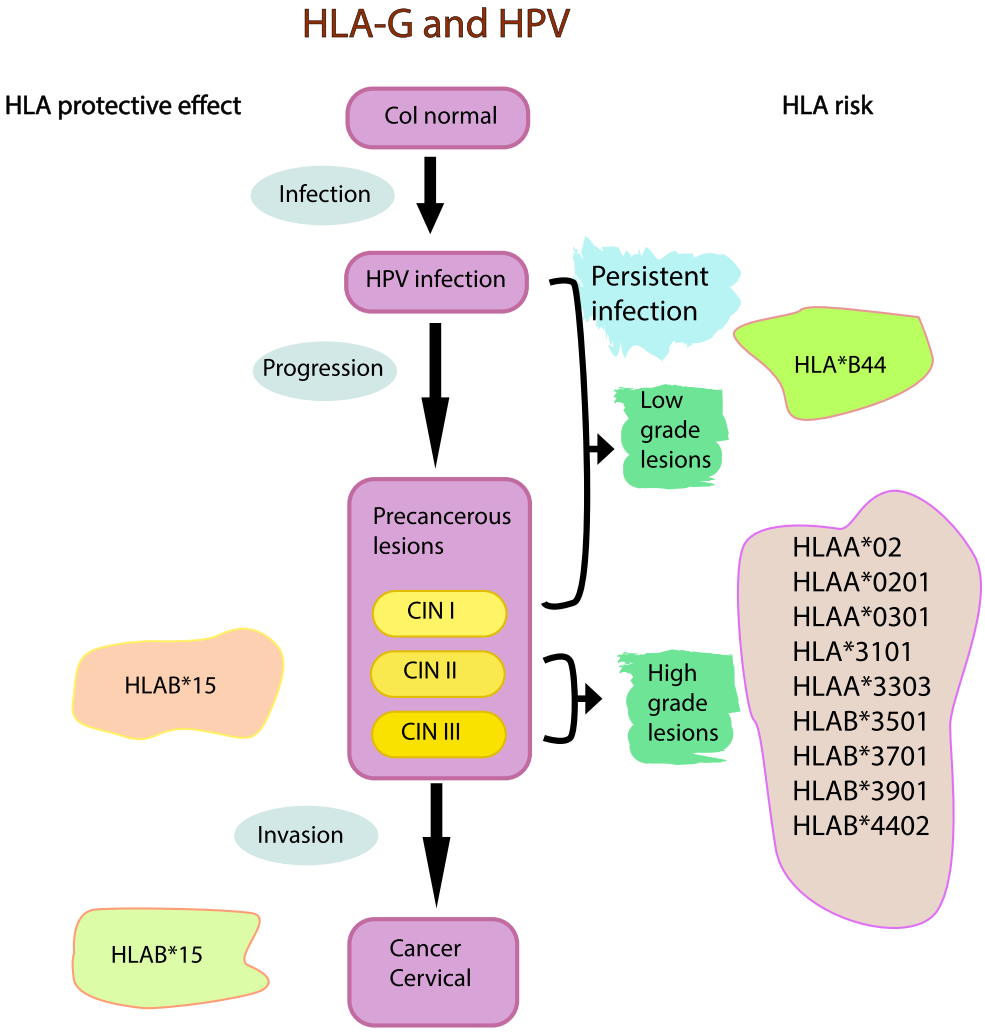

Fig. 4 HLA class I alleles that are associated with HPV infection or progression to cervical cancer. *Abbreviations.* HLA-B, human leukocyte antigen alleles B; HPA, human papillomavirus; CIN, cervical intraepithelial neoplasia

neutralizing antibodies produced by prophylactic vaccines are no longer effective against the cells infected with HPV. Therefore, therapeutic HPV vaccines are being developed to eradicate HPV abrasions or the previous HPV-linked infections (Cheng et al. 2018).

Contrary to prophylactic vaccines, therapeutic vaccines aim to eradicate the precancerous abrasions and the continued infection of lesions produced by HPV (R. Wang et al. 2020). To eradicate developed abrasions or lesions, therapeutic vaccines produce T cell–mediated immunity by precisely pointing to HPV early antigens that are constitutively exposed around both infected and malignant cells (Cheng et al. 2018). Consequently, early genes are targeted upon exposure during the viral life cycle and help control the development of HPV-linked premalignant and malignant abrasions. E6 and E7 proteins particularly signify two ideal targets of therapeutic HPV vaccine because these two proteins are continuously expressed and implicated in the cancerous transformation of HPV-linked cancers (Vici et al. 2016). Other proteins E1 (viral helicase) and E2 are beneficial for targeting early viral abrasions and these proteins are expressed before viral genome incorporation at very early stages to a higher rate than E6 and E7. These proteins would be the target of ideal therapeutic vaccines because these vaccines stimulate powerful cytotoxic T lymphocyte (CTL) and cancer-specific T cell type 1 response that can destroy cancerous and infected cells (Chabeda et al. 2018).

These discoveries have originated several attempts to develop an ideal immunotherapeutic cure against HPV lesions and disorders (Yang et al. 2017). But at present, the use of human therapeutic vaccines for HPV has not been authorized. However, several and broad findings have produced promising vaccine contenders checked in clinical trials [61, 62, 5]. Several forms of therapeutic vaccines have been created for the treatment of HPV and checked in clinical and preclinical trials, and the main targets of these vaccines are HPV early proteins E6 and E7 (Yang et al. 2017). These recent therapeutic strategies against HPV consist of peptide-/protein-based, whole cell–based, live vector–based, and nucleic acid–based vaccines (Cheng et al. 2018).

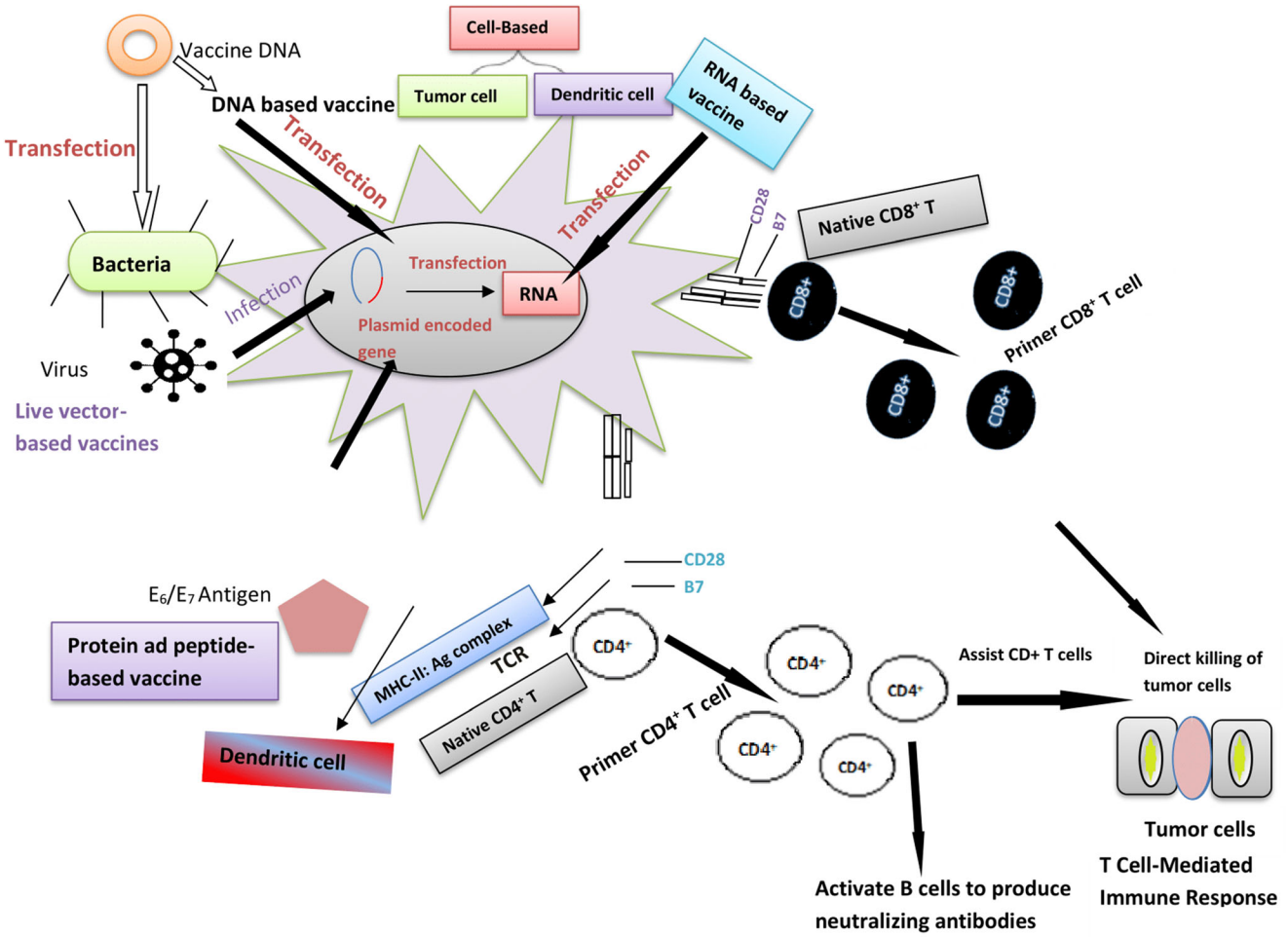

Fig. 5 Immune response activation by various forms of therapeutic vaccination. Induction of antigen into the body in diverse varieties is triggered by the processing of many forms of therapeutic vaccines. (A) The antigens E6 and E7 encoded by DNA plasmids can be induced into DCs either through induction of DNA vaccines directly or through altered live vector vaccine indirectly (Yang et al. 2017). Upon transfection of these E6 and E7 HPV antigens directly or through the transmission of these antigens indirectly via cross-presentation, antigen-presenting cells (APCs) are stimulated. Through major histocompatibility complexes (MHCs) dendritic cells home towards draining lymph nodes where naive T cells can be primed upon introduction of antigenic peptides to T cells. Major histocompatibility complex molecules and the antigens (i.e., MHC: antigen [Ag] complex) interact with the T cell receptor and co-stimulatory compounds, such as CD28 present on T cells and B7 present on dendritic cells assist in this interaction. To activate a cellular immune response MHC-I molecules are presented to CD8+ T cells and MHC II molecules are presented to CD4+ T cells. CD8+ T cells once stimulated destroy cancerous cells directly by provoking apoptosis. CD4+ T cells further assist immune responses, which aid in destroying cancerous cells (Cheng et al. 2018). (B)The antigens that encode for DNA will be transcribed into RNA that can also be induced through RNA vaccination into the cell. Furthermore, this transcribed RNA will be translated into antigenic large peptides or proteins, that can also be engulfed by the dendritic cells via process phagocytosis after peptide- or protein-based vaccination (Yang et al. 2017). (C) Moreover, the protein products can be inducted into the DC's directly. However, recombinant protein vaccines are typically comprised of E6 and E7 fusion proteins in the case of HPV (Shanmugasundaram and You 2017). To be introduced to T cell receptors (TCR) of CD8+ T cells, processing of antigenic large peptides and proteins into shorter peptides occurs by means of the proteasome's activity, which are encumbered on major histocompatibility complex (MHC I) interior to the endoplasmic reticulum (ER) (Yang et al. 2017). (D) Cultured monocytes taken from the patients in fusion with a specific peptide or antigen are used to prepare dendritic whole cell–based vaccines. These customized DCs are then induced into the patient's immune system and the same cell-mediated and antibody-mediated immune responses are activated through the stimulation of B cells and helper T cells (Shanmugasundaram and You 2017). *Abbreviations*: APCs, antigen-presenting cells; MHCs, major histocompatibility complexes; TCR, T cell receptors; MHC I, major histocompatibility complex; ER, endoplasmic reticulum

Activation mechanism of the immune system *via* therapeutic HPV vaccines

To reinforce and extend the immune response against HPV, presenting specific antigens to a subset of antigen-presenting cells (APCs) is the main purpose of therapeutic vaccines (Fig. 5). Recently, clinical investigations on effectual therapeutic vaccines are also being carried out, which contrary to prophylactic vaccines, fight against HPV abrasions through immunotherapy (Shanmugasundaram and You 2017). Dissimilar to

prophylactic vaccines which depend on stimulating memory B cells and specific antibodies (Hus et al. 2015), therapeutic vaccines attempt to boost the T cell adaptive immune response against HPV (Shanmugasundaram and You 2017). E6 and E7 antigens are present in several forms in a majority of therapeutic vaccines, and their purpose is to stimulate antigen presentation after delivering these antigens to APCs through the MHC class I and MHC class II (Yang et al. 2017).

The vital subset of APCs are dendritic cells, which have been the main target of several therapeutic vaccines and these cells are implicated in capturing and introducing antigens to T cells [65, 66]. This is attained through making naive T cells to generate cytotoxic T lymphocytes (CTLs) that point cells infected with HPV, thus producing CD4+ T cells which generate the essential cytokines and reinforce APCs (Shanmugasundaram and You 2017). MHC class II molecules present helper CD4+T cells while MHC class I molecules present CTLs or cytotoxic CD8+ T cells. Amplification of CTL responses occurs via differentiation of CD4+ T cells into TH cells. This differentiation of CD4+ T cells into TH cells also accelerates humoral B cells to create more neutralizing antibodies. CTLs facilitate the antigen-targeted destruction of cancerous cells (Cheng et al. 2018).

For the CD8+ T cell response activation, processing of E6 and E7 antigens and their digestion into smaller peptides occurs by the proteasome present in the antigen-presenting cells, before their presentation on the major histocompatibility class I molecule. All peptide fragments cannot be efficaciously identified by antigen-peculiar T cells and encumbered on the MHC molecule. The sequence of antigenic fragments (epitopes) contained in short peptides can attach to the MHC molecule with high specificity and elicit a humoral and cell-mediated immune response after interacting with the T cell receptor of antigen peculiar T cells (Yang et al. 2017), hence leading to the death of cancerous cell through the stimulation of helper B cells, T cells, and cytotoxic T cells (Shanmugasundaram and You 2017). E7 antigen is well described immunologically than E6 antigen in preclinical trials; therefore, therapeutic vaccines emphasized triggering immune responses against the E7 antigen (Yang et al. 2017).

Efficacy and effectiveness of various therapeutic vaccines

Several forms of therapeutic vaccines have been established for the cure of cervical malignancies comprising of live vector (bacterial or viral)–, protein-/peptide-, nucleic acid–, and whole cell–based vaccines (Yang et al. 2017). HPV DNA and protein vaccines appear to be the less effective amongst these several categories of therapeutic vaccines. This is because they are not able to generate an adequate early immune response. Therefore, different types of adjuvant, for example, imiquimod or cidofovir, are essential along with these vaccines because this adjuvant acts as agonists to several toll-like receptors as well as enhance the initial immune response to the vaccine and impart long-term defense (Shanmugasundaram and You 2017).

Live vector vaccines

Bacterial and viral vector–based vaccines are the main types of live vector–based vaccines (H. J. Kim and Kim 2017). Weakened bacteria or viruses are used in live vector vaccines to carry desired genes into cells (Liu et al. 2019). Live vector vaccines are genetically modified virus or bacterial vectors that can enable the antigens to propagate by reproducing inside the host cells. Antigenic expression is triggered then through both major histocompatibility complex class I and class II routes, thus accelerating CD4+ helper T cells and CD8+cytotoxic T cells and, correspondingly, ultimately delivering a high level of immunogenicity (Chabeda et al. 2018).

Bacterial vector–based therapeutic vaccine

For the production of live vector therapeutic vaccines, bacteria have been extensively analyzed (Bogani et al. 2018). Species of the bacterial vector comprised of *Lactobacillus lactis*, *Lactobacillus casein*, *Listeria monocytogenes*, and *Salmonella*. Listeria is a guaranteeing vector because of its characteristics; for instance, it has the capacity to target antigen processing through MHC I and MHC II routes and it has the capability to infect macrophages without undergoing phagocytosis (Chabeda et al. 2018). *L. monocytogenes* (Lm) is of specific importance and is a promising live vector for vaccine production. This is because of its ability to serve as a natural adjuvant, the capacity of infecting macrophages without phagocytosis, and the capability of enabling antigen processing through MHC I and MHC II routes [1, 74].

GLBL101c (comprising of *L. casei* expressing E7) was given orally (6 capsules per day) to seventeen females having a diagnosis of CIN 3 in a phase I/II investigation. Enzyme-linked immune spot (ELISPOT) assay assessed precise E7 immune response and it was identified in all the patients. In 8 of 27 patients (30%) after 9 weeks of treatment, CIN 1 histologic regression or less happened and these patients experienced LEEP; 70% of these patients had a decrease in abrasion to CIN 2. Any woman did not experience detrimental side effects. Clear evidence is provided by these findings between the recession of disease and HPV E7 cell–mediated immunity (Barra et al. 2020).

LM-LLO-E7, a promising Listeria-based vaccine, is developed through HPV16 E7 fusion with LLO (Liu et al. 2019). An E7-based vaccine, Lm-LLO-E7, is based on these bacteria and it has been analyzed for curing advanced cervical melanoma, thus indicating an appropriate safety profile (Barra et al.

2020). A phase I analysis of fifteen patients suffering from recurring, terminal, refractory, and metastatic squamous cell cervical carcinoma showed a decrease in tumor size in four patients and increment in the E7-specific T cells identified among peripheral blood mononuclear cells (PBMCs) in three patients. More studies are underway on HPV-related cancers currently (Liu et al. 2019).

L. casei–based vaccine BLS-M07 is an E7 protein expressing vector and delivered by mouth. Immune response in the gut-related lymphoid tissues can be stimulated by this vaccine and triggers the production of humoral antibodies against antigens having the same homology as HPV E7. This vaccine has been analyzed in HPV-16 patients in open-label dose-intensification phase I/II an investigation and CIN 3 diagnosis was observed along with pathological responses (Barra et al. 2020).

Viral vector–based therapeutic vaccines

Viral vectors can trigger cellular expression of directed antigens by infecting the host cells (Bogani et al. 2018). In preclinical models, the effectiveness of viral vectors such as alphaviruses, adenoviruses, vaccine viruses, and fowl pox has been studied (Skeate et al. 2016). Delivery of HPV E2, E6, and E7 antigens into vaccines was carried out by adenoviruses, adeno-associated viruses, vaccine viruses, and alphaviruses (H. J. Kim and Kim 2017).

E6 and E7 oncoproteins of HPV type 16/18 are shown by a genetically modified vaccine virus named TA-HPV. For analyzing a DNA-based therapeutic vaccine, TAHPV was combined with pNGVL4a-Sig/E7, in a phase II clinical trial in patients infected by high-grade CIN. In the cervico-vaginal tract, TA-HPV achieved success in developing CD8 antigen-specific T cells. A dose of 20μL TA-HPV given by a dermal scarification method has been checked in various studies. Vaccination was not shown to contribute to severe systemic adverse outcomes. However, myalgia, malaise, and headache were the most common. Low to moderate local reaction to scarification site having swelling and erythema, accompanied by the ulceration, can be settled in 17 days (Barra et al. 2020).

TG4001 comprises the Ankara virus, a genetically modified virus having the sequence those codes for human interleukin (IL)-2 gene and HPV-16 early genes E6 and E7 (Barra et al. 2020). Forty-eight percent of patients have undergone regression of disorder, while 38% of them showed clearance of HPV DNA in a phase I analysis of 21 cases of $HPV16^{+}$patients with a diagnosis of CIN2/3 (Liu et al. 2019).

MVA E2, which comprises the bovine Papillomavirus E2 protein, is based on the vaccine virus Ankara (Santesso et al. 2016). In total, 90% clearance of infection was recorded in female patients and 100% clearance of infection was recorded in male patients in a phase III analysis of patients having HPV stimulated genital intraepithelial neoplasia (Liu et al. 2019).

Since live vectors can replicate themselves in the organism, therefore, live vector vaccines produce strong immune responses to antigen vaccines. Both virus- and bacterial-neutralizing antibodies, obtained from either pre-existing immunity or vaccination, typically restrict the booster effect produced by repeated vaccination (H. J. Kim and Kim 2017).

Peptide-/protein-based vaccines

Peptide-based vaccines

Peptide vaccines are easier to develop but, for effectual depiction, they must be matched with the patient's HLA type, and often they are MHC-specific. Immunogenic epitopes should therefore be recognized for every person that makes it impossible to implement this strategy in mass immunizations (Chabeda et al. 2018). These vaccines appear to have low antigenicity, and to enhance vaccine potential for potent $CD8^{+}$T cellular responses, they need to be administrated with adjuvants such as cytokines, different molecules, and ligands like Toll-like receptor (Khong and Overwijk 2016), (Yang et al. 2016). However, peptide vaccines have safety and stability benefits (Hancock et al. 2018).

The peptide-based vaccine HPV16-SLP (ISA101) consists of four synthetic HPV16 E7 large overlying peptides fused to ISA51 (adjuvant montanide) and nine HPV16 E6. Fifteen out of nineteen patients in phase II clinical trial reported a clinical response of 79% in patients suffering from $HPV16^{+}$ having a diagnosis of VIN3 along with a full response in nine patients (47%). Furthermore, T cell response stimulated by the vaccine was developed in all patients but the more probable systematic response was obtained in patients with stronger CD8 + T cells and IFN-γ-linked CD4+. The therapeutic ability of ISA101 has also been shown in other studies (Liu et al. 2019).

A vaccine that is PepCan having four synthetic HPV16 E6 peptides and Candin as an adjuvant in the clinical study of dose-escalation phase 1 of HSIL patients, reported that 50 μg dose was the most effective, and among all patients, 45% of histological reversion of illness was reported (Greenfield et al. 2015).

A liposomal nanoparticle vaccine named PDS0101 is comprised of 6 E6/E7 peptides of human HPV type 16 encapsulated by a cationic lipid. There are no research findings on its use in humans. The PDS0101 is currently being tested in females with biopsy-proven CIN 1 (NTC02065973) and high-risk HPV infection in an open-label phase I clinical trial (Barra et al. 2020).

Protein-based vaccines

The E6 /E7 proteins are used in protein-based vaccines to immunize humans. They are comprised of all epitopes and exclude MHC restrictions in comparison with peptide-based

vaccines, but they continue to raise humoral immunity and have low immunogenicity due to their exogenous origin, mainly provided by a pathway named MHC II. Such issues can be solved by the use of fusion protein targeted at dendritic cells and by giving them exposure to the antigen presentation pathway of MHC I (Liu et al. 2019).

GTL001 (Procervix) was combined by bonding E7 of the HPV16 and HPV18 to the *Bordetella pertussis* cyclase (CyaA), which was catalytically inactive. An essential *Bordetella pertussis* toxin CyaA insets its N-terminal in the cytoplasm by attaching to integrins on the cell membrane. Antigens are transported into the cytoplasm by this feature of CyaA and the MHC I antigen presentation path is originated. HPV16- or HPV18-positive patients demonstrated efficacy and acceptability but with normal cytology, in a phase I analysis of GTL001 fused to topical imiquimod (Van Damme et al. 2016). A ligand of TLR5, flagellin, has been shown by its anti-cancerous effects in a mouse model and has also recently been found to form a fusion protein with HPV16 E7 (Lin et al. 2016).

GTL002 contains customized E7 proteins from HPV16, 18, 45, 31, 33, and 52 and it is an evolving second-generation vaccine. Models in mice and beagle dogs showed that T cell immune response specific to E7 is triggered against each of the genotypes. There have been no human data on its use so far (Barra et al. 2020).

The therapeutic protein-based vaccine SGN-00101 is a second vaccine consisting of the complete sequence of E7oncoprotein of HPV type 16 connected to the heat shock protein BCG. This vaccine acquired an incomplete response in 32 women (55%) in the phase II trial. This vaccine was given subcutaneously to 58 patients having a diagnosis of CIN 3(500 micrograms/proteins 3X in 1 month separately). There were only moderate, self-limiting side effects associated with the injection site. During the observation, no patient had significant drug-associated side effects supporting SGN-00101 tolerability and safety (Barra et al. 2020).

E6, E7, and L2 oncoproteins of HPV type 16 are contained in the TA-CIN vaccine as a single fusion protein. This vaccine stopped the HPV 16 positive tumor cells from growing out and demonstrated good immunogenic responses to both L1 and E2in a mouse model (Bogani et al. 2018). In 24 of the 32 vaccinated patients, TA-CIN-specific IgG and cell-mediated immunity were demonstrated by testing on healthy patients.63% abrasion response 1 year after vaccination was reported when VIN 2/3 was combined with TA-CIN and topical imiquimod in patients undergoing phase II clinical trials (Liu et al. 2019).

TVGV-1 is a fusion protein that comprises the E7 peptide sequence of HPV type 16 combined with the exotoxin A of *Pseudomonas aeruginosa* (PE) and retention signal of endoplasmic reticulum (ER). Da Silva et al. (2019) reported that after reliable results from in vitro study, all the CIN 2–3 patients with TVGV-1 or without GPI-0100 adjuvant (0.6 mL±0.6 mg) were tested in phase II clinical trial. The effectiveness and safety of TVGV-1 were tested in another clinical trial against HPV-stimulated cervical HSIL (NCT02576561) ((Barra et al. 2020).

Nucleic acid–based vaccines

DNA-based vaccines These include plasmid DNAs that carry desired genes and transfect host cells for the continued expression of antigens (Liu et al. 2019). DNA vaccines are based on plasmid DNA injections that aid specialized viral antigens to be encoded in the host cells, including myocytes (in case of intramuscular injection) or DCS. However, they require adjuvant because they have low immunogenicity (Bogani et al. 2018).

Since DNA-based vaccines can stimulate both humoral- and cell-mediated immune responses and allow for sustained antigenic expression, therefore these are desirable tools for therapeutic HPV vaccination. For booster vaccinations, DNA-based vaccines can be regularly administrated, unlike live vector–based vaccines because of their non-replicating, non-living, and less immunogenic nature relative to live vectors and are comparatively reliable. In addition, DNA-based vaccines are easily manufactured, and these are cost-effective and reliable. HPV DNA vaccines in clinical trials showed positive therapeutic results (H. J. Kim and Kim 2017).

The reliability, effectiveness, and immunogenicity of pNGVL4a-CRTE7 (detox), a calreticulin-related plasmid DNA vaccine (Barra et al. 2020), were evaluated in 32 HPV16-associated CIN2/3 patients in a clinical phase I trial. This vaccine was given to patients either intramuscularly, intradermally, or directly into the cervical abrasion. Twenty-two out of 32 (69%) patients reported adverse effects linked to vaccines. Constitutional and local injection sites were the most common vaccine-linked incidents and they were of grade 1 or less severe (Alvarez et al. 2016). The pNGVL4aCRT-E7 is currently undergoing clinical studies in many clinical trials for curing women having a diagnosis of CIN 2–3: it is being tested by an ongoing non-randomized open-label experimental study (through gene weapons at weeks 0, 4, and 8 until their lesion has been therapeutically rejected at week 15).

In addition, the pNGVL4aSig / E7 associated with HSP70 is being studied with or without TA- HPV in anon randomized ongoing open-label clinical phase I multi arms study, and this nonrandomized clinical phase I multi arms study also tested topical imiquimod in HPV-16 + patients with a diagnosis of CIN 3 (NCT00788164) (Barra et al. 2020).

E6 and E7oncoproteins of HPV type 16/18 are expressed by a genetically modified DNA vaccine named GX-188. To increase the expression of antigens by DCs to T lymphocytes, these HPV-specific E6 /E7 are bonded to Fms-like tyrosine kinase-3 ligand (Flt3L) extracellular domain. Nine patients

having a diagnosis of CIN 3 abrasions were given GX-188 through electroporation (EP) in phase I clinical trial. All 9 patients having a diagnosis of CIN3 showed a considerable E6- and E7-specific IFN gamma producing a T cell response. Significant increase in proliferative ability and cytolytic activities, effector molecules secretion resulted in an improved multifunctional HPV-specialized CD8 T cell response in 8 out of 9 patients. In addition, seven out of nine patients demonstrated complete reversion of their abrasions and viral prohibition within 36 weeks of monitoring. Administration of GX-188E does not induce significant adverse effects associated with the vaccine at all provided doses (Bogani et al. 2018).

In the case of HPV16/18 + CIN 2/3 patients, VGX-3100, a DNA vaccine that encodes for E6 and E7 oncoproteins of HPV type 16/18, has finished its phase IIb clinical trial and given intramuscularly with electroporation. A total of 53/107 (49.5%) of VGX-3100 patients in the per-protocol study displayed histopathological regression, compared with 11/36 (30.6%) of placebo subjects. In the updated intention-to-treatment study, 55/114 patients (48.2%) with VGX-3100 treatment had histopathological relapse compared with 12/40 (30%) with placebo patients (Trimble et al. 2015). The most frequent adverse responses were site reactions, but in the VGX3100 group (98/125, 78.4%), only in the injection site erythema was significantly higher than in the placebo group (24/42, 57.1%). Fatigue, myalgia, nausea, and arthralgia were also the other adverse effects. For women having confirmed diagnosis of CIN 2 and 3, a phase III randomized, placebo-controlled study is ongoing to determine the effectiveness, protection, and resistance of VGX-3100 when given intramuscularly superseded by electroporation (NCT03185013) (Barra et al. 2020).

ZYC101 is a vaccine that consists of a human MHC class I antigen (HLA-DRα) residue that is attached with a peptide from the HPV type 16 E7 oncoproteins. This vaccine was examined in an open-label uncontrolled trial against HPV16-associated cervical dysplasia and anal dysplasia, in which five out of fifteen CIN diagnosed patients showed complete reversion and three out of twelve patients (40.0%) demonstrated incomplete reversion with anal intraepithelial neoplasia (Barra et al. 2020).

RNA replicon–based DNA vaccines The properties of RNA and DNA vaccines are analogous because they are innocuous and do not produce neutralizing antibodies, and they can be given several epochs. Furthermore, no possibility of cellular transformations or chromosomal fusion is posed by RNA-based replicating forms (Chabeda et al. 2018). However, they are hard to manufacture and cannot proliferate across cells (Lundstrom 2015).

RNA replicon is encoded in a DNA vaccine in case of suicidal DNA vaccines to solve this problem. In transfected cells, genomic integration is prevented by suicidal DNA translation into RNA that stimulates apoptosis. But this approach has directed to weak immunogenicity due to apoptosis of transfected dendritic cells. To fix this problem, a pre-clinical model described that the anti-apoptotic gene is incorporated into the suicidal DNA to improve APC persistence.

The usage of a Kunjin flavivirus (KUN) vector also permits and extends the immediate presentation of antigen via transected DCs. This later approach protected mice with an E7 expressing tumor and led to E7-specific T cell responses. Many RNA vaccines for other HPV-related malignances have proceeded to clinical trials; nevertheless, more work needs to be done in the production of RNA vaccines for HPV (Chabeda et al. 2018).

On the whole, regardless of promising outcomes shown by these vaccines in preclinical investigations and clinical trials against other types of cancer, replica vaccines against HPV and HPV related disorders did not yet reach the stage of the clinical trial, except for the genetically modified SFV expressing HPV 16 E6 / E7 (Vvax001; ViciniVax BV) (Vonsky et al. 2019). These vaccines seem highly promising for the cure of HPV lesions; however, further research needs to be conducted (Liu et al. 2019).

Whole cell–based vaccines

These vaccines have been developed as a promising therapeutic vaccine against disorders related to HPV (Barra et al. 2020). These vaccines involve isolation and removal of cells (such as T lymphocytes or dendrite cells) from the expunged tumors of patients or peripheral blood, propagating and maneuvering them ex vivo, and ultimately transmitting the mutated and picked cells back to the patients (Liu et al. 2019)

DC-based vaccines Dendritic cells are inserted on HPV antigens for the production of DC-based vaccines. Origination and regulation of T cell responses are greatly demonstrated by these dendrite cells in vitro. Because they promote the identification of specific cancer-related antigens that are not usually found on human cells, therefore, they are considered hypothetically the best candidates for immunotherapeutic approaches. The genes that encode for cytokines such as IL-2, IL-12, and granulocyte-macrophage colony-stimulating factor (GM-CSF) aid in the loading of these cells to enhance the immune response. Such therapeutic vaccines were previously studied in the treatment of progressive cancers (Barra et al. 2020)

DCS has been pulsated with HPV16/18 E7 and then given back to patients with IL-2 in phase I clinical trial. All patients have had an E7-specific CD8 + response. Dendrite cells were pulsated with HPV16/18 E7 along with peephole limpet hemocyanin in another phase I clinical trial and it was managed in patients with phase Ib or IIa cervical tumor, stimulating DC maturation. Consequently, a rise in CD8+ T lymphocytes specific to E7 was shown by 8 of 10 patients (Liu et al. 2019).

A subcutaneous injection was administered to the patient. During or after DC vaccinations, no major local or systemic

Table 1 Main therapeutic vaccine for the cure of cervical cancer

Names of vaccines	Effectiveness	Limitations	References
Bacterium and virus-based live attenuated vaccines			
Lm-LLO-E7 MVA GLBL101c BLS-M07 TA-HPV	Extremely immune accelerating agents, Huge variety of existing vectors; Antigen-presenting cells can produce both genetically modified plasmid and expressed protein, Imitates normal progression of infection.	Preceding immune response against vector, No frequent processing, Safety hazards for immune-compromised persons	Barra et al. (2020) Vonsky et al. (2019) Marzi et al. (2015) (Hancock et al. (2018)
Peptide vaccines			
PDS0101 Pep can ISA 101 TG4001	Permanence, protection, easy to produce; capability to contain a varied variety of epitopes; chance of alteration to make better attachment to MHC	HLA limited, minimal immunogenicity, adjuvant needs to be co-administrated, compulsory preceding mapping of epitopes as an element of prospective immunogenic choice;	Vonsky et al. (2019) Cheng et al. (2018) van Poelgeest et al. (2016) Greenfield et al. (2015) Hancock et al. (2018)
Protein vaccines			
GTL001 TA-CIN GTL002 SGN-00101 TVGV-1	Non-MHC limited, (all antigens originate from antigen-presenting cells intracellular procedure), Harmless, Stabling, and ease of manufacturing, not HLA limited	Minimal immunogenicity, adjuvant needs to be co-administrated, Produces antibodies in place of cytotoxic T lymphocytes	Hancock et al. (2018) Vonsky et al. (2019) Cheng et al. (2018)
DNA vaccines			
ZYC 101 GX-188 pNGVL4a-CRT-E7 VGX-3100	Stimulate both humoral and cell-mediated immune responses, harmless, stabling, have a low price	Minimal antigenicity, continued cellular gene expression since they have minimal immunogenicity, adjuvant needs to be co-administrated	H. J. Kim and Kim (2017) Hancock et al. (2018) Bogani et al. (2018) Alvarez et al. (2016) Y. Zhang et al. (2019)
RNA-based vaccines			
Vaccines have been manufacturing for several years. RNA replicon vaccines against HPV and HPV linked disorders have not undergone the clinical trial	Temporary abrasions, several modes of administrating vaccines, continued antigenic expression, No possibility of	Hard to manufacture and stock, non-stability, labor exhaustive, no intercellular dispersal, Dose-restrictive harmfulness, reduced immunogenicity,	Vonsky et al. (2019)

Table 1 (continued)

Names of vaccines	Effectiveness	Limitations	References
phase, apart from for the Vvax001,(a recombinant SFV expressing HPV 16 E6 and E7)	cellular transformation and chromosomal integration	the origination of apoptosis in transfected cells, complications in creation, scaling up and manufacturing, Various mRNAs cannot be amalgamated in the same preparation, safer data of humans for RNA has not been completely established	Kübler et al. (2015) Cheng et al. (2018)
Whole cell–based			
HPV E6-E7 encumbered monocytes	DC-based vaccines: Highly immune-stimulating encompassing several methods of antigen loading Tumor cell vaccines: Target to enhance the immunogenicity of cancer cells by raising the expression of immune modulator proteins, for example, GM-CSF, IL-2, and IL-12	Costly, Labor exhaustive, Safety hazards, Highly engineering task	Barra et al. (2020) Vonsky et al. (2019) Cheng et al. (2018) H. J. Kim and Kim (2017)

reactions were reported (Barra et al. 2020). The disadvantages of DC-based vaccines are short half-life, problems in acquiring large numbers of antilogous DC from the patient, and lack of propagation that restricts enduring immune response. Furthermore, dendrite cell–based vaccines contributed no clinical responses despite being able to stimulate cell-mediated and serological immunity against HPV [61, 5]. In conclusion, even though progressed incidents of cervical cancer make use of DC vaccines, it is unsuitable these DCs will be used in the treatment of CIN abrasions because the processes involved are expensive and labor-intensive (Barra et al. 2020).

Tumor cell–based vaccine Granulocyte-macrophage colony-stimulating factors and cytokines like IL-2 and IL-12 are expressed by designed isolated cancer cells. Tumor cell–based vaccines upon re-administration greatly enhance the tumor cells' immunogenicity, thus stimulating immune removal of abrasions. Such type of vaccines was studied in different types of cancer in clinical trials and ought not to recognize other cancerous antigens. Vaccines based on tumor cells may not be the earliest option for its treatment because cervical cancer is known to have particular antigens, like E6 and E7. Nevertheless, tumor cell vaccines are related to the disadvantage of establishing new tumors in patients, which restricts their clinical applicability, especially in HPV-positive patients with typical cytology or patients with low-grade abrasions (Liu et al. 2019).

Conclusion

The most common sexually transmitted infection in the USA is not only human papillomavirus infection, but it is the source of several other cervical, vulvar, vaginal, anal, penile, and head and neck cancers. Subsequently, it is a major public health issue particularly for youths who are extremely affected. The production of HPV vaccines has directed the capability of defending and preventing HPV infection and its sequela. Since existing vaccines have no therapeutic impact, therapeutic HPV vaccines are desperately needed to lessen the risk of cervical cancer. Even if the public has been able to control HPV infections with prophylactic vaccines like Gardasil, Cervarix, and Gardasil-9, still, a substantial number of people are also at risk for developing HPV-related malignancies and cancer with current HPV infection or HPV-related illnesses. Thus, it is more important than ever to use HPV therapeutic vaccines.

To date, no commercially available therapeutic vaccine for HPV infection treatment and related malignancies has been authorized. Clinical trials of HPV therapeutic vaccines, including whole cell–based vaccines, DNA, peptide/protein, DNA, and live vector, indicate that these HPV vaccines have the significant ability for safe, reliable, and non-invasive cure of cervical cancer as well as emphasizing deficiencies in their functional use. But therapeutic vaccines of each class have their efficacy, benefits, and limitations (Table 1). To date, in phase I–II clinical studies, most of the HPV therapeutic vaccines have been analyzed (Table 2). Further phase III clinical studies are also required to determine the optimum age and gender of the population and for the exact description of the function of therapeutic vaccines for the cure of preinvasive abrasions and cervical HPV illness.

Nonetheless, several clinical trials show the advancement achieved using numerous vaccine approaches and two vaccine candidates, ADXS11-001 bacterial vector vaccine and VGX3100 DNA vaccine. Both of these vaccines are in phase III clinical trials, indicating that the vaccine has promising

Table 2 Summary on therapeutic HPV vaccines clinical trials, studies, and their outcomes

Vaccines	Antigens	Trial design	Trial outcome	Side effects	References
Bacterial vector–based vaccines					
GLBL101c	E7oncoprotein of HPV type 16	Phase I/IIa clinical trial was conducted on 17 HPV16 positive patients having a diagnosis of CIN3	The substantial rise in E7-CMI in the Cervical tract of the vagina, Disease relapse was observed in 9 patients to CIN2, and 5 patients further relapsed to LSIL	No serious adverse effects reported	Barra et al. (2020) Yang et al. (2017) Kawana et al. (2014)
Lm-LLo-E7	E7 oncoproteins of HPV type 16	Phase I clinical trial was conducted on 15 patients suffering from recalcitrant chronic, metastatic, or progressed squamous cell cervical carcinoma.	E7-specific T cells rise was found in 3 PBMCs patients. 4 patients experienced a decrease in tumor size and progression.	The major side effects reported were vomiting, the agony of the skeleton Pyrexia, chills, anemia, tachycardia, nausea, and headache.	Barra et al. (2020) Yang et al. (2017)
Viral vector–based vaccines					
TA-HPV	E6 and E7oncoproteins of HPV type 16/18	Phase I/II clinical trial was conducted on 8 patients suffering from the progressed stage of cervical cancer	CTL immune response specific to HPV triggered by vaccination was observed in 3 out of 8 members (almost 28 % patients), Two patients were free of tumors 15-21 months after the following vaccination	Adequate and mild toxicity was reported after single-dose administration	Barra et al. (2020) Yang et al. (2017)
		Phase I clinical trial was conducted on 29 patients suffering from Stage Ib or IIa cervical cancer	Cytotoxic T lymphocytes specific to HPV were observed in 4 patients after a single vaccination. Serological responses unique to HPV were established in 8 patients (28%).	Minor to modest Local toxicity was observed.	Barra et al. (2020) Yang et al. (2017)
		Phase II clinical trial was conducted on 12 patients aged 42–54 suffering from 15 years with high-grade HPV-positive intraepithelial vaginal or vulval neoplasia.	At least a 50% decrease in total abrasion span was observed in24 weeks in 5 out of 12 patients with 1 patient exhibiting total reversion of the abrasion. On the whole, an average decline in abrasion size of 40% was observed in 83% of women. An enhanced T cell and immunoglobulin Gtiter response to the vaccinia virus was observed in all patients.	Local response was found near the vaccination site between days 7–10 and 2 patients were identified with momentarily confined movement of the arm.	Barra et al. (2020) Yang et al. (2017)
MVAE2	E2oncoproteins of HPV type 16	Phase III clinical trial was conducted on 180 males and 1176 females suffering from HPV-stimulated AGIN	90% removal of abrasion was reported in female cured patients and 100% removal of abrasion was reported in male cured patients. All checked patients experienced antibody and T cell responses.	The major adverse effects observed were headache, symptoms of the flu, fever, frost, pain, joint and abdominal pain were.	Barra et al. (2020) Yang et al. (2017) Rosales et al. (2014)
BLS-M07	E7oncoproteins of HPV type 16	Phase I/IIa clinical trial was conducted on HPV-16 infected patients having CIN3. 19 patients undergone phase I trial and 8 patients	Safety and effectiveness evaluation (primary endpoint), development of systemic immunoglobulin IgG against HPVE7; and the Reid Colposcopic	No serious adverse effects were reported.	Barra et al. (2020)

Table 2 (continued)

Vaccines	Antigens	Trial design	Trial outcome	Side effects	References
		undergone phase IIa trial.	Index (RCI) assessed abrasion-grade change (secondary end points)		
TG4001	E6 and E7oncoproteins of HPV type 16	21 patients having HPV16+ infection and CIN2/3 diagnosis undergone phase I clinical trial	Disease relapse was observed in 10 out of 21 patients (48%). 8 patients showed HPV DNA removal and7 patients showed mRNA removal.	Major adverse effects reported were fever, headache, pain in bone, inflammation, pruritus, edema, lymphadenopathy, asthenia, vaginal release.	Barra et al. (2020) Brun et al. (2011)
Peptide vaccines					
ISA101	E6 and E7oncoproteins of HPV type 16	Phase II clinical trial was conducted on 34 patients having HPV-16+ Irredeemable solid tumors (vaginal, cervical, vulvar, penile, and anal cancer along with or pharyngeal squamous cell carcinoma).	18 patients out of 34 (53%; 95 % showed clinical response with confidence interval (CI) (35.1 to 70.2) at 3 months and 15patients out of 29 (52%; 95 %) showed clinical responses with confidence interval (CI) at 12 months. The complete histological response was shown by 8 patient	The ulceration and inflammation of the skin was observed in patients along with local reactions, even these adverse effects persisted for 12 months	Barra et al. (2020)
PDS0101	E6 and E7oncoproteins of HPV type 16	A phase I clinical trial is ongoing in 18 estimated female patients having high-grade HPV infection or diagnosis of CIN1	There are no findings in the literature on its use in humans.		Barra et al. (2020)
Pepcan	E6oncoproteins of HPV type 16	Phase I clinical trial was conducted on 24 CIN 2/3 diagnosed patients proved by biopsy	A decrease in abrasion rate of 83% was reported. Immune responses triggered by vaccines were observed after 4 vaccinations in 65% of women	Reactions at the injection site, no dose-limiting toxicities have been encountered by either patient	Barra et al. (2020) Coleman et al. (2016)
		A phase II clinical trial is ongoing	Colposcopy-driven quadrant biopsies showed clinical response		
Protein vaccines					
SGN-00101	The BCG heat shock protein associated with E7oncoproteins of HPV type 16	Phase II clinical trial was conducted on 58 patients with a diagnosis of CIN 3	13 patients (22.5%) showed complete histological response (CR) and 32 (55%) females showed incomplete response	There were only moderate, self-limiting side effects associated with the injection site	Barra et al. (2020)
TA-CIN +	E6/E7/L2oncoproteins of HPV type 16	Phase I clinical trial was conducted on 40 healthy patients	24 out of 32 vaccinated patients produced TA-CIN specific immunoglobin IgG. CMI was produced by 25 out of 32 vaccinated patients	Adverse effects reported were reactions at the injection site, headache, tenderness, and fatigue	Barra et al. (2020)
		Phase II clinical trial was conducted on 19 patients with a diagnosis of VIN2/3	63% abrasion response was shown 1 year after vaccination.	Imiquimod-related local reactions were observed.	Barra et al. (2020)
TVGV-1	The E7 peptide sequence of HPV type 16.	Phase IIa clinical trial is ongoing on 51 expected patients having a diagnosis of CIN 2–3	Since the trial is ongoing, no findings have yet been reported.		Barra et al. (2020)
GTL001	E7 oncoproteins of HPV type 16 and 18	Phase I clinical trial was conducted on 47 HPV-16 or HPV-18 +vepatients having either usual or	Analyzed GTL00 resistance, safety, and immunogenicity	Slight to moderate injection-site reactions include itching induration,	Barra et al. (2020) Van Damme et al.

Table 2 (continued)

Vaccines	Antigens	Trial design	Trial outcome	Side effects	References
		slightly anomalous cervical cytology		pain tenderness, and swelling. The most common systemic reactions were myalgia, Headache, and fatigue	(2016)
	Imiquimod is an adjuvant that was checked with it	239 HPV-16 or HPV-18 +ve patient underwent phase II clinical trial having either usual or slightly anomalous cervical cytology	Between placebo groups and GTL001there was arithmetically substantial variance in the removal of virus and advancement of abrasions to high-grade	There was no unforeseen incident reported and vaccination was well tolerated	Barra et al. (2020)
GTL002	HPV type 16, 18, 45, 31, 33 and 52modified E7 proteins	Prototypes of Beagle dogs and mice. There are no human details on its use so far	T cell immune response specific to E7 is triggered against each of the genotypes		Barra et al. (2020)
DNA vaccines					
pNGVL4a-CRT/E7(detox)	E7oncoproteins of HPV type 16	32 HPV16+ patients having a diagnosis of CIN2/3 undergone phase I clinical trial	Histological relapse to CIN1 or less was experienced in 30% of vaccinated patients. After vaccination, a rise in intraepithelial C8+ T cells in the filtrate was reported.	Reactions at the injection site were reported.	Barra et al. (2020) Alvarez et al. (2016)
VGX-3100	E6 and E7oncoproteinsof HPV type16,18	Phase I clinical trial was conducted on 18 HPV16/18 + patients with a diagnosis of CIN2/3	Antibody-mediated immune response specific to HPV was detected in all patients while 78% of patients showed HPV-specific CMI.	Major side effects reported were reaction at the injection site, fever, tenderness, and pain.	Barra et al. (2020) Yang et al. (2017)
		167 HPV16/18 + CIN2/3 patients undergone Phase IIb clinical trial	Relapse was shown by 49.5% of immunized patients compared to 30.6% in the placebo group. Humoral and T cell immune responses are boosted by vaccinations.	Reaction at the injection site, headache, nausea, arthralgia, myalgia fatigues erythema	Barra et al. (2020) Yang et al. (2017)
GX-188E	E6 and E7 oncoproteinsof HPV type16,18	Phase I clinical trial was conducted on nine HPV 16/18+patients having a diagnosis of CIN3	An enhanced HPV-specific CMI was shown in all patients. Complete regression in abrasion was shown by 7 patients at the end of the trial.	Major side effects reported were chills, hypoesthesia, swelling, aching at injection site nuisance, rhinitis, exhaustion	Barra et al. (2020) Kim et al. (2014)
Cell vaccines					
DC vaccinations	Antigens of HPV	Phase I clinical trial was conducted on 14HPV+ patients having progressed, chronic cervical cancer.	There was no substantial rise in lymphocyte propagation.	Major side effects reported were reaction at the local site, chills, abdominal discomfort, fever, nausea	Barra et al. (2020) Ramanathan et al. (2014)

potential shortly. In addition, another important subject is the financial dimension correlated to therapeutic vaccines; one study has attempted to investigate the prospective price of this HPV therapeutic vaccine for females living in the Netherlands with cervical abrasions caused by HPV. The cost of the vaccine was less than the normal medication price for patients having a diagnosis of cervical malignancies and CIN 2/3. Hence, the main focus of this review was to discuss primarily the therapeutic HPV vaccines presently available and or those that are established for the cure of HPV illnesses and HPV-related disorders.

Future perspectives

With the information collected from the current and prior researches along with sustained efforts in the production of therapeutic HPV vaccines, we think that these therapeutic

approaches will go onto obtain progress. We are assured that soon these therapeutic vaccines will become clinically accessible and these vaccines will commonly use along with other remedies involving surgery, chemotherapy, and radiation therapy, for the prevention of HPV and HPV-linked disorders. Prime-boost treatment and other combinatorial techniques may offer a better therapeutic HPV vaccine approach to boost T cell immune responses. For this reason, increased immunogenicity is the most important criterion for the clinical implementation of all therapeutic vaccines. These ongoing efforts to produce therapeutic vaccines help to manage and control malignancies related to HPV along with traditional approaches for treating HPV. Further work is currently needed on the effects of integrated methods and their basic mechanisms to improve various synergistic strategies individually customized for each patient.

In summary, the organized use of different approaches may work in conjunction against HPV infection. The fusion of prophylactic vaccines with therapeutic ones, or several forms of therapeutic vaccines as in prime-booster approach, anti-viral, or checkpoint inhibitors, and other similar fusions, may have a great effect on the cure of HPV infection.

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Declarations

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References

Alvarez RD, Huh WK, Bae S, Lamb LS Jr, Conner MG, Boyer J, Wang C, Hung C-F, Sauter E, Paradis M (2016) A pilot study of pNGVL4a-CRT/E7 (detox) for the treatment of patients with HPV16+ cervical intraepithelial neoplasia 2/3 (CIN2/3). Gynecol Oncol 140(2):245–252

Alves BM, Prellwitz IM, Siqueira JD, Meyrelles ÂR, Bergmann A, Seuánez HN, Machado ES, Soares MA, Soares EA (2015) The effect of human leukocyte antigen G alleles on human papillomavirus infection and persistence in a cohort of HIV-positive pregnant women from Brazil. Infect Genet Evol 34:339–343

Barra F, Della Corte L, Noberasco G, Foreste V, Riemma G, Di Filippo C, Bifulco G, Orsi A, Icardi G, Ferrero S (2020) Advances in therapeutic vaccines for treating human papillomavirus-related cervical intraepithelial neoplasia. J Obstet Gynaecol Res 46(7):989–1006

Bhaskaran M, Murali SV, Rajaram B, Krishnasamy S, Devasena CS, Pathak A, Ravi V, Swaminathan K, Ayyappa A, Vedhantham S (2019) Association of HLA-A,-B, DRB, and DQB alleles with persistent HPV-16 infection in women from Tamil Nadu, India. Viral Immunol 32(10):430–441

Bogani G, Maggiore ULR, Signorelli M, Martinelli F, Ditto A, Sabatucci I, Mosca L, Lorusso D, Raspagliesi F (2018) The role of human papillomavirus vaccines in cervical cancer: prevention and treatment. Crit Rev Oncol Hematol 122:92–97

Bowden SJ, Bodinier B, Kalliala I, Zuber V, Vuckovic D, Doulgeraki T, Whitaker MD, Wielscher M, Cartwright R, Tsilidis KK (2021) Genetic variation in cervical preinvasive and invasive disease: a genome-wide association study. The Lancet Oncology 22(4):548–557

Brun J-L, Dalstein V, Leveque J, Mathevet P, Raulic P, Baldauf J-J, Scholl S, Huynh B, Douvier S, Riethmuller D (2011) Regression of high-grade cervical intraepithelial neoplasia with TG4001 targeted immunotherapy. Am J Obstet Gynecol 204(2):169–1e1

Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, de Sanjosé S, Castellsagué X (2016) Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. Lancet Glob Health 4(7):e453–e463

Cai H, Feng Y, Fan P, Guo Y, Kuerban G, Chang C, Yao X, Peng Y, Zheng Wang R (2021). HPV16 E6-specific T cell response and HLA-A alleles are related to the prognosis of patients with cervical cancer. https://doi.org/10.21203/rs.3.rs-209456/v1

Chabeda A, Yanez RJ, Lamprecht R, Meyers AE, Rybicki EP, Hitzeroth II (2018) Therapeutic vaccines for high-risk HPV-associated diseases. Papillomavirus Research 5:46–58

Chan PK, Cheung JL, Cheung T-H, Lin C, Tam AO, Chan DP, Zhou DX, Lo KW, Yim S-F, Siu S-SN (2006) HLA-B alleles, high-risk HPV infection and risk for cervical neoplasia in southern Chinese women. Int J Cancer 118(6):1430–1435

Chan PK, Cheung T-H, Lin CK, Siu S-SN, Yim S-F, Lo KW, Cheung JL, Tam AO, Tang JW (2007) Association between HLA-DRB1 polymorphism, high-risk HPV infection and cervical neoplasia in southern Chinese. J Med Virol 79(7):970–976

Cheng MA, Farmer E, Huang C, Lin J, Hung C-F, Wu T-C (2018) Therapeutic DNA vaccines for human papillomavirus and associated diseases. Hum Gene Ther 29(9):971–996

Coleman HN, Greenfield WW, Stratton SL, Vaughn R, Kieber A, Moerman-Herzog AM, Spencer HJ, Hitt WC, Quick CM, Hutchins LF (2016) Human papillomavirus type 16 viral load is decreased following a therapeutic vaccination. Cancer Immunol Immunother 65(5):563–573

Cuzick J, Terry G, Ho L, Monaghan J, Lopes A, Clarkson P, Duncan I (2000) Association between high-risk HPV types, HLA DRB1* and DQB1* alleles and cervical cancer in British women. Br J Cancer 82(7):1348–1352

Da Silva DM, Skeate JG, Chavez-Juan E, Lühen KP, Wu J-M, Wu C-M, Kast WM, Hwang K (2019) Therapeutic efficacy of a human papillomavirus type 16 E7 bacterial exotoxin fusion protein adjuvanted with CpG or GPI-0100 in a preclinical mouse model for HPV-associated disease. Vaccine 37(22):2915–2924

de Araujo Souza PS, Villa LL (2003) Genetic susceptibility to infection with human papillomavirus and development of cervical cancer in women in Brazil. Mutation Research/Reviews in Mutation Research 544(2–3):375–383

de Araujo Souza PS, Sichero L, Maciag PC (2009). HPV variants and HLA polymorphisms: the role of variability on the risk of cervical cancer. Future Oncol 5(3):359–70. https://doi.org/10.2217/fon.09.8

Dong D, Yang H, Li K, Xu G, Song L, Fan X, Jiang X, Yie S (2010) Human leukocyte antigen-G (HLA-G) expression in cervical

lesions: association with cancer progression, HPV 16/18 infection, and host immune response. Reprod Sci 17(8):718–723

Fahim NM, Shehata IH, Taha SE, Fahmy RA, Elsayed MS (2018) Human Leukocyte Antigen-G (HLA-G) Expression in precancerous and cancerous cervical lesions: association with human papilloma virus infection and host immune response. The Egyptian J Immunol 25(1):125–134

Ferguson R, Ramanakumar AV, Richardson H, Tellier P-P, Coutlée F, Franco EL, Roger M (2011) Human leukocyte antigen (HLA)-E and HLA-G polymorphisms in human papillomavirus infection susceptibility and persistence. Hum Immunol 72(4):337–341

Gillio-Tos A, da Graça Bicalho M, Fiano V, Grasso C, Tarallo V, De Marco L, Trevisan M, Xavier M, Slowik R, Carvalho NS (2012) Case–control study of HLA-G promoter methylation status, HPV infection and cervical neoplasia in Curitiba, Brazil: a pilot analysis. BMC Cancer 12(1):1–10

Gokhale P, Mania-Pramanik J, Sonawani A, Idicula-Thomas S, Kerkar S, Tongaonkar H, Chaudhari H, Warke H, Salvi V (2014) Cervical cancer in Indian women reveals contrasting association among common sub-family of HLA class I alleles. Immunogenetics 66(12): 683–691

Gonçalves CA, Lopes-Júnior LC, Nampo FK, Zilly A, Mayer PCM, Pereira-da-Silva G (2019) Safety, efficacy and immunogenicity of therapeutic vaccines in the treatment of patients with high-grade cervical intraepithelial neoplasia associated with human papillomavirus: A systematic review protocol. BMJ Open 9(7):e026975

Goodman MT, McDuffie K, Hernandez B, Bertram CC, Wilkens LR, Guo C, Seifried A, Killeen J, Le Marchand L (2001) CYP1A1, GSTM1, and GSTT1 polymorphisms and the risk of cervical squamous intraepithelial lesions in a multiethnic population. Gynecol Oncol 81(2):263–269

Greenfield WW, Stratton SL, Myrick RS, Vaughn R, Donnalley LM, Coleman HN, Mercado M, Moerman-Herzog AM, Spencer HJ, Andrews-Collins NR (2015) A phase I dose-escalation clinical trial of a peptide-based human papillomavirus therapeutic vaccine with Candida skin test reagent as a novel vaccine adjuvant for treating women with biopsy-proven cervical intraepithelial neoplasia 2/3. Oncoimmunology 4(10):e1031439

Guimarães MC, Soares CP, Donadi EA, Derchain SF, Andrade LA, Silva TG, Hassumi MK, Simões RT, Miranda FA, Lira RC (2010) Low expression of human histocompatibility soluble leukocyte antigen-G (HLA-G5) in invasive cervical cancer with and without metastasis, associated with papilloma virus (HPV). J Histochem Cytochem 58(5):405–411

Hancock G, Hellner K, Dorrell L (2018) Therapeutic HPV vaccines. Best Practice & Research Clinical Obstetrics & Gynaecology 47:59–72

Harper DM, DeMars LR (2017) HPV vaccines–a review of the first decade. Gynecol Oncol 146(1):196–204

Hernández-Hernández DM, Cerda-Flores RM, Juárez-Cedillo T, Granados-Arriola J, Vargas-Alarcón G, Apresa-García T, Alvarado-Cabrero I, García-Carrancá A, Salcedo-Vargas M, Mohar-Betancourt A (2009) Human leukocyte antigens I and II haplotypes associated with human papillomavirus 16-positive invasive cervical cancer in Mexican women. Int J Gynecol Cancer 19(6):1099–1106

Hildesheim A, Wang SS (2002) Host and viral genetics and risk of cervical cancer: a review. Virus Res 89(2):229–240

Hu Y, Wu J-Z, Zhu H, Zhang S-H, Zhu Y-Y, Wu Y-Y, Shuai C-X (2017) Association of HLA-DRB1, HLA-DQB1 polymorphisms with HPV 16 E6 variants among young cervical cancer patients in China. J Cancer 8(12):2401–2409

Hus I, Gonet-Sebastianka J, Surdacka A, Bojarska-Junak A, Roliński J (2015). Analysis of peripheral blood immune cells after prophylactic immunization with HPV-16/18 ASO4-adjuvanted vaccin. Advances in Hygiene & Experimental Medicine/Postepy Higieny i Medycyny Doswiadczalnej, 69, p543–548. 6p

Ivansson EL, Magnusson JJ, Magnusson PKE, Erlich HA, Gyllensten UB (2008) MHC loci affecting cervical cancer risk: distinguishing the effects of HLA-DQB1 and non-HLA genes TNF, LTA, TAP1 and TAP2. Genes Immun 9(7):613–623

Kawana K, Adachi K, Kojima S, Taguchi A, Tomio K, Yamashita A, Nishida H, Nagasaka K, Arimoto T, Yokoyama T (2014) Oral vaccination against HPV E7 for treatment of cervical intraepithelial neoplasia grade 3 (CIN3) elicits E7-specific mucosal immunity in the cervix of CIN3 patients. Vaccine 32(47):6233–6239

Khong H, Overwijk WW (2016) Adjuvants for peptide-based cancer vaccines. Journal for Immunotherapy of Cancer 4(1):1–11

Kim HJ, Kim H-J (2017) Current status and future prospects for human papillomavirus vaccines. Arch Pharm Res 40(9):1050–1063

Kim TJ, Jin H-T, Hur S-Y, Yang HG, Seo YB, Hong SR, Lee C-W, Kim S, Woo J-W, Park KS (2014) Clearance of persistent HPV infection and cervical lesion by therapeutic DNA vaccine in CIN3 patients. Nat Commun 5(1):1–14

Kübler H, Scheel B, Gnad-Vogt U, Miller K, Schultze-Seemann W, Vom Dorp F, Parmiani G, Hampel C, Wedel S, Trojan L (2015) Self-adjuvanted mRNA vaccination in advanced prostate cancer patients: a first-in-man phase I/IIa study. Journal for Immunotherapy of Cancer 3(1):1–14

Landy R, Windridge P, Gillman MS, Sasieni PD (2018) What cervical screening is appropriate for women who have been vaccinated against high risk HPV? A simulation study. Int J Cancer 142(4): 709–718

Leo PJ, Madeleine MM, Wang S, Schwartz SM, Newell F, Pettersson-Kymmer U, Hemminki K, Hallmans G, Tiews S, Steinberg W (2017) Defining the genetic susceptibility to cervical neoplasia—a genome-wide association study. PLoS Genet 13(8):e1006866

Lin K-H, Chang L-S, Tian C-Y, Yeh Y-C, Chen Y-J, Chuang T-H, Liu S-J, Leng C-H (2016) Carboxyl-terminal fusion of E7 into Flagellin shifts TLR5 activation to NLRC4/NAIP5 activation and induces TLR5-independent anti-tumor immunity. Sci Rep 6(1):1–10

Liu Y, Li H, Pi R, Yang Y, Zhao X, Qi X (2019) Current strategies against persistent human papillomavirus infection. Int J Oncol 55(3):570–584

Louvanto K, Roger M, Faucher M-C, Syrjänen K, Grenman S, Syrjänen S (2018) HLA-G and vertical mother-to-child transmission of human papillomavirus infection. Hum Immunol 79(6):471–476

Lundstrom K (2015) RNA-based drugs and vaccines. Expert Review of Vaccines 14(2):253–263

Maciag PC, Schlecht NF, Souza PS, Franco EL, Villa LL, Petzl-Erler ML (2000) Major histocompatibility complex class II polymorphisms and risk of cervical cancer and human papillomavirus infection in Brazilian women. Cancer Epidemiology and Prevention Biomarkers 9(11):1183–1191

Madeleine MM, Brumback B, Cushing-Haugen KL, Schwartz SM, Daling JR, Smith AG, Nelson JL, Porter P, Shera KA, McDougall JK (2002) Human leukocyte antigen class II and cervical cancer risk: a population-based study. J Infect Dis 186(11):1565–1574

Madeleine MM, Johnson LG, Smith AG, Hansen JA, Nisperos BB, Li S, Zhao L-P, Daling JR, Schwartz SM, Galloway DA (2008) Comprehensive analysis of HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci and squamous cell cervical cancer risk. Cancer Res 68(9):3532–3539

Mahmud SM, Robinson K, Richardson H, Tellier P-P, Ferenczy AS, Roger M, Coutlée F, Franco EL (2007) HLA polymorphisms and cervical human Papillomavirus infection in a cohort of Montreal University students. J Infect Dis 196(1):82–90

Marzi A, Kercher L, Marceau J, York A, Callsion J, Gardner DJ, Geisbert TW, Feldmann H (2015) Stat1-deficient mice are not an appropriate model for efficacy testing of recombinant vesicular stomatitis virus–based filovirus vaccines. J Infect Dis 212(suppl_2):S404–S409

Matsumoto K, Yasugi T, Nakagawa S, Okubo M, Hirata R, Maeda H, Yoshikawa H, Taketani Y (2003) Human papillomavirus type 16 E6

variants and HLA class II alleles among Japanese women with cervical cancer. Int J Cancer 106(6):919–922
Metcalfe S, Roger M, Faucher M-C, Coutlée F, Franco EL, Brassard P (2013) The association between human leukocyte antigen (HLA)-G polymorphisms and human papillomavirus (HPV) infection in Inuit women of northern Quebec. Hum Immunol 74(12):1610–1615
Mousavi T, Saravi SS, Valadan R, Haghshenas MR, Rafiei A, Jafarpour H, Shamshirian A (2020) Different types of adjuvants in prophylactic and therapeutic human papillomavirus vaccines in laboratory animals: a systematic review. Arch Virol 165(2):263–284
Odunsi K, Terry G, Ho L, Bell J, Cuzick J, Ganesan TS (1996) Susceptibility to human papillomavirus-associated cervical intraepithelial neoplasia is determined by specific HLA DR-DQ alleles. Int J Cancer 67(5):595–602
Paaso A, Jaakola A, Syrjänen S, Louvanto K (2019) From HPV infection to lesion progression: The role of HLA alleles and host immunity. Acta Cytol 63(2):148–158
Panahi HA, Bolhassani A, Javadi G, Noormohammadi Z, Agi E (2020) Development of multiepitope therapeutic vaccines against the most prevalent high-risk human papillomaviruses. Immunotherapy 12(7): 459–479
Ramanathan P, Ganeshrajah S, Raghanvan RK, Singh SS, Thangarajan R (2014) Development and clinical evaluation of dendritic cell vaccines for HPV related cervical cancer-a feasibility study. Asian Pac J Cancer Prev 15(14):5909–5916
Roden RB, Stern PL (2018) Opportunities and challenges for human papillomavirus vaccination in cancer. Nat Rev Cancer 18(4):240–254
Rosales R, López-Contreras M, Rosales C, Magallanes-Molina J-R, Gonzalez-Vergara R, Arroyo-Cazarez JM, Ricardez-Arenas A, del Follo-Valencia A, Padilla-Arriaga S, Guerrero MV (2014) Regression of human papillomavirus intraepithelial lesions is induced by MVA E2 therapeutic vaccine. Hum Gene Ther 25(12): 1035–1049
Sanjeevi CB, Hjelmström P, Hallmans G, Wiklund F, Lenner P, Angström T, Dillner J, Lernmark (1996) Different HLA-DR-DO haplotypes are associated with cervical intraepithelial neoplasia among human papillomavirus type-16 seropositive and seronegative Swedish women. Int J Cancer 68(4):409–414
Santesso N, Mustafa RA, Wiercioch W, Kehar R, Gandhi S, Chen Y, Cheung A, Hopkins J, Khatib R, Ma B (2016) Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. Int J Gynecol Obstet 132(3):266–271
Shanmugasundaram S, You J (2017) Targeting persistent human papillomavirus infection. Viruses 9(8):229
Silva TG, Crispim JC, Miranda FA, Hassumi MK, de Mello JM, Simões RT, Souto F, Soares EG, Donadi EA, Soares CP (2011) Expression of the nonclassical HLA-G and HLA-E molecules in laryngeal lesions as biomarkers of tumor invasiveness. Histol Histopathol: 1487–1497
Simoes RT, Gonçalves MAG, Castelli EC, Junior CM, Bettini JS, Discorde ML, Duarte G, Quintana SM, Simoes AL, Moreau P (2009) HLA-G polymorphisms in women with squamous intraepithelial lesions harboring human papillomavirus. Mod Pathol 22(8):1075–1082
Skeate JG, Woodham AW, Einstein MH, Da Silva DM, Kast WM (2016) Current therapeutic vaccination and immunotherapy strategies for HPV-related diseases. Human Vaccines & Immunotherapeutics 12(6):1418–1429
Smith MA, Tellier P-P, Roger M, Coutlée F, Franco EL, Richardson H (2014) Determinants of human papillomavirus coinfections among Montreal university students: the influence of behavioral and biologic factors. Cancer Epidemiology and Prevention Biomarkers 23(5):812–822
Tota JE, Chevarie-Davis M, Richardson LA, Devries M, Franco EL (2011) Epidemiology and burden of HPV infection and related diseases: implications for prevention strategies. Prev Med 53:S12–S21
Trimble CL, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J, Edwards L, Parker RL, Denny L, Giffear M (2015) Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: A randomised, double-blind, placebo-controlled phase 2b trial. Lancet 386(10008): 2078–2088
Valentino K, Poronsky CB (2016) Human papillomavirus infection and vaccination. J Pediatr Nurs 31(2):e155–e166
Van Damme P, Bouillette-Marussig M, Hens A, De Coster I, Depuydt C, Goubier A, Van Tendeloo V, Cools N, Goossens H, Hercend T (2016) GTL001, A therapeutic vaccine for women infected with human papillomavirus 16 or 18 and normal cervical cytology: results of a phase I clinical trial. Clin Cancer Res 22(13):3238–3248
van Poelgeest MI, Welters MJ, Vermeij R, Stynenbosch LF, Loof NM, Berends-van der Meer DM, Löwik MJ, Hamming IL, van Esch EM, Hellebrekers BW (2016) Vaccination against oncoproteins of HPV16 for noninvasive vulvar/vaginal lesions: lesion clearance is related to the strength of the T-cell response. Clin Cancer Res 22(10):2342–2350
Vici P, Pizzuti L, Mariani L, Zampa G, Santini D, Di Lauro L, Gamucci T, Natoli C, Marchetti P, Barba M (2016) Targeting immune response with therapeutic vaccines in premalignant lesions and cervical cancer: hope or reality from clinical studies. Expert Review of Vaccines 15(10):1327–1336
Vonsky MS, Runov AL, Gordeychuk IV, Isaguliants MG (2019) Therapeutic vaccines against human papilloma viruses: achievements and prospects. Biochem Mosc 84(7):800–816
Wang SS, Hildesheim A, Gao X, Schiffman M, Herrero R, Bratti MC, Sherman ME, Barnes WA, Greenberg MD, McGowan L (2002) Comprehensive analysis of human leukocyte antigen class I alleles and cervical neoplasia in 3 epidemiologic studies. J Infect Dis 186(5):598–605
Wang R, Pan W, Jin L, Huang W, Li Y, Wu D, Gao C, Ma D, Liao S (2020) Human papillomavirus vaccine against cervical cancer: opportunity and challenge. Cancer Lett 471:88–102
Wu Y, Liu B, Lin W, Xu Y, Li L, Zhang Y, Chen S, Xu A (2007) HPV16 E6 variants and HLA class II polymorphism among Chinese women with cervical cancer. J Med Virol 79(4):439–446
Yang A, Farmer E, Lin J, Wu T-C, Hung C-F (2017) The current state of therapeutic and T cell-based vaccines against human papillomaviruses. Virus Res 231:148–165
Zhang X, Lv Z, Yu H, Wang F, Zhu J (2015) The HLA-DQB1 gene polymorphisms associated with cervical cancer risk: a meta-analysis. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie 73:58–64. https://doi.org/10.1016/j.biopha.2015.06.002
Zhang Y, Yang J, Li M, Cui M, Fu ZF, Zhao L, Zhou M (2019) A recombinant rabies virus expressing Fms-like tyrosine kinase 3 ligand (Flt3L) induces enhanced immunogenicity in mice. Virol Sin 34(6):662–672