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Strategies for the prevention of cervical cancer by human papillomavirus vaccination

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As cervical cancer is causally associated with 14 high-risk types of human papillomavirus (HPV), a successful HPV vaccine will have a major impact on this disease. Although some persistent HPV infections progress to cervical cancer, host immunity is generally able to clear most HPV infections. Both cell-mediated and antibody responses have been implicated in influencing the susceptibility, persistence or clearance of genital HPV infection. There have been two clinical trials that show that vaccines based on virus-like particles (VLPs) made from the major capsid protein, L1, are able to type specifically protect against cervical intra-epithelial neoplasia and infection. However, there is no evidence that even a mixed VLP vaccine will protect against types not included in the vaccine, and a major challenge that remains is how to engineer protection across a broader spectrum of viruses. Strategies for

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production of HPV vaccines using different vaccine vectors and different production systems are also reviewed.

Key words: human papillomavirus vaccines; virus-like particles; cervical cancer vaccines.

Human papillomaviruses (HPVs) are part of the taxonomic family *Papillomaviridae*, and genital-infecting viruses are in the genus *Alpha-papillomavirus*.[1] HPVs have ~55-nm isometric non-enveloped virions, which encapsidate a ~8000-base double-stranded circular DNA genome. The capsid is built from 72 pentameric capsomeres of the major L1 capsid protein (~55 kDa) and at least 30 copies of the minor (~50 kDa) L2 protein.[2] The viruses encode a number of 'early' or regulatory proteins (E1–E7) and two 'late' or structural proteins (L1 and L2). The latter are only expressed late in the infection cycle, when the cells harbouring the genome are near to terminally differentiated.[3]

HPVs can be broadly divided into those infecting cutaneous epithelium and those infecting mucosal epithelium, and further divided into high risk and low risk depending on their association with malignancy. Of more than 118 different HPV types described, 40 infect the genital tract.[1] In a pooled analysis of 11 case–control studies from nine countries, HPV DNA was detected in 90.7% of the cancer cases and 13.4% of the controls.[4] HPV types 16, 18, 31, 33,35, 39, 45, 51, 52, 58, 59, 68, 73 and 82 were found to be high-risk types and HPV types 26, 53 and 66 were found to be 'probable' high risk types. Persistent cervical infection with high-risk HPV types is an essential part of the multistep process leading to cervical cancer. Therefore, vaccination strategies to prevent HPV infection could have a major impact on the incidence of cervical cancer.

IMMUNE RESPONSES TO HPV IN NATURAL INFECTION

HPV infection of the cervix is relatively common in young sexually active women. The majority of these infections are, however, transient and are not clinically evident with 70–90% of infected women spontaneously clearing their infections within 12–30 months.[5,6] This suggests that host immunity is generally able to clear HPV infection. The fact that HPV does not disseminate and remains localised further indicates that local cervical immune responses are sufficient in controlling and often resolving an HPV infection. Both cell-mediated (CMI) and antibody responses have been implicated in influencing the susceptibility, persistence or clearance of genital HPV infection.[7–10]

Immune evasion in HPV infection

Although it is important to understand natural immunity to HPV infection, it is also important to reconcile this with the fact that HPV is an elusive target for the immune system. HPV does not readily stimulate an inflammatory response because it uses deliberate strategies to avoid detection by the host immune system. This is evidenced by the fact that HPV-specific antibody and CMI responses are much more difficult to detect compared with many other viral pathogens.[11] HPV is non-cytopathic, causes cell proliferation instead of lysis, and does not have a systemic phase of infection. For these reasons, the mucosal immune system serves a major role in protection against HPV.

Although the mechanisms employed by HPV to avoid immune detection are too numerous to review here (reviewed in Ref. 12), several important mechanisms should