HARNESSING THE IMMUNE SYSTEM TO PREVENT CERVICAL CANCER

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Abstract

Cervical cancer can be attributed to infection with a subset of high risk human papillomaviruses. While anogenital human papillomaviruses infection is common, persistence of infection is rare and conveys a significant lifetime risk of anogenital cancer. Vaccines based on human papillomaviruses, like particles produced using recombinant DNA technology, are in late stage clinical trial and are designed to induce neutralising antibody. These vaccines have demonstrated >90% efficacy at preventing persisting high risk human papillomaviruses infection, cervical intraepithelial neoplasia and anogenital warts. They provide a significant addition to strategies to prevent cervical cancer.

The viral aetiology of cervical cancer

Cervical cancer kills about 250,000 women worldwide each year. Uniquely among human cancers, cancer of the cervix can be entirely attributable to an infectious agent, human papillomavirus (HPV). Shope showed that papillomavirus could cause cancer in rabbits and papillomaviruses were subsequently associated with tumours in cattle and horses. The hypothesis that some human papillomaviruses might be responsible for cervical cancer was developed by Professor Harald zur Hausen and his colleagues in the 1980s[1] and strengthened by the epidemiological studies of the International Agency for Research on Cancer (IARC) on the global association of HPVs with cervical cancer.[2] Thus, observations of Rigoni-Stern in the 19th century on the prevalence of cervical cancer among nuns and prostitutes, suggesting an infectious agent, were vindicated. Human papillomaviruses appear also to be important in the aetiology of other anogenital cancer including vulval and anal cancer and contribute to the aetiology of some head and neck cancer.

Papillomaviruses and cervical cancer

Papillomaviruses come in at least 200 different varieties,[3] in four broad groups.[4] Two groups infect the genital tract of humans, one associated with genital warts and one associated with genital cancer. Detailed epidemiological evidence gathered by IARC and others has allowed the conclusion that a subset of about 10 human papillomaviruses, termed high risk genital HPVs, are responsible for ~100% of cervical cancer, with two types (HPV16 and HPV18) accounting for more than 75% of cancers in most countries. The molecular basis by which papillomaviruses promote cancer is still the subject of intense study; studies in mice transgenic for HPV transforming proteins (E6 and E7) and mutated in several other genes suggest that the E6 and E7 proteins together are sufficient to promote cervical malignancy in the presence of oestrogen.[5] Such models also suggest that induction of epithelial proliferation by viral gene products to facilitate viral replication can be distinguished from initiation of carcinogenesis as an unexpected consequence of some other viral gene function unique to high risk HPVs.

The natural history of infection with high risk human papillomavirus

Infection of the genital tract with high risk HPVs is extremely common, with up to 50% of women becoming infected during the first five years after commencing sexual intercourse.[6] Up to 98% of these infections, which are associated with cellular abnormalities in the cervix generally termed low grade squamous intraepithelial lesion (LSIL) or cervical intraepithelial neoplasia 1 (CIN1), regress without intervention in humans with a competent immune system, though humans immunocompromised by immunosuppressive drugs or viral infection are much less likely to clear infection. Persistent infection with a high risk HPV genotype conveys substantial risk of cervical cancer,[7] which can develop as early as five years after infection but more commonly takes 15-30 years to develop.

Screening as a method to prevent cervical cancer

Prevention of cervical cancer at present relies on screening programs which are designed to detect premalignant changes (HSIL) in squamous cervical cells; such changes are generally associated with integration of the papillomavirus genome into host genetic material and overexpression of the viral non-structural proteins E6 and E7. Physical destruction of high grade cervical abnormalities results in a greater than 95% reduction in lifetime risk of cervical cancer and is the current basis of prevention of cervical cancer through screening.

Vaccines to prevent cervical HPV infection and cervical cancer

Future programs to prevent cervical cancer will likely also incorporate use of vaccines designed to prevent infection with the papillomaviruses (PVs) responsible for cancer. Initial studies in cattle and dogs showed that PV vaccines based on inactivated wart derived PVs could protect against challenge with live bovine PV.[8,9] However, human PVs cannot be grown in the laboratory and vaccines for human PVs are therefore based on virus like particles (VLPs).[10-13] The current vaccines are constructed using recombinant DNA technology from the L1 major capsid protein of the relevant human papillomavirus expressed in recombinant yeast, or in insect cells using baculovirus vectors. Such VLPs resemble the viral capsid physically and immunologically. Early animal studies showed that virus like particles could induce humoral immune responses cross reactive with the natural virus and that neutralising antibody raised by VLP based vaccines could protect animals against challenge with the corresponding animal papillomavirus.[14,15]

Clinical trials of HPV vaccines

Initial studies in humans demonstrated that VLPs administered with alum or AS04 adjuvant induce HPV type specific antibody[15-20] and protect against infection with the corresponding HPV type.[21-23] Two Phase III trials of quadrivalent vaccines based on HPV virus like particles are currently underway. Vaccine administered on three occasions over six months has proven in interim analysis to be 100% effective at preventing not only persistent infection with high risk HPVs, also HSIL/CIN2, 3 and anogenital warts in young sexually active women.

Vaccines to prevent HPV infection, genital warts and cervical cancer are about one year away from approval for general use in the US and Australasia. If administered prior to sexual activity, the two vaccines currently under development (Cervarix™ and Gardasil™) which both incorporate HPV16 and HPV18 VLPs, should prevent up to 70% of cervical cancer in an unscreened population and the majority of abnormal pap smears in screened populations. The quadrivalent vaccine (Gardasil™) which incorporates HPV6 and HPV11 VLPs will additionally prevent >90% of genital warts. Use of these vaccines should not impact on delivery of existing cervical cancer screening programs because they protect against only two types of HPV associated most commonly with cervical cancer. All sexually active women can potentially benefit from vaccination, particularly if they are likely to change partners in the future. The best benefits will however, follow immunisation before sexual activity, as the vaccine can prevent infection but is unlikely to alter the natural history of existing infection. Duration of protection in women and vaccine efficacy in males is yet to be established, though antibody studies available to date suggest that duration of protection will be long-lasting with high and stable levels of antibody observed in vaccinated subjects up to four years after vaccination.

Immunotherapeutics to eliminate HPV infection and cervical cancer

Immunotherapeutics designed to eliminate existing HPV infection are also being considered as a part of a broad strategy to prevent cervical cancer. Therapeutic vaccines have no precedent in human immunotherapy and HPV therapeutic vaccines are at an earlier stage of development than HPV prophylactic vaccines. These products are generally targeted at viral non-structural proteins and are expected to induce killer T-cells which can eliminate virus infected cells in the cervix. Although several possible vaccine products based on HPV16 E6 and E7 protein have been subjected to early phase clinical trials,[24] there are significant scientific and technical challenges to meet before such vaccines become available for routine clinical use. No surrogate markers of effective immunotherapy have been identified, though helper T-cell responses particularly to viral non-structural proteins E2 and E6 may correlate with clearance of persisting HPV infection. Animal models of HPV infection suggest that a major problem with HPV infection may not be a lack of vaccine immunity, but rather a problem with targeting effector T-cells to the HPV infected tissue.[25]

Conclusions

Cervical cancer is a preventable disease. Future strategies to reduce the cervical cancer burden, particularly in the developing world where screening is not available, are likely to focus on HPV prophylactic vaccines based on VLPs. Deployment will depend on development of a strategy for delivering vaccines to young women and, in the developing world, on the availability of adequate funding for the vaccines. □

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