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Human Papillomavirus Vaccines in Preclinical Development

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To enhance the immunogenicity of HPV vaccines, we studied various experimental vaccines; genetic adjuvant-encapsidated virus-like particles (VLP) vaccines, mucosal VLP vaccines, and genetic chimeric vaccines. First, following vaccination of HPV 16 L1 VLP encapsidating a cytokine genetic adjuvant, enhanced mucosal and systemic immunogenicity was observed. After intramuscular immunization into mice, the highest vaginal and salivary HPV16 L1-specific IgA titers were observed in pIL2-encapsidated VLP, followed by VLP plus pIL2 in separate plasmid, and VLP alone. Similar to mucosal responses, serum IgG, IgG_1, and IgG_{2a} antibody titers were the highest in the group treated with pIL2-encapsidated VLP. Moreover, the adjuvanticity of pIL2 encapsidated in VLP was stronger in IgG_{2a} antibody relative to IgG_1 antibody. These results indicate that the encapsidation of a genetic cytokine adjuvant pIL2 would be beneficial for more effective induction of mucosal and systemic immune responses to VLP vaccines. Secondly, we tested the effect of thermosensitive mucoadhesive vaginal vaccine delivery systems on the local and systemic antibody responses to HPV 16 L1 virus-like particles (VLP). HPV 16 L1 VLP were delivered in phosphate-buffered saline or thermosensitive mucoadhesive delivery systems, composed of poloxamers (Pol) and varying amounts of polyethylene oxide (PEO). Vaccine vehicles affected the vaginal and salivary immune responses to HPV 16 L1 VLP intravaginally administered into mice. Intravaginal coadministration of HPV 16 L1 VLP and cholera toxin in Pol/PEO 1.0% showed 31- and 39-fold higher titers compared to the PBS-based HPV 16 L1 VLP groups administered by intravaginal and intramuscular routes, respectively. Our results indicate that the use of in situ-gelling vaginal vaccine delivery systems with increased mucoadhesiveness would be beneficial for more effective induction of mucosal and systemic immune responses to intravaginally administered HPV 16 L1 VLP vaccines. Thirdly, we constructed a series of HPV16 L1 vaccines genetically fused with a secretion signal and/or immune cell-recruiting RANTES. The DNA vaccines encoding secretory HPV L1 were constructed by inserting HPV L1 gene into a vector with an ER-targeting secretory signal sequence. Of RANTES-fused vaccines, pER/L1/R encoding the secreted fusion protein induced the highest humoral and CD8 T cell-stimulating responses. These results suggest that the immunogenicity of HPV L1 DNA vaccines could be enhanced by genetic fusion to a chemokine and secretory signal peptide sequences.