

VACCINATION WITH VIRAL VECTORS EXPRESSING NP, M1 AND CHIMERIC HEMAGGLUTININ INDUCES BROAD PROTECTION AGAINST INFLUENZA VIRUS CHALLENGE IN MICE

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Seasonal influenza virus infections cause up to half a million deaths each year, the majority of which are older adults. Annual influenza virus vaccination protects against disease, but in the event of a mismatch between the circulating strain and vaccine strain, vaccine effectiveness is severely impacted. Therefore, there is an urgent need for a vaccine that induces broad protection against drifted seasonal and emerging pandemic influenza viruses. One approach in designing such a universal influenza virus vaccine is based on targeting conserved regions of the influenza virus hemagglutinin (HA), the major glycoprotein on the surface of the virus. Using chimeric hemagglutinin constructs (cHA), the immune system can be primed to produce antibody responses against the conserved immunosubdominant stalk region rather than the variable immunodominant head region. Furthermore, replication deficient viral vectors based on Chimpanzee Adenovirus (ChAdOx1) and Modified Vaccinia Ankara (MVA) virus expressing the influenza virus internal antigens, such as the nucleoprotein (NP) and the matrix protein 1 (M1), are capable of inducing strong influenza specific T cell responses in vaccinated individuals. This is another approach towards a broadly cross-protective influenza vaccine given the degree of conservation of NP and M1 across different influenza virus strains. Here, we combine these two platforms to evaluate the efficacy of a viral vector-based group 2 cHA intramuscular vaccination regime in mice to confer protection against influenza virus challenge of matched and mismatched group 2 strains. We show that vectored vaccines expressing both cHA and an NP-M1 fusion protein, in a prime-boost regimen (with different cHAs given at each vaccination), provide enhanced protection against H3N2 and H10N8 virus challenge when compared to vaccination with cHA alone or NP-M1 alone. The vaccine induced antibody responses against divergent HAs, NP, M1, and whole virus correlated with nature of administered vaccine and extent of protection seen across vaccinated groups. Influenza specific T cell responses were also increased in the vectored vaccines expressing both the cHA and the NP-M1 fusion protein. For further characterization, we are interested in looking at an optimal vaccination regimen, the possibility of an additional boost to induce cross-reactive antibodies, and the nature of the induced antibodies. Overall, these results improve our understanding of vaccination platforms capable of harnessing cellular and humoral immunity with the ultimate goal of designing a universal influenza vaccine.