A universal influenza vaccine based on the HA2 subunit of the viral hemaggultinin

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Current influenza vaccines induce strain-specific antibodies (Abs) against the highly evolving HA1 subunit of the viral hemagglutinin which shield the more conserved HA2 subunit. Thus, enhancing immune response against HA2 could potentially elicit broadly neutralizing Abs and provide universal protection. Here, we investigated CD40L, a key regulator of the immune system, as an adjuvant and targeting molecule to augment the immunogenicity and protective efficacy of influenza HA2-subunit. We determine the protective immunity of a recombinant adenovirus (rAd) encoding secreted fusion protein consisting of codon-optimized HA2-subunit of A/California/7/2009(H1N1) virus fused to a trimerized form of CD40L upon intranasal immunization. Compared to untargeted HA2, CD40-targeted HA2 completely protected mice against lethal challenges with divergent influenza A subtypes including H1N1, H3N2 and H9N2. Codon-optimization of HA2 and the use of CD40L were indispensable to enhance HA2-specific mucosal IgA and circulating IgG levels. Interestingly, induction of HA2-specific T-cell responses was dependent on CD40L as untargeted HA2 failed to induce any significant levels of T-cell cytokines. Importantly, sera obtained from mice immunized with CD40-tragted HA2 were capable of neutralizing 13 subtypes of influenza A viruses *in vitro*. These results provide proof of concept for a prototype HA2-based universal influenza vaccine.

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