New universal flu vaccine offers broad protection against influenza A virus infections, researchers find

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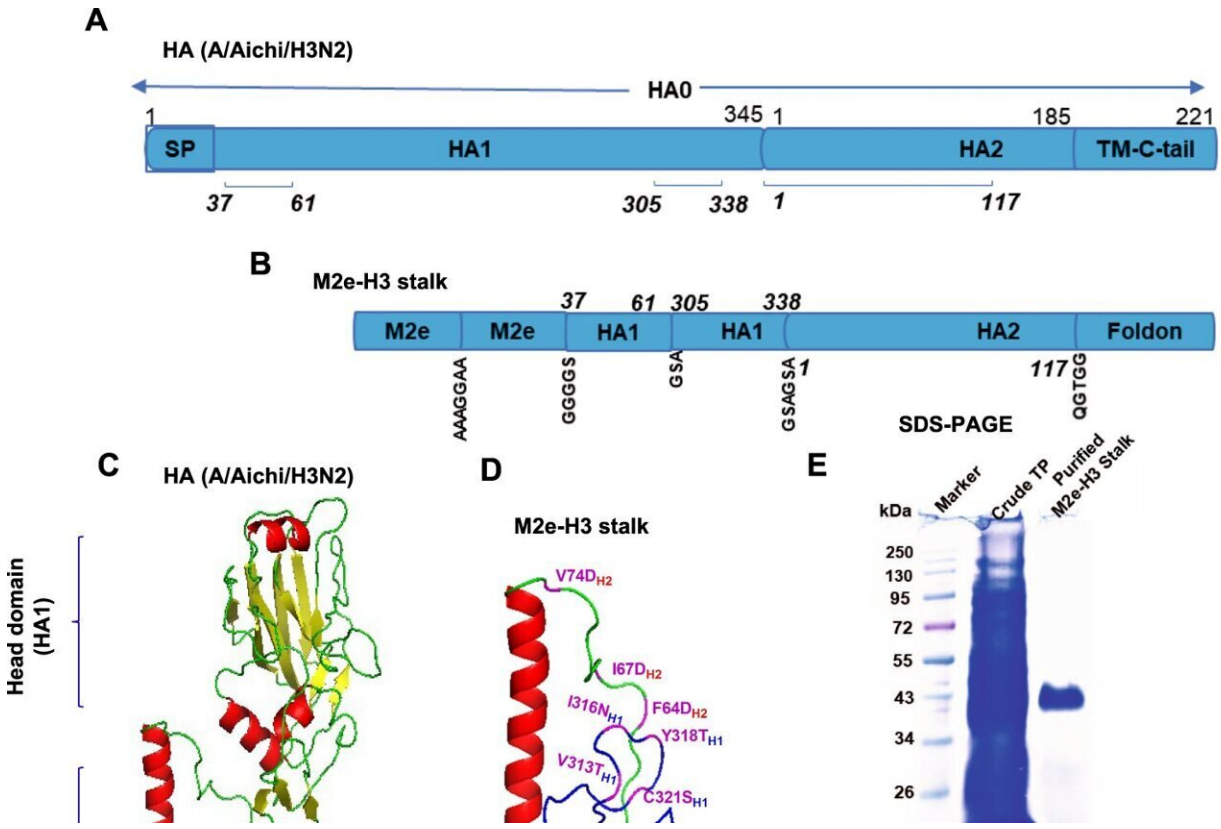

Rationale design of chimeric M2e-H3 stalk protein, purification, and confirmation. A Schematic of full-length HA gene of influenza A virus (A/Aichi/H3N2), and the selective domains as a vaccine target are numbered in amino acid (aa 37-61, 305-338, 1-117) residues. B M2e-H3 stalk vaccine construct with flexible and soluble linker sequences (AAAGGAA; GGGGS; GSA; GSAGSA; QGTGG). C The monomeric H3 HA 3D cartoon structure as

predicted by the SWISS model and visualized in PyMol. D Illustration of monomeric cartoon structure of M2e-H3 stalk domain marking the positions of point mutations. M2e and foldon structures were modeled using PDB ID codes 4N8C and 1RFO, respectively. E Coomassie Blue staining of M2e-H3 stalk protein. Marker: protein size marker (kDa), Crude TP: Total cell lysates (25 μg); M2e-H3 stalk: purified M2e-H3 stalk protein (15 μg). F Western blot of M2e-H3 stalk protein. 14C2: M2e-specific mAb; stalk: anti-fusion peptide (FP) polyclonal antibody (pAb) recognizing HA2 aa1-14 epitope. Credit: *npj Vaccines* (2022). DOI: 10.1038/s41541-022-00498-6

A new universal flu vaccine constructed with key parts of the influenza virus offers broad cross protection against different strains and subtypes of influenza A viruses in young and aged populations, according to a new study by researchers in the Institute for Biomedical Sciences at Georgia State University.

The researchers developed the universal flu vaccine by genetically linking two highly conserved (relatively unchanged over time) portions of the virus—the extracellular domain of matrix 2 (M2e) and the stalk protein found in influenza A H3N2 viruses. The findings, published in the journal *npj Vaccines*, show that M2e-stalk protein vaccination induced broad protection against different influenza virus strains and subtypes by universal vaccine-mediated immunity in adult and aged mice.

Scientists have faced obstacles in the development of effective vaccines for influenza viruses because the head portion of the influenza virus is constantly changing. When comparing the H1N1 and H3N2 influenza A viruses, particular challenges exist in H3N2 subtypes because of stalk mutations in circulating strains and the unstable structure of stalk proteins for H3N2 viruses. These drawbacks have been difficult to overcome in developing effective H3 stalk-based vaccines.

Vaccine effectiveness against H3N2 was low during the past decade, only about 33 percent, and dropped to 6 percent during the 2014–2015 flu season. New mutations of H3N2 variants emerged with increased virulence. Also, the outbreak of H7N9, another influenza A subtype, caused concern for potential pandemics. Therefore, developing an effective vaccine to protect against these viruses is a high priority.

"The M2e-stalk protein, for the first time, could be easily produced in bacterial cell cultures at high yields and was found to confer protection against heterologous and heterosubtypic cross-group subtype viruses (H1N1, H5N1, H9N2, H3N2 and H7N9) at similar levels in adult and aged mice," said Dr. Sang-Moo Kang, senior author of the study and a professor in the Institute for Biomedical Sciences at Georgia State. "These results provide evidence that M2e-stalk genetic fusion proteins can be produced in a large scale at low cost and developed as a universal influenza A virus vaccine candidate for young and aged populations."

The study found this novel M2e-stalk protein vaccine induced M2e and stalk-specific Immunoglobulin G (IgG) antibodies that recognized antigenically diverse influenza viral antigens on virus particles and on the infected cell surface. In addition, the vaccine stimulated protective cellular T cell immunity and effective lung influenza viral clearance in mice.

More information: Jeeva Subbiah et al, A chimeric thermostable M2e and H3 stalk-based universal influenza A virus vaccine, *npj Vaccines* (2022). DOI: 10.1038/s41541-022-00498-6

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