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Vaccine-induced anti-HA2 antibodies promote virus fusion and enhance influenza virus respiratory disease

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Abstract

Vaccine-induced disease enhancement has been described in connection with several viral vaccines in animal models and in humans. We investigated a swine model to evaluate mismatched influenza vaccine-associated enhanced respiratory disease (VAERD) after pH1N1 infection. Vaccinating pigs with whole inactivated H1N2 (human-like) virus vaccine (WIV-H1N2) resulted in enhanced pneumonia and

disease after pH1N1 infection. WIV-H1N2 immune sera contained high titers of cross-reactive anti-pH1N1 hemagglutinin (HA) antibodies that bound exclusively to the HA2 domain but not to the HA1 globular head. No hemagglutination inhibition titers against pH1N1 (challenge virus) were measured. Epitope mapping using phage display library identified the immunodominant epitope recognized by WIV-H1N2 immune sera as amino acids 32 to 77 of pH1N1-HA2 domain, close to the fusion peptide. These cross-reactive anti-HA2 antibodies enhanced pH1N1 infection of Madin-Darby canine kidney cells by promoting virus membrane fusion activity. The enhanced fusion activity correlated with lung pathology in pigs. This study suggests a role for fusion-enhancing anti-HA2 antibodies in VAERD, in the absence of receptor-blocking virus-neutralizing antibodies. These findings should be considered during the evaluation of universal influenza vaccines designed to elicit HA2 stem-targeting antibodies.

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