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Intermonomer interactions in hemagglutinin subunits HA1 and HA2 affecting hemagglutinin stability and influenza virus infectivity

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Influenza virus hemagglutinin (HA) mediates virus entry by binding to cell surface receptors and fusing the viral and endosomal membranes following uptake by endocytosis. The acidic environment of endosomes triggers a large-scale conformational change in the transmembrane subunit of HA (HA2) involving a loop (B loop) to helix transition, which releases the fusion peptide at the HA2 N-terminus from an interior pocket within the HA trimer. Subsequent insertion of the fusion peptide into the endosomal membrane initiates fusion. The acid stability of HA is influenced by residues in the fusion peptide, fusion peptide pocket, coiled-coil regions of HA2, and interactions between the surface (HA1) and HA2 subunits, but details are not fully understood and vary among strains. Current evidence suggests that HA from the circulating pandemic 2009 H1N1 influenza A virus [A(H1N1)pdm09] is less stable relative to other seasonal influenza strains. We found that residue 205 in HA1 and 399 in the B loop of HA2 (residue 72, HA2 number) in different monomers of the trimeric A(H1N1)pdm09 HA are involved in functionally important intermolecular interactions and that a conserved histidine in this pair helps regulate HA stability. An arginine-lysine pair at this location destabilizes HA at acidic pH and mediates fusion at higher pH, while a glutamate-lysine pair enhances HA stability and requires a lower pH to induce fusion. Our findings identify key residues in HA1 and HA2 that interact to help regulate H1N1 HA stability and virus infectivity.

Biography

Wei Wang obtained his PhD from University of Saskatchewan and completed Post-doctoral trainings from National Cancer Institute and US Food and Drug Administration. He is a reviewer and research scientist at Center for Biologics Evaluation and Research, US Food and Drug Administration.

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