Receptor binding, structure, and tissue tropism of cattle-infecting H5N1 avian influenza virus hemagglutinin

Presenter: Yu-Qin Zheng

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Commentator: Hsiang-Chi Huang,Ph.D

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Background:

Highly pathogenic avian influenza viruses (HPAIVs) of the H5N1 subtype typically infect birds, but in 2024, H5N1 was unexpectedly detected in dairy cattle—a major deviation from its known host range. This spillover raised urgent questions about how bovine H5N1 establishes infection in cattle and whether it carries traits that could facilitate cross-species transmission.

Objective and experimental approach:

This study investigated how avian-origin H5N1 infects cattle by defining the receptor-binding and tissue-tropism features of the bovine isolate. The authors quantified hemagglutinin (HA) binding to α2,3 (avian-type) and α2,6 (human-type) sialic acid receptors using surface plasmon resonance. Tissue tropism was examined through glycan-binding assays, immunohistochemistry, and viral replication in bovine mammary epithelial cells, human airway epithelial cells, and human conjunctival epithelial cells. High-resolution cryo-EM was then used to identify structural determinants underlying altered receptor specificity and potential mammalian adaptation.

Results:

Bovine H5N1 HA maintains strong affinity for α2,3 receptors but shows enhanced binding to α2,6 receptors, resulting in an intermediate receptor-binding profile. Cryo-EM structures reveal subtle yet functionally important changes in the 190-helix and 130-loop that partially accommodate α2,6 glycans, indicating early-stage adaptation toward mammalian hosts. Functionally, the virus replicates efficiently in bovine mammary epithelial cells and can infect human conjunctival and upper-airway epithelial cells, consistent with reported clinical presentations. However, respiratory transmission in ferrets remains inefficient, suggesting limited capacity for sustained human-to-human spread. Overall, bovine H5N1 displays partial mammalian adaptation while retaining avian-like features, with a distinctive tropism for mammary gland and conjunctival tissues. These findings highlight a previously unrecognized adaptation pathway and underscore the need for continued surveillance to monitor its zoonotic risk.