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ANTIVIRALS

New clues for broad-spectrum flu combat

Potential resistance to current anti-influenza drugs, as well as challenges in developing vaccines to combat emerging influenza strains, mean that new strategies to combat both seasonal and potential pandemic influenza outbreaks are needed. A trio of recent studies offer new insight into highly conserved sites on influenza virus proteins, and suggest strategies to develop broad-spectrum influenza treatments.

In the first study, published in *Nature*, Liu and colleagues determined the crystal structure of the amino-terminal domain of the PA subunit (PA_N) — one of the three proteins that forms the viral RNA polymerase complex — from an avian type A virus isolate (H5N1). The structure revealed a negatively charged cavity that contained an Mg^{2+} ion, suggesting that PA_N might contain an endonuclease active site, which is crucial for initiating mRNA transcription. This was confirmed by further structural studies and functional assays. Moreover, the high conservation of residues in the endonuclease site among different influenza viruses indicates that it could provide a promising target for broad-spectrum antiviral drugs.

In the second study, reported in *Nature Structural and Molecular Biology*, Marasco and colleagues used a recombinant trimeric ectodomain of haemagglutinin — a protein antigen present on the viral envelope — from an H5 virus to select ten unique neutralizing antibodies (nAbs) that had neutralizing activity against all group 1 influenza viruses tested, including H5N1. The authors then determined the crystal structure of one antibody in complex with the H5 ectodomain. The results suggested a common mechanism of H5 virus neutralization by the nAbs: by preventing the large structural reorganizations that are required for membrane fusion.

Moreover, sequences of the nAb epitope were nearly always conserved within all group 1 influenza subtypes, providing a rationale for the cross-neutralization of H5 strains, and the authors were unable to select escape variants to the nAbs, suggesting that the targeted region could be resistant to antigenic drift. Finally, in mice infected with H5N1 viruses, prophylactic or therapeutic treatment with any of three nAbs that had been converted into full-length human immunoglobulin G1 protected 80–100% of mice when challenged with a lethal dose of virus.

In the third study, published in *Science*, Wilson and colleagues determined crystal structures of a previously identified human antibody, CR6261, in complex with haemagglutinins from the human H1N1 pandemic virus and the avian H5N1 virus. The structures showed that CR6261 also recognizes the highly conserved helical region in the membrane-proximal end of each haemagglutinin, approximately parallel to the plane of the viral envelope. The authors provided proteolysis data to show that the antibody neutralizes the virus by blocking conformational rearrangements that are associated with the fusion of viral and cellular membranes.

Overall, these papers highlight conserved viral sites and strategies to target them — by blocking viral mRNA transcription or blocking virus–host membrane fusion — that might eventually lead to broadly crossreactive therapies to fight influenza.

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ORIGINAL RESEARCH PAPERS Yuan, P. *et al.* Crystal structure of an avian influenza polymerase PA_N reveals an endonuclease active site. *Nature* 4 Feb 2009 (doi:10.1038/nature07720) | Sui, J. *et al.* Structural and functional bases for broad-spectrum neutralization of avian and human influenza A viruses. *Nature Struct. Mol. Biol.* 22 Feb 2009 (doi:10.1038/nsmb.1566) | Ekiert, D. C. *et al.* Antibody recognition of a highly conserved influenza virus epitope. *Science* 26 Feb 2009 (doi: 10.1126/science.1171491)