Computational studies revealed determinants of the specificity in the swine and avian flu.

Viral strains may differ from each other markedly in their phenotypic properties, in spite of the high similarity of their genomes. For example, the various influenza strains exhibit a wide spectrum of pathogenicities and specificities to different hosts. With the outbreak of the highly pathogenic avian H5N1 influenza in 1996, and the H1N1 swine origin influenza in 2009, considerable research has focused on studying these strains. We developed a computational approach for the identification of key amino acid positions that determine pathogenicity, species barriers, etc of selected groups of proteins. This is a novel application to protein sequence analysis of a well-established classification approach. In my seminar I will present applications of the method to the H5N1 and H1N1 influenza strains.

Highly pathogenic in humans, although yet to become widespread in the population, the H5N1 strain constitutes a major threat owing to significant similarity between avian and human infecting viruses. The hemagglutinin (HA) protein of influenza A is the main antigen on the viral surface, mediating binding to the host receptors and virus entry into the cell. An alteration from avian-to-human like recognition via HA is thought to be one of the changes that must take place before avian influenza viruses can replicate efficiently in human cells, thus acquiring the capability to cause a human pandemic. Through a computational approach, using a supervised learning algorithm and the complete H5N1 NCBI sequence database, we successfully identified all the known specificity determinants for avian to human transmissibility described in the literature. Interestingly, we also detected residues that form the known H5N1 antigenic sites as host-distinguishing positions, offering a possible immune-related mechanism for virus specificity. Our analysis also identified novel specificity determinant candidates that may help decipher the basis for human vs. avian host selectivity. A structural analysis identified amongst these novel positions, residues in which mutations can have a direct effect on the binding conformation of the HA receptor. These new findings may provide a better understanding of the species barrier of H5N1 and assist in designing antiviral agents.

Application of the method to the novel swine-origin influenza H1N1 virus, we surprisingly discovered that all identified residues were situated in and around the known H1N1 antigenic sites, Considering that many of the predicted substitutions significantly changed the physicochemical nature of amino acids in these positions, we suggest that the alterations would result in variation of the stereochemistry of the antibody binding sites, interfering with the ability of the immune system to recognize the HA protein. We suggest that the basis for immune avoidance of the novel virus possibly associates within the signature sites presented in our study, which best discriminate the new isolates of the novel human pandemic from previous ones. The computational analysis presented here is generic and can also be applied to gain insight into the molecular determinants of host discrimination, pathogenicity and transmissibility in other viral proteins and strains.