Section «Bioengineering Bioinformatics»

Identification of amino-acid residues vital for influenza neuraminidase receptor-binding specificity using bioinformatic analysis

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One of the major surface glycoproteins of influenza virus - neuraminidase - plays a key role in virus replication cycle by cleaving sialic acid from host cell surface thus facilitating subsequent release of virions and spread of infection. Acquisition of the ability to recognize and cleave human-specific type of receptors by neuraminidases from highly pathogenic avian influenza virus is thought to be the limiting step in human-to-human transmission pathway. Identification and analysis of key amino-acid residues seems to be an important step to reveal the molecular basis of neuraminidase receptor-binding specificity.

Bioinformatic analysis was used to explore subfamily-specific positions, conserved within human- and avian-type receptor specific neuraminidases but different between them and supposed to be responsible for functional discrimination. Nine subtypes of influenza neuraminidase with different sequence identity are known, making a full analysis impossible without experimental knowledge of function. In order to provide functional subfamilies, the grouping of another surface glycoprotein - haemagglutinin - was used. Both proteins interact with sialylated carbohydrate chains supporting the idea of the activity balance between haemagglutinin (receptor binding) and neuraminidase (receptor cleavage). The corresponding pairs of sequences from different strains as well as host organisms for both proteins were downloaded from NCBI Influenza Virus Resource, filtrated to obtain non-redundant set and aligned. The residues (226, 228, 190 and etc.) known from the literature as structural determinants responsible for specificity switch in haemagglutinin were used as a guide for subfamilies search. These results were used in the analysis of corresponding set of neuraminidases. Structural study of derived residues explored 43 conserved and 34 subfamily-specific positions within 10 Å area of receptor-binding pocket. Majority of residues reported to be critical for neuraminidase activity (Arg118, Asp151, Arg224 and etc.) were found conserved, while a number residues were discovered to be specific and capable to mediate the binding of widely used neuraminidase inhibitors.

Bioinformatic and structural analysis revealed the targets for further molecular modeling and experimental validation study to address the ability of neuraminidases to cleave substrates and thus take a step forward in solving the challenge of evolution and adaptation of influenza viruses.