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The structural basis for the essential PA-PB1 subunit interaction in influenza RNA polymerase

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Influenza A virus is a major human and animal pathogen with the potential to cause catastrophic loss of life. Recently, the emergence of a novel H1N1 viral strain has affected the entire world. Additionally, a highly pathogenic avian influenza caused by H5N1 strain, has a potential of a next pandemic. Most current influenza drug target is haemagglutinin(HA) or neuraminidase(NA), and these protein present at the virion surface. Sixteen different HA subtypes and nine different NA subtypes have been identified. Oseltamivir(Tamiflu) and zanamivir(Relenza) are NA inhibitors, and prevent viral particles being released from infected cells. These drugs have been stocked in world wide, but resistant influenza is already emerging. Another anti-influenza drug amantagine targets the M2 protein of the viral proton channel. However, a single residue change is sufficient to confer resistance. Both oseltamivir and amantadine target proteins with a single known function and substantial sequence variation between viral strains.Therefore, we have to prepare a new method for a new highly pathogenic and oseltamivir-resistant influenza.

The viral RNA polymerase is not yet a target of any approved pharmaceutical, but has recently become a focus for the development of new anti-influenza drugs since it is highly conserved in avian and human influenza. It carries out a number of essential processes in the viral life cycle, many of which remain poorly understood. The three subunits, PB1, PB2 and PA play different roles within the polymerase, and are all essential for viral replication but despite considerable functional analysis relatively little is known about their structure.

Here, we solved the crystal structure of PA-PB1 subunit interaction. The carboxy-terminal domain of PA forms a novel fold, and forms deep, highly hydrophobic groove into which the amino-terminal residues of PB1 can fit by forming a helix.[1] Furthermore, we have found highly conserved residues which are essential for these interactions, and demonstrated that the interruption of these interfaces dramatically reduces viral replication. These interfaces have considerable potential as a drug target sites, which are entirely independent of surface antigen type.

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Crystal structure of measles virus hemagglutinin with its human receptor CD46

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Measles virus (MV) remains as a worldwide disease even though there is an effective vaccine available since the sixties. Almost eradicated in most industrialized countries, MV still causes frequent outbreaks, although in developing countries 20 million cases and 300,000 deaths are reported every year annually mainly due to deficiencies in vaccine administration. Therefore, MV has been a priority in World Health Organization vaccination programs for its complete eradication by the end of the 20th century.

Despite all the efforts against MV, little is known about the molecular machinery used by the virus to infect host cells and the early events occurring after virus particle attachment to the host cell. Infection is initiated by attachment of the measles virus hemagglutinin (MV-H), a glycoprotein anchored to the virus envelope, to the host cell receptors CD46 or signaling lymphocyte activation molecule (SLAM).

In this work, we report the crystal structure of MV-H in complex with a CD46 protein spanning the two N-terminal domains. A unique groove at the side of the MV-H β-propeller domain, which is absent in homologous paramyxovirus attachment proteins, engages residues in both CD46 domains. Key contacts involve a protruding loop in the N-terminal CD46 domain that carries two sequential proline residues (PP motif) and penetrates deeply into a hydrophobic socket in MV-H. Viral residues within this extended groove can have certain variability whereas less accessible residues are conserved, which leads to an extended MV tropism by increasing CD46 binding affinity and preserving SLAM binding. The relatively variable and concave surface onto which the CD46 interdomain interface and the SCR2 dock represents an area well suited to accommodate diverse receptor molecules binding to an inaccessible socket in the MV-H protein. Therefore, the use of an extended surface on the side of the β-propeller domain for receptor binding by MV forms the basis for a strategy to extend the virus tissue tropism by receptor-specificity switching.

Keywords: measles, CD46, hemagglutinin.

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Studying interactions between vaccinia virus protein a46 and the cellular protein MyD88

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Vaccinia virus, closely related to smallpox virus, is a member of the poxvirus family. It is well known for its various strategies to inhibit the immune response of cells of the innate immune system, but the mechanisms of the majority of these important interactions have not been clearly studied. Vaccinia virus encodes a wide range of proteins, which target the pathogen signal transduction pathway from the plasma membrane to the nucleus, and finally prevent production of proinflammatory and antiviral cytokines. Our main goal is to define mechanisms of inhibition of NFκB (the central transcriptional factor during an antiviral response) activation by certain vaccinia proteins by solving their structure and structural mechanisms of interaction with cellular proteins. A profound knowledge of such viral interference strategies will help to understand molecular aspects of viral pathogenesis and to develop novel cell defense approaches. It will give also a deeper insight into cell defense mechanisms.