Structural Basis of Measles Virus Entry and Effective Measles Vaccine

The measles virus (MV), one of the most contagious viruses, causes a common febrile disease. Although its pathological implications are well documented, the molecular mechanism of MV entry remains unclear. In this study, we determined the complex structures of MV hemagglutinin (MV-H) bound to its cellular receptor, the signaling lymphocyte activation molecule (SLAM, also called CD150). The crystal structures revealed two forms of the MV-H-SLAM tetrameric assembly, which has implications in fusion triggering for MV entry. Furthermore, the structures provided a clear explanation as to why the MV vaccine is highly effective.

Measles is a major cause of child morbidity and mortality, accounting for 4% of deaths in children under 5 years of age worldwide. The disease is characterized by fever, cough and a rash accompanied by profound immune suppression. MV, the causative agent of the disease, was first isolated in 1954, and MV vaccine was successfully developed in 1963. For nearly the past 50 years, MV vaccine has been effective against all MV strains around the world.

MV is a member of the genus *Morbillivirus* in the family *Paramyxoviridae*. MV possesses two distinct envelope glycoproteins, the attachment protein hemagglutinin (MV-H) and the fusion protein (MV-F). MV uses SLAM expressed on immune cells as a receptor. CD46, ubiquitously expressed on nucleated cells, has also been reported to be a MV receptor. However, only vaccine strains can interact with CD46, and clinically isolated (wild type) strains cannot use it as a receptor. A third epithelial cell receptor was recently identified, called Nectin 4.

To enter the target cell, MV must bind to its receptors by MV-H, then its envelope membrane must fuse with the host plasma membrane on the cell surface by MV-F. Although the mechanism by which receptor binding leads to fusion has been elusive, two models have been proposed. In the first model, upon receptor binding, MV-H undergoes a conformational change, which destabilizes the pre-fusion MV-F, leading to its refolding for membrane fusion. In the second model, MV-H serves as a clamp that stabilizes the pre-fusion MV-F. Upon receptor binding, MV-H releases the pre-fusion MV-F from the clamp to facilitate its spontaneous structural change.

To better understand the mechanism of MV entry, we determined the crystal structure of MV-H bound to its cellular receptor, SLAM (MV-H-SLAM) [1]. We had previously reported the crystal structure of MV-H alone [2]. Based on both the receptor-free and SLAM-bound forms of MV-H structures, we propose a new model for MV entry.

Initial crystals of MV-H-SLAM diffracted to 7–8 Å resolution, and then the diffraction was finally improved using protein engineering techniques [3] and collected at BL-5A to a resolution of 3.15 Å. The structural or conformational change could not be observed in either MV-H monomer or dimer with and without SLAM binding. However, two forms of the MV-H: SLAM tetrameric assembly (dimer of two dimers) were detected, termed form I (3.55 Å) and form II (3.15 Å) (Fig. 1). We propose a new model for MV entry based on these crystallographic evidences: (1) Upon binding of MV-H to the receptors, the binding mode of MV-H and SLAM allows the viral envelope and host cell membrane to come close to each other. (2) The binding to the receptors also facilitates the tetrameric assembly of MV-H, and a conformational shift from form I to form II. (3) This conformational shift serves as a trigger for the structural change of MV-F, which allows its refolding and fusion with the host cell membrane.

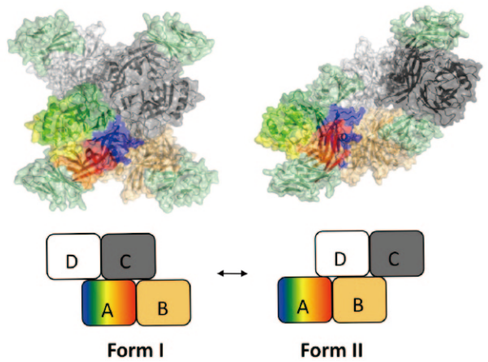

Figure 1
Two forms of MV-H: SLAM tetrameric assembly.
Top: crystal structures of MV-H: SLAM tetramers (left, form I; right, form II). Monomer A (rainbow) and B (light orange) form a dimer, while monomer C (gray) and D (white) form a second dimer. SLAM (pale green) binds to individual MV-H monomers Bottom: schematics of two forms of MV-H tetramers.

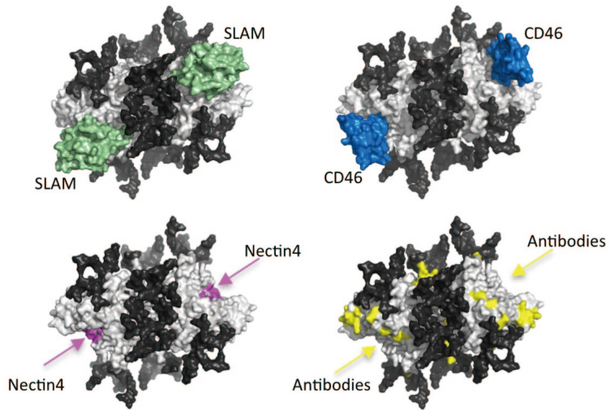

Figure 2
Structural basis for the effectiveness of the measles vaccine.
Receptor binding sites of SLAM, CD46, and Nectin 4 on MV-H overlap with a major area targeted by anti-MV-H antibodies. This region is uncovered by N-linked sugars.

MV vaccine is known as one of the most successful and effective vaccines. The structures of receptor-free and receptor-bound MV-H provide a clear explanation for its effectiveness. A large part of the MV-H surface is covered by N-linked sugars, but the receptor-binding region is exposed (Fig. 2). As a result, this area is also targeted by neutralizing antibodies. Inability to use the receptors SLAM and Nectin 4 is detrimental for MV. Therefore, MV is not allowed to have escape mutations in this receptor-binding region. In fact, this region is highly conserved in all MV strains and even in other morbilliviruses. This conservation nicely explains why MV occurs as serologically monotypic. Thus, from the structural data collected at BL-5A, we were able to not only propose a new entry model for MV, but also demonstrate why only one MV vaccine is sufficient against all strains of MV.

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