

## DYNAMIC FUNCTIONALITY OF MEMBRANE-PROTEIN NETWORK IN VIRUS INFECTION

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Dynamic functionality of membrane-protein network is addressed by model systems based on virus infection cycles. Critical molecular components of biological machines often include local environments of non-equivalence where dynamic pathways of action can only be characterized by including less ordered transition states. Structural analyses by rapid-freezing procedure have made it feasible to quantify chemical descriptors of many biological processes at various degrees of details. Time-resolved reactivity within various cellular compartments can here be observed and integrated at molecular and cellular levels.

Through 3D conformational analysis, we have revealed the dynamic process of virus maturation, cell entry and antibody neutralization by approaching intermediate viral structures at their entry-activated form by in-vitro triggering. Two model systems successfully established to study the conformation changes relevant to early steps of viral infection, namely cellular receptor molecules and acidic pH, mimicking the situation in the endosome. To detail the molecular mechanism of antibody-neutralization in virus infection, selected antibody-bound virus complexes were characterized structurally, where the key domains of Fab footing were identified by with atomic-model docking as well as real-time sensor surface techniques.

Moreover, our focus on cellular tomography has been to recognize macromolecules within cells or organelles, based on comparison with higher-resolution structures obtained from isolated macromolecules. Here, the 3D objects of study include membrane- and cytoskeleton-mediated transport, assembly, and signal transduction throughout virus maturation based on lipid-enveloped alphavirus and flavivirus to demonstrate the essences of lateral interaction between viral membrane proteins. Glycoprotein interactions above the lipid membrane hold a direct role in guiding the maturation process of the virus. In contrast, the structure of a non-enveloped picornavirus presents another ways of membrane protein manipulation by utilizing cellular receptor to mediate capsid disassembly and the subsequent genome release in re-entering the host. To this aspect, we are developing protocols to observe the stepwise genome release by referencing the capsid structure with internal pressure relevant to virus genome packaging.

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