

STRUCTURAL MECHANISMS OF HIV ENTRY

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Understanding the molecular structures of trimeric Env and the mechanisms by which viruses are delivered to the surface of CD4+ T-cells is essential for developing effective strategies for blocking HIV entry. Under physiological conditions, viruses arrive at the T-cell surface either by diffusion within the extracellular space, or by targeted delivery to specialized structures known as the virological synapse formed between the T-cell and antigen-presenting cells such as macrophages and dendritic cells. Using emerging technologies for electron tomography and ion abrasion scanning electron microscopy, we are studying the 3D structure of the virological synapse and distribution of viruses within the synapse. In parallel with studies of the synapse, we are using cryo-electron tomography combined with 3D image averaging to determine the three-dimensional structures of trimeric Env in complex with CD4 as well as Env-specific antibodies with the goal of describing molecular architectures of the viral surface glycoproteins in unliganded and a variety of liganded states. Together, these studies provide insights into mechanisms underlying the targeting of viruses to T-cells and the conformational changes in Env that trigger HIV entry into CD4+ T-cells.