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Preface

Infection of eukaryotic cells by enveloped viruses requires the fusion between the cellular and viral membranes. Specific viral envelope proteins mediate this process, which likely involves highly curved non-bilayer membrane structures. The activity of viral ''fusion'' proteins is tightly regulated, generally being triggered by target-cell-derived specific components, as diverse as interactions with cell surface receptors or acidification of the fusion protein environment following endocytosis. In this manner, fusion proteins' activity is not misfired. How this strict control is achieved is not fully understood, but in most cases the target cell-derived mechanisms are believed to induce changes in the interactions between different envelope proteins or between different subunits within an envelope protein, and to trigger conformational changes in the fusion proteins. Indeed, a proper understanding of the membrane fusion process will require both a comprehensive knowledge of the conformational changes that the viral proteins undergo and how these structural rearrangements are coupled to membrane merging. Paradoxically, the very changing nature of this process, as a consequence of which both protein and membrane structures are altered, is what renders its study most challenging. In this issue, our current understanding of several aspects of the process is discussed and novel hypotheses are put forward.

Hemagglutinin, the fusion protein of influenza, an Orthomyxovirus, has been for many years one of the most studied and best understood viral fusion machines. The availability of high-resolution structures of both the pre-fusion and post-fusion conformations of most of its extraviral domain (both the fruit of the outstanding work of the late Don C. Wiley and his co-workers [1,2], as well as the pioneering protein-dissection experiments of Peter S. Kim and his co-workers [3]) that led to the hypothesis of the spring-loaded mechanism by which the N-terminal hydrophobic segment (so-called fusion peptide) of the molecule is relocated to the target cell membrane is the foundation on which most of our current knowledge about membrane fusion induced by Type I envelope proteins is based. The review in this issue by Herrmann and his co-workers discusses recent studies on how the pH modulates the stability of the trimeric hemagglutinin ectodomain and proposes a model for the initial steps of low-pH induced conformational change. The article by Tamm focuses on recently determined structures of hemagglutinin fusion peptides and their interactions with target membranes and, based on these observations, postulates a novel ''spring-loaded boomerang'' mechanism of membrane fusion. Bentz and Mittal review detailed kinetic studies to suggest that the site at which membrane fusion begins contains an aggregate of at least eight hemagglutinin molecules and that the conformational change of only two of these molecules would suffice for the formation of the first fusion pore.

The mechanism of HIV cell entry (as well as that of other Retroviruses) shares many commonalities with the hemagglutinin-mediated reaction; although, in this case the process is started by the interaction of the HIV envelope proteins with receptor proteins (CD4 and one of several possible coreceptors) on the surface of the target cell. Over the last years many studies have added detail to our knowledge about the specific conformational intermediates that the HIV envelope proteins populate during the fusion reaction. However, less attention has been paid to the possible roles played by the ''cellular environment'' (e.g. membrane micro-domains, cytoskeleton rearrangements, or signaling). The article in this issue by Blumenthal and his co-workers presents an updated model for the HIV Env-mediated fusion reaction that also considers these cellular events and, based on recent kinetic experiments, adds a temporal component to the model. The article by Golding and colleagues describes the current understanding of the molecular interactions between the HIV-1 envelope glycoprotein (gp120) and both CD4 and coreceptors on target cells. These interactions trigger the chain of conformational changes both in the gp120 and the transmembrane gp41 and the transition from a metastable to a thermostable six-helix structure that brings the two membranes close enough for fusion pore formation. Golding et al. also summarize important features of coreceptor regulation in primary cells and describe the several classes of entry-inhibitors designed to specifically target HIV coreceptors. Cell entry is not the only process in which viral proteins induce a rearrangement of the cell membranes. The article by Scarlata and Carter addresses the role of the HIV Gag polyprotein in the budding reaction, another crucial process in the viral life cycle that involves a protein-mediated alteration of the plasma membrane. The successive steps of cell attachment and membrane fusion are mediated in most Paramyxoviruses by two different proteins (attachment is mediated by HN, HA, or G—depending on the particular virus; whereas

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fusion is mediated by F). Newcastle disease virus (NDV) has become a prototype for the study of Paramyxovirus infection, for the structure of most of the ectodomains of its HN and F proteins (in this case the pre-fusion conformation) are known. In her article, Morrison discusses a wealth of information derived from mutation, antibody reactivity, and protein-dissection experiments done with different Paramyxoviruses, in the context of the current structural knowledge.

The article by Phogat and Dimitrov reviews selected topics from the 3rd International Frederick meeting on the cell biology of virus entry, specifically focusing on the recent advances on envelope structures from Flavi- and Alphaviruses, two families whose Type II fusion proteins are known to markedly differ from those of Ortho-, Retro-, and Paramyxoviruses, discussed earlier. The mechanism by which human Hepadnaviruses, of which Hepatitis B virus (HBV) is a representative, is still poorly characterized, in part for the lack of appropriate animal model. Shaul and his co-workers discuss here our current understanding of the early steps in HBV infection, mostly derived from studies conducted with the duck hepadnavirus DHBV.

The high-resolution 3D information on the structure of fragments of viral fusion protein ectodomains, gained from both NMR and X-ray crystallography, has dramatically boosted our understanding of the molecular mechanisms of membrane fusion. However, the specific membrane-interacting segments of the viral envelope proteins (i.e. the fusion peptides and transmembrane domains) are membrane-embedded during the crucial steps of fusion and therefore not accessible to the mentioned structure-determination methods. The article by Martin, Goormaghtigh and Ruysschaert illustrates why attenuated total reflection Fourier transformed infrared spectroscopy (ATR-FTIR) is a powerful technique to gain information on the structure, orientation and accessibility to the water phase of the fusogenic regions of viral envelope proteins. The high hydrophobicity that allows fusogenic regions to preferentially interact with membranes during the fusion process has indeed rendered their study in the context of the full-length ectodomains a very difficult task. For this reason, a protein-dissection strategy, in which the interaction between membranes and synthetic peptides corresponding to the fusogenic domains is studied, has been developed. Indeed, this strategy has provided very important and relevant information on the specific mechanism by which these hydrophobic regions induce membrane destabilization and fusion. The validity of this approach as well as the knowledge we have gained from it are the focus of the article by Nieva and Agirre. Along this line, Epand discusses in detail the possible mechanism of membrane destabilization by fusion peptides, which could include the promotion of negative curvature, lowering the rupture tension of the lipid monolayer, and transmitting the force generated by the envelope protein conformational changes to the membrane. Finally, the review by Peisajovich and Shai discusses recent diverse experimental observations that argue against the simple picture of a viral fusion protein interacting with the cell and/or viral membranes by means of only two localized segments (the fusion peptide and transmembrane domain). Instead, the current view postulates that multiple regions within viral proteins interact with membranes and participate in their destabilization and fusion.

References

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