Inhibitors that target fusion

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Introduction

The process of viral entry offers several advantages for drug intervention. Targeting extracellular events eliminates challenges in ensuring adequate drug delivery into cells. Disabling HIV before integration of viral DNA into host cells also prevents the potential for establishment of viral persistence in long-lived cells. Recent progress in understanding the molecular basis of the HIV entry process points to new therapeutic strategies. In this chapter, we focus on agents that target the step of virus-cell fusion from a mechanistic point of view. Issues related to product development of fusion inhibitors for eventual clinical use are covered in the Chapter by Greenberg.

Conformational changes leading to fusion

HIV enters cells through a multi-step process (Fig. 1, also reviewed in the Chapter by Tilton/Doms). Binding of gp120 to the CD4 receptor triggers conformational changes that facilitate gp120 interactions with a coreceptor (chemokine receptors CCR5 or CXCR4) [1, 2]. This interaction induces further conformational changes in the oligomeric envelope glycoprotein (Env) complex that activate the membrane fusion activity of gp41. gp41 draws viral and cellular membranes together as it refolds from its native, metastable structure to its final, thermostable structure (reviewed in [3]), leading to fusion of the outer leaflets of the membranes (hemifusion) and then complete membrane fusion with fusion pore formation (reviewed in [4]). Widening of the fusion pore allows the viral nucleocapsid to be delivered into the host cell.

The gp41 ectodomain (Fig. 2A) contains five essential regions for fusion: a fusion peptide (FP), two heptad repeats (HR1 and HR2), a membrane proximal region (MPR) and a transmembrane domain (TM). The FP, containing predominantly hydrophobic residues, begins at the extreme N terminus of the gp41 ectodomain and precedes HR1 (amino acid positions 29–82), a predicted -helical, coiled-coil domain, also called the N heptad or N peptide region. An intervening sequence, which contains a small loop formed by an intramol-
Figure 1. Multi-step process of HIV entry. Binding of the native, metastable envelope glycoprotein (gp120/41) to CD4 and chemokine cellular receptors (X4 or R5) activates conformational changes that lead to fusion. The changes involve opening up of gp41 to form the pre-hairpin fusion intermediate, in which gp41 becomes embedded in both viral and target membranes and the gp41 heptad repeats (HR1 and HR2) are relatively exposed. Further folding to form the compact, thermostable six-helix structure facilitates merger of viral and target membranes. Current fusion inhibitors target the pre-hairpin fusion intermediate conformation(s) of the envelope glycoprotein (inside box).