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Review paper

FIV Gag: Virus assembly and host-cell interactions

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ABSTRACT

Infection of domestic cats with virulent strains of the feline immunodeficiency virus (FIV) leads to an acquired immunodeficiency syndrome (AIDS), similar to the pathogenesis induced in humans by infection with human immunodeficiency virus type 1 (HIV-1). Thus, FIV is a highly relevant model for anti-HIV therapy and vaccine development. FIV is not infectious in humans, so it is also a potentially effective non-toxic gene therapy vector. To make better use of this model, it is important to define the cellular machinery utilized by each virus to produce virus particles so that relevant similarities can be identified. It is well understood that all replication-competent retroviruses encode *gag*, *pol*, and *env* genes, which provide core elements for virus replication. As a result, most antiretroviral therapy targets *pol*-derived enzymes (protease, reverse transcriptase, and integrase) *or env*-derived glycoproteins that mediate virus attachment and entry. However, resistance to drugs against these targets is a persistent problem, and novel targets must be identified to produce more effective drugs that can either substitute or be combined with current therapy. Elements of the *gag* gene (matrix, capsid, nucleocapsid, and "late" domains) have yet to be exploited as antiviral targets, even though the Gag precursor polyprotein is self-sufficient for the assembly and release of virus particles from cells. This process is far better understood in primate lentiviruses, especially HIV-1. However, there has been significant progress in recent years in defining how FIV Gag is targeted to the cellular plasma membrane, assembles into virions, incorporates FIV Env glycoproteins, and utilizes host cell machinery to complete virus release. Recent discoveries of intracellular restriction factors that target HIV-1 and FIV capsids after virus entry have also opened exciting new areas of research. This review summarizes currently known interactions involving HIV-1 and FIV Gag that affect virus release, infectivity, and replication.

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1. Introduction: FIV is a relevant model for AIDS and lentiviral gene therapy

FIV is endemic in the wild and has evolved for millennia, along with its ancestral hosts (Pedersen et al., 1987; Troyer et al., 2005). FIV infection of its native host induces feline AIDS, characterized by a progressive decline in $CD4^+$ T-cells that is clinically asymptomatic for years unless challenged with an opportunistic pathogen (Burkhard and Dean, 2003). Unlike SIV-induced simian AIDS, development of feline AIDS does not require a cross-species transmission, which provides some clear advantages for studying both horizontal and vertical transmission in relatively inexpensive cat colonies and feral cats (Coats, 2005; Willett et al., 1997). FIV pathology is similar to that of HIV-1 and is best described in domestic cats (*Felis catus*) infected with FIV_{fca}, due to a high incidence of infection (~1–30%) with apparently no evolution of host resistance (Troyer et al., 2005; Winkler et al., 1999). Despite centuries of close contact, there is no evidence of FIV transmission to humans, possibly due to poor recognition of the FIV promoter (5′-LTR) in human cells (Mustafa et al., 2005). This block can be overcome for FIV-based gene therapy, applicable to both dividing and non-dividing cells of virtually any type, by substitution of the FIV 5′-LTR with a CMV promoter (Johnston et al., 1999). Thus, understanding FIV biology in human cells is also potentially relevant to clinical applications. FIV is the only lentivirus for which a vaccine is readily available (Hohdatsu et al., 1997), which is protective against a subset of known FIV subtypes. Mechanisms of protection appear to involve both humoral and cellular immunity (Pu et al., 1997). Thus, FIV is clearly a useful model for the development of AIDS vaccines, antiretroviral drugs, and non-pathogenic gene therapy vectors. Compared to primate lentiviruses, many fundamental aspects of FIV cellular biology are not well understood. However, significant progress has been made in recent years in identifying molecular mechanisms of infection, in part based on comparative studies with HIV-1 and other lentiviruses (Elder et al., 2008; Luttge et al., 2008).

2. FIV and HIV-1 genome homology

Both FIV and HIV-1 contain essential elements found in all retroviruses (*gag*, *pol*, *env*), possibly derived from a common ancestral lentivirus (Katzourakis et al., 2007), with the addition of accessory factors that enhance replication *in vivo* but are often dispensable in cell culture models [reviewed in Elder et al., 2008]. Since FIV has evolved independently in cats, it has virtually no sequence similarity to primate lentiviruses in homologous open reading frames and the collection of accessory factors is the least conserved (Olmsted et al., 1989; Pecon-Slattery et al., 2008). With the exception of Rev and Vif, most accessory factors encoded by HIV-1 (including Tat, Nef, Vpr, and Vpu) have not been clearly identified in FIV, although FIV Orf2/OrfA may have functions partially related to both Tat and Vpr (Sundstrom et al., 2008). Earlier studies with FIV Vif suggested a possible analogy with HIV-1 Vif, but their functional similarity has only recently been clearly demonstrated (Münk et al., 2008).

3. The Gag protein is a self-contained virus assembly "machine"

Expression of retroviral Gag polyprotein precursors alone, within a suitable host cell, is sufficient for the production of virus-like particles (VLPs) (Fig. 1A) [reviewed in Adamson and Freed, 2007; Ganser-Pornillos et al., 2008]. All retroviral Gag proteins contain domains required for membrane targeting, Gag–Gag interaction, and virus release (Fig. 1B). Through interactions and modifications of the membrane-targeting domain, lentiviral assembly typically occurs at the plasma membrane (PM) while budding away from the cytoplasm of the infected cell. Other steps in virus assembly and release are driven by interactions of Gag with itself and with host cell factors via "late" domains (Fig. 1C). After these domains have exerted their functions in assembly and release, the Gag precursor is cleaved by the virally encoded protease (PR), if present, into the final mature Gag proteins. For HIV-1 and FIV these include matrix (MA), capsid (CA), nucleocapsid (NC), spacer peptides (SP1, SP2) flanking NC, and a C-terminal peptide (p6 in HIV-1, p2 in FIV) (Elder et al., 1993; Ganser-Pornillos et al., 2008; Lin et al., 2006). Activation of PR, and the resulting cleavage of Gag, appears to coincide with final events in virus release. However, retrovirus release itself does not depend upon PR function; immature VLPs containing unprocessed Gag are released efficiently in the absence of PR (Calistri et al., 2009; Fu et al., 2006; Huang et al., 1995; Ono et al., 2000, 2004, 2005; Peng et al., 1989; Tomonaga et al., 1998).

3.1. Matrix (MA)

Lentiviral MA domains play important roles in the assembly of infectious particles by directing Gag to the PM, mediating the association between Gag and the inner leaflet of the PM lipid bilayer, and recruiting the viral envelope (Env) glycoproteins into virions (Freed, 1998; Freed and Martin, 1995, 1996) (Fig. 1B).