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Review

Cell-to-cell transmission of retroviruses: Innate immunity and interferon-induced restriction factors

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ABSTRACT

It has been known for some time that retroviruses can disseminate between immune cells either by conventional cell-free transmission or by directed cell-to-cell spread. Over the past few years there has been increasing interest in how retroviruses may use cell-to-cell spread to promote more rapid infection kinetics and circumvent humoral immunity. Effective humoral immune responses are intimately linked with innate immunity and the interplay between retroviruses and innate immunity is a rapidly expanding area of research that has been advanced considerably by the identification of cellular restriction factors that provide barriers to retroviral infection. The effect of innate immunity and restriction factors on retroviral cell-to-cell spread has been comparatively little studied; however recent work suggests this maybe changing. Here I will review some recent advances in what is a budding area of retroviral research.

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Cell-to-cell spread of retroviruses

Retroviruses are a diverse family of enveloped RNA viruses that encompass a number of medically important human pathogens including the Human Immunodeficiency Virus (HIV), which alone has accounted for approximately 25 million deaths worldwide. Over the past decade huge scientific and medical endeavour has been focussed towards understanding the biology of viral pathogenesis and transmission between and within hosts. Like a number of other mammalian viruses, retroviruses can disseminate between susceptible cells either by cell-free infection or by direct cell-to-cell spread (reviewed in (Sattentau, 2008)). Retroviruses spread directly between cells by taking advantage of their immunotropic properties to infect $CD4^+$ T cells, macrophages and dendritic cells that inherently form intimate, dynamic and transient contacts (Jolly and Sattentau, 2004). In this way, retroviruses can co-opt specialized properties of immune cells that normally operate during intercellular communication such as antigen presentation and T cell activation to promote their dissemination between cells.

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Direct cell-to-cell spread of the human retroviruses HIV type-1 (HIV-1) and HTLV-1 (Human T-lymphotropic Virus Type-1) predominantly takes place at specialized contact-induced structures known as virological synapses (VS) that act as "hot-spots" for virus transmission (Igakura et al., 2003; Jolly et al., 2004; Jolly and Sattentau, 2002; McDonald et al., 2003). VS were so named because of their resemblance to immunological synapses (IS) and the term VS was coined to describe a specific membrane receptor architecture that evolves following intimate contact between a HIV-infected T cell and an uninfected target T cell (Jolly and Sattentau, 2002). Cell-to-cell spread of HIV-1 at synapses is a generalized feature of viral dissemination and VS have been described between infected and uninfected $CD4^+$ T cells (Jolly et al., 2004), between macrophages and $CD4^+$ T cells (Gousset et al., 2008; Groot et al., 2008) and between virus-exposed dendritic cells and $CD4^+$ T cells (McDonald et al., 2003). This phenomenon is not restricted to HIV-1, and one of the first VS described was that of HTLV-1 (Igakura et al., 2003). Longer-range intercellular transmission of HIV-1 between T cells has also been observed along cellular projections known as membrane nanotubes (Sowinski et al., 2008), while the related retrovirus murine leukeamia virus (MLV) utilizes virus-induced filopodia for efficient dissemination (Sherer et al., 2007). The relative contribution of cell-to-cell spread at VS, membrane nanotubes and via cell-free infection is difficult to quantify, but *in vitro* culture systems have demonstrated that cell-cell spread is the predominant mode of HIV-1 dissemination and this is mostly via VS (Sourisseau et al., 2007). At present there is considerable effort towards delineating retroviral protein trafficking in infected cells during cell-to-cell spread and understanding the molecular regulators of transmission in both donor and target cells (Arrighi et al., 2004; Chen et al., 2007; Gousset et al., 2008; Groot et al., 2008; Hubner et al., 2009; Rudnicka et al., 2009; Turville et al., 2004; Igakura et al., 2003; McDonald et al., 2003; Barnard et al., 2005; Jolly et al., 2004, 2007a,b; Jolly and Sattentau, 2005, 2007; Llewellyn et al., 2010; Nejmeddine et al., 2005, 2009) and readers are directed to a recent series of comprehensive reviews that consider this in detail (Feldmann and Schwartz, 2010; Jolly, 2010; McDonald, 2010; Mothes et al., 2010; Nejmeddine and Bangham, 2010; Sattentau, 2010; Waki and Freed, 2010).

In the context of viral pathogenesis, direct cell-to-cell transmission is likely to confer a number of advantages for retrovirus compared to classical cell-free infection. Firstly, cell-to-cell spread increases infection kinetics by directing virus assembly and budding to sites of cell-to-cell contact and may be one or more orders of magnitude more efficient than equivalent cell-free infection (Dimitrov et al., 1993; Mazurov et al., 2010; Chen et al., 2007; Martin et al., 2010; Sato et al., 1992; Sourisseau et al., 2007). This is achieved by obviating the rate-limiting step of extracellular diffusion that is required of cell-free virus to find a susceptible target cell. Furthermore, polarizing virus budding towards sites of cell-to-cell contact at which viral entry receptors are clustered increases the number of potentially productive transmission events and increases the likelihood of productive infection.

Secondly, it has been hypothesised that cell-to-cell spread of retroviruses could provide a replicative advantage to the virus by limiting exposure of particles to neutralizing antibodies (Martin and Sattentau, 2009). It has generally been assumed that cell-to-cell spread of retroviruses at VS might allow escape from neutralizing antibodies either by limiting the window of opportunity for antibody to engage viral antigens, or by providing a relatively protected domain at cell-to-cell interfaces that could physically exclude the relative bulk of antibodies from gaining access to virions before they attach and enter to target cells. Whether VS protect retroviruses from humoral immunity is still unclear and there are conflicting reports on this in the literature (Chen et al., 2007; Ganesh et al., 2004; Martin et al., 2010; Massanella et al., 2009). Possible explanations for disparate results have been considered elsewhere (Sattentau, 2010) and so will not be elaborated in detail here.

Humoral immunity to human retroviruses such as HIV-1, the causative agent of Acquired Immune Deficiency Syndrome is of particular interest within the context of cell-to-cell spread because of the implications of immune evasion for vaccine design and viral pathogenesis. The innate immune response is intimately linked to the generation of an effective adaptive immune response. Thus retroviral-induced innate immune responses may have a direct impact on cell-to-cell transmission but may also modulate adaptive immunity and thereby control of viral infection. The role of innate immunity during cell-to-cell spread of retroviruses has only recently been explored; however, it is increasingly apparent that harnessing innate immunity might provide a crucial opportunity to tackle HIV-1 at some of the earliest steps of infection, and that the interplay between HIV-1 and innate immunity has important implications for disease pathogenesis (Borrow et al., 2010). In the context of HIV-1 cell-to-cell spread the balance between viral suppression and enhancement by innate immune responses is intriguing, although relatively little studied. Here I will discuss some recent insights into cell-to-cell spread and innate immunity and consider how the interplay between HIV-1 and innate effectors may modulate cell-to-cell dissemination. I will focus predominantly on HIV-1, but it is likely that some aspects of innate immunity and HIV-1 will be applicable to other retroviruses.

Recognition of HIV-1 by innate immune receptors during cell-to-cell spread

At the earliest time points after infection, before adaptive immunity has been activated, the innate immune system provides the first line of antiviral defences and alerts the wider immune system of challenge. An important feature of innate immunity that facilitates such rapid response is the recognition of generalized pathogen-associated molecular patterns (PAMPS). This is mediated by via a range of pattern recognition receptors (PRR) including C-type lectins (CLR), Toll-like receptor (TLRs) and cytosolic sensors such as NOD-like receptors and the retinoid acid-inducible gene (RIG) like receptors RIG-I and MDA5. Recognition of ubiquitous microbial patterns leads to signal transduction, activation of the transcription factors such as NF-κB, mitogen-activated protein kinase (MAPK) and interferon regulatory factor (IRFs), and culminates in secretion of proinflammatory and immunomodulatory cytokines such as type-1 interferons (interferon-α and interferon-β). TLRs are located at the cell surface or in endocytic compartments and collectively recognize a range of viral and bacterial ligands including hydrophobic molecules, glycoproteins, bacterial cell wall components and nucleic acid, the latter being a particularly potent activator. To date, 10 different TLRs have been identified in humans. In addition, other receptors such as C-type lectins and scavenger receptors on cell surfaces can act as TLR coreceptors and bind to microbes via PAMPs which culminates in a signaling cascade that alerts the wider immune system of danger. In the context of HIV-1, a number of steps in the viral life cycle have been shown to activate immunity via PRR recognition including attachment of the HIV-1 envelope glycoprotein (Env) subunit gp120 by the C-type lectin DC-SIGN (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin) (Gringhuis et al., 2010); TLR7/8-mediated detection of HIV-1 RNA (Beignon et al., 2005; Heil et al., 2004; Meier et al., 2007) and more recently the identification of an intrinsic dendritic cell sensor that detects the interaction between newly synthesized HIV-1 capsid and cylophilin A and activates the transcription factor IRF3 (Manel et al., 2010). Interestingly, cell-free HIV-1 infection may escape innate immune detection in some situations and it has been proposed that that macrophages lack a functional PRR for HIV-1 therefore attenuating NF-κB and IRF3 activation and type-1 interferon induction (Noursadeghi et al., 2009; Tsang et al., 2009).

So far, most studies examining innate immune recognition of HIV-1 have utilized cell-free virus or viral constituents, and characterized their effects on dendritic cells and macrophages. Therefore, it is