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Mechanisms of HIV-1 cell-to-cell transmission and the establishment of the latent reservoir

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ABSTRACT

HIV-1 spreads through both the release of cell-free particles and by cell-to-cell transmission. Mounting evidence indicates that cell-to-cell transmission is more efficient than cell-free transmission of particles and likely influences the pathogenesis of HIV-1 infection. This mode of viral transmission also influences the generation and maintenance of the latent reservoir, which represents the main obstacle for curing the infection. In this review we will discuss general cell contact-dependent mechanisms that HIV-1 utilizes for its spread and the evidence pointing to cell-to-cell transmission as a mechanism for the establishment and maintenance of latent infection.

1. Introduction

Animal viruses reproduce mainly through the production and release of cell-free particles for infecting new host cells and for spreading to new individuals. However, cell-free spread exposes viral particles to the challenges of surviving the extracellular environment. In addition, viral particles must survive a number of innate and adaptive immune defenses if the virus is to successfully establish a population in a new animal host. To circumvent these challenges, some viruses have evolved ways of exploiting normal cellular processes to protect progeny particles. An example of such a strategy is transmission across cell-cell contacts. This mode of virus spread, known as virus cell-to-cell transmission, is employed by several enveloped viruses, including HIV-1, and provides important advantages for viral survival, which in turn influences viral pathogenesis.

By concentrating the release of viral particles at the site of cell-cell contact, HIV-1 cell-to-cell transmission increases the efficiency of viral spread several orders of magnitude compared to the dissemination of cell-free particles (Carr et al., 1999; Chen et al., 2007; Dimitrov et al., 1993; Iwami et al., 2015; Martin et al., 2010; Zhong et al., 2013a), it provides protection from neutralizing antibodies (Abela et al., 2012; Chen et al., 2007; Dufloo et al., 2018; Ganesh et al., 2004; Gombos et al., 2015; Gupta et al., 1989; Li et al., 2017; Malbec et al., 2013; Massanella et al., 2009; McCoy et al., 2014; Reh et al., 2015; Zhong et al., 2013a) and it overcomes the inhibitory effects of some anti-viral restriction factors such as tetherin and TRIM5α under certain conditions (Casartelli et al., 2010; Coleman et al., 2011; Giese and Marsh, 2014; Jolly et al., 2010; Kuhl et al., 2010; Richardson et al., 2008; Zhong et al., 2013a). This mode of viral transmission also influences the treatment and pathogenesis of the infection. For example, some antiretroviral drugs poorly inhibit HIV-1 cell-to-cell transmission when administered as mono-therapies (Agosto et al., 2014; Duncan et al., 2013; Kim et al., 2018; Sigal et al., 2011; Titanji et al., 2013). Another example is that HIV-1 cell-to-cell transmission to lymph node-derived resting CD4 + T cells induces a highly inflammatory form of apoptosis, known as pyroptosis, which has been suggested to contribute to depletion of CD4 + T cells in lymphoid tissues. (Doitsh et al., 2010, 2014; Galloway et al., 2015; Monroe et al., 2014; Munoz-Arias et al., 2015). Importantly, HIV-1 cell-to-cell transmission is a route that leads to the establishment of latent infection.

Latent infection in CD4 + T cells represents the main obstacle to the eradication of HIV-1 from infected individuals (Margolis et al., 2016; Mbonye and Karn, 2017; Siliciano and Greene, 2011). The best characterized mechanism for the generation of latent infection is the return of productively infected activated CD4 + T cells to a resting state, a cell state that is restrictive for proviral gene transcription (Han et al., 2007; Pace et al., 2011; Schiralli Lester and Henderson, 2012). However, direct infection of resting CD4 + T cells also results in the generation of latent infection and may play an important role for the generation of latent infection *in vivo* (Agosto et al., 2007; Cameron et al., 2010; Chan

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et al., 2016; Lassen et al., 2012; Swiggard et al., 2005; Tabler et al., 2014; Vatakis et al., 2007; Zerbato et al., 2016; Zhang et al., 1999, 2004). Since cell-to-cell transmission of HIV-1 facilitates efficient infection of CD4 + T cells, several laboratories are investigating how contact with virus-carrying cells supports infection of resting CD4 + T cells and the cellular and molecular mechanisms that are involved in the generation of proviral latency in this context (Agosto et al., 2018; Evans et al., 2013; Kumar et al., 2015; Schilthuis et al., 2018; Shen et al., 2013). Cell signaling mediated by cell-cell contacts and cytokine release, and the transfer of large numbers of particles to target CD4 + T cells, could have profound effects on the establishment of latent infection and will likely impact the design of therapeutic approaches that target the latent reservoir. How these mechanisms mediate HIV-1 cell-to-cell transmission and their influence on the generation of latent infection in resting CD4 + T cells are critical questions that need to be addressed.

2. Mechanisms of cell-to-cell transmission

Several modes of cell-to-cell transmission have been described for HIV-1 (Bracq et al., 2018; Chen, 2012; Sattentau, 2008; Zhong et al., 2013b). The best described of these utilize direct cell-cell contacts that resemble the immunological synapse (IS) and are known as infectious or virological synapses (Fig. 1). Similar to the IS, cell-cell contacts involved in viral transmission result in signal transduction and biological changes in both the virus-donor and the virus-target cells, which in turn influence viral spread and pathogenesis.

2.1. HIV-1 infectious synapses

The infectious synapse is formed when HIV-1 is captured by a cell without itself becoming infected and the virus-carrying cell subsequently directs the intact particles to a target cell during cell-cell contact (Kijewski and Gummuluru, 2015; McDonald, 2010; McDonald et al., 2003). This mechanism, also known as HIV-1 *trans*-infection, is typically associated with viral transmission from myeloid antigen-presenting cells (APCs) to CD4 + T cells, such as macrophages and dendritic cells (DCs), but can occur between other cell types as well. For example, mucosal fibroblasts and mammary epithelial cells have been suggested to capture and transmit HIV-1 to CD4 + T cells in a *trans*-infection-like manner (Dorosko and Connor, 2010; Neidleman et al., 2017). HIV-1 has evolved to take advantage of the normal cell-cell contacts and immune functions of myeloid APCs for this mechanism of dissemination.

HIV-1 is captured by APC surface molecules, such as the C-type lectin SIGLEC-1, and retained within non-lysosomal compartments where it avoids degradation and antibody neutralization (Gummuluru et al., 2014; Izquierdo-Useros et al., 2012; Puryear et al., 2013, 2012; Waki and Freed, 2010). The infectious synapse is formed following initial interactions between virus-carrying APCs and target cells mediated by the attachment proteins ICAM-1 and LFA-1 (Rodriguez-Plata et al., 2013; Sanders et al., 2002). Following attachment, the APC recruits a variety of molecules to the site of contact including those found in an IS, as well as HIV-1 bound to SIGLEC-1 (Akiyama et al., 2015). Meanwhile in the CD4 + T cell, a complimentary process is occurring with the reorganization of the local cytoskeleton, and a recruitment of a variety of molecules to the site of contact including CD4, CXCR4 and CCR5, the receptors required by HIV-1 for entry. This process is thought to benefit HIV-1 by concentrating particles and receptors in a discrete area of close contact. The generation of a synaptic structure demonstrates how HIV-1 is capable of co-opting the normal APC function to enable viral dissemination.

2.2. HIV-1 virological synapses

HIV-1 virological synapses depend on the interaction between HIV-1 envelope on infected donor cells and CD4 on uninfected target cells (Chen et al., 2007; Jolly et al., 2004; Vasiliver-Shamis et al., 2009, 2008) (Fig. 1). These cell-cell contacts can take place between adjacent cells or over relatively long distances such as in the case of filopodia (Sherer et al., 2007; Sowinski et al., 2008). These cell-cell contacts initiate signaling cascades in both the HIV-1 producer cells and the

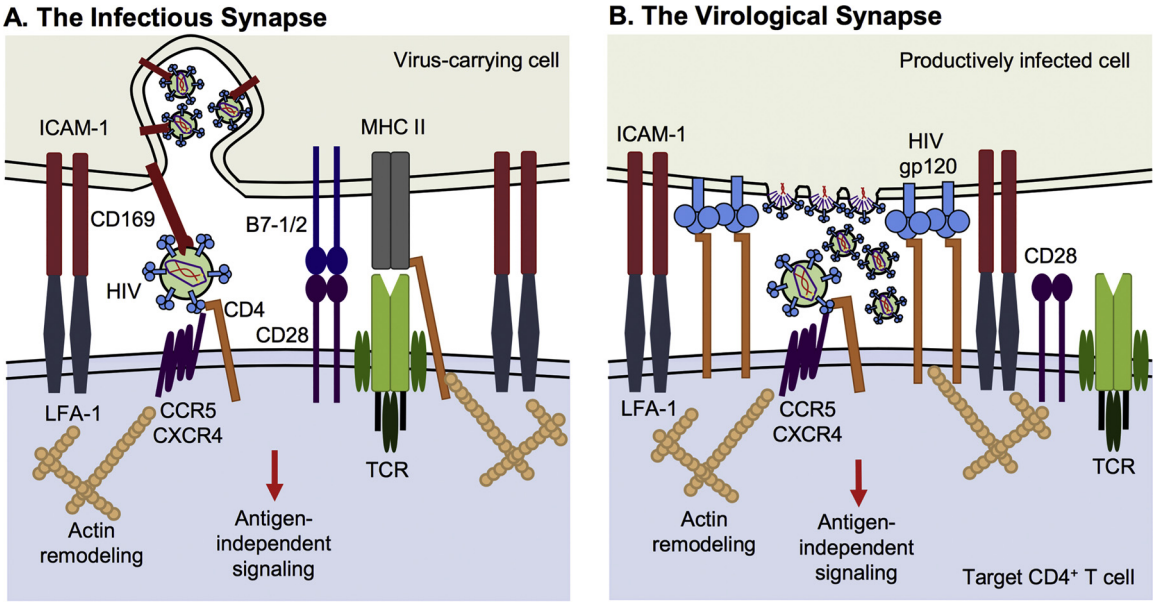

Fig. 1. Cell-cell synapse-dependent transmission of HIV-1. **A**. The infectious synapse. HIV-1 is captured by cell surface molecules such as CD169 (SIGLEC-1) and sequestered as intact particles in non-lysosomal compartments. Upon cell-cell contact and attachment via LFA-1 and ICAM-1, bound virus is brought to the site of contact where it is brought into close proximity with CD4, CXCR4 and CCR5 on the uninfected target CD4 + T cell, facilitating efficient transmission of virus. **B.** The virological synapse. A productively infected donor cell establishes contact with an uninfected CD4 + T cell in a gp120-CD4-dependent manner. The interaction is strengthened by binding of the attachment proteins LFA-1 and ICAM-1, and the HIV-1 co-receptors CCR5 and CXCR4 are trafficked to the site. Polarization of the infected donor cell towards the target cell results in the directed release of *de novo* viral particles across the synapse towards the uninfected target cell. Both forms of cell-to-cell transmission generate antigen-independent cell signaling likely impacting the outcome of HIV-1 infection in the target CD4 + T cell.

uninfected target cells (Len et al., 2017). In uninfected target cells, this interaction leads to the recruitment of LFA-1 to the site of cell-cell contact and it interacts with ICAM-1 on the HIV-1-producer cell, which strengthens the cell-cell junction (Jolly et al., 2007; Rudnicka et al., 2009; Starling and Jolly, 2016). Additional cell membrane molecules such as GM1 and other lipid raft-associated molecules (Jolly and Sattentau, 2005), and tetraspannins (Jolly and Sattentau, 2007; Krementsov et al., 2009) to the synaptic junction in an actin- and filamin-A-dependent fashion (Agosto et al., 2013; Jimenez-Baranda et al., 2007; Jolly et al., 2004). This interaction results in the polarization of HIV-1 assembly, and transit of CD4, CXCR4 and CCR5 to the site of cell-cell contact. This re-organization of viral assembly results in the delivery of many particles to target cells effectively increasing the probability of target cell infection with multiple viruses (Del Portillo et al., 2011; Law et al., 2016; Russell et al., 2013; Zhong et al., 2013a).

2.3. Synapse-independent cell-cell transmission

Alternative modes of HIV-1 cell-to-cell transmission are being investigated and each may have its own repercussions on the spread and pathogenesis of the virus. While these observations are certainly intriguing, further validation, a clearer understanding of the molecular mechanisms involved and additional evidence of their impact on viral spread *in vivo* are required.

2.3.1. Phagocytosis

Work from the Sattentau laboratory proposes that macrophages phagocytosing dying HIV-1-infected CD4 + T cells subsequently become infected (Baxter et al., 2014). Since phagocytosis of infected cells occurs in an HIV-1 envelope-CD4-independent manner, infection of the macrophage is unlikely to result from virological synapse formation. Further work will reveal the precise mechanism for infection of the macrophage during phagocytosis.

2.3.2. Syncytia

Syncytium formation was one of the earliest observations of HIV-1 infection of cells in culture, and occurs as a consequence of HIV-1-gp120 on infected cells engaging CD4 on uninfected target cells resulting in the fusion of the two cell membranes (Bracq et al., 2018; Lifson et al., 1986). However, the relevance of this mechanism for the pathogenesis of HIV-1 *in vivo* is less clear. Recent evidence conducted in humanized mice and 3D cultures suggest that multi-nucleated cells resulting from HIV-1-mediated cell-cell fusion are viable and may contribute to the spread of HIV-1 (Bracq et al., 2017; Compton and Schwartz, 2017; Law et al., 2016; Murooka et al., 2012; Symeonides et al., 2015).

2.3.3. Tunneling nanotubes

Long distance cell-cell connections, such as tunneling nanotubes, have been described for some myeloid cells and T cells. These thin cell-cell junctions have been suggested to mediate cell-cell communication in the form of cytoplasmic and plasma membrane components, vesicles, endosomes and some organelles (Buszczak et al., 2016). These structures were originally suggested to enable the transfer of extracellular viral particles between cells (Sowinski et al., 2008), but nanotubes generated by macrophages have also been proposed to allow the transfer of intracellular infectious particles contained within endosomes (Kadiu and Gendelman, 2011a, b).

2.3.4. Transcytosis

Mucosal epithelial cells likely play an important role during sexual transmission of HIV-1 (Anderson, 2014). These cells are capable of internalizing viral particles into vesicles at the apical surface, transport the vesicles to the basal layer and transmit the particles to CD4 + T cells in a process known as transcytosis (Bomsel, 1997; Kinlock et al., 2014). Transcytosis naturally mediates the transport of large molecules across epithelial barriers such as some vitamins and immunoglobulins (Tuma and Hubbard, 2003). Transcytosis of HIV-1 transport provides a mechanism for viral particles to cross the epithelial barrier and reach CD4 + T cells during mucosal transmission.

3. HIV-1 cell-to-cell transmission involves cell signaling

It has been hypothesized that synapses facilitate HIV-1 infection by activating cell signaling cascades similar to the IS. IS formation leads to the activation of signaling molecules downstream of the T cell receptor (TCR) such as Lck, CD3ζ, ZAP70, LAT, SLP-76, ITK, and PLCγ in response to strong antigen-dependent MHC/TCR and B7/CD28 interactions between APCs and CD4 + T cells (Dustin and Choudhuri, 2016; Smith-Garvin et al., 2009). These signaling cascades results in the activation of a series of transcription factors, most notably AP-1, NFAT and NFκB, which lead to the regulation of effector molecules, such as cytokines and chemokines, and the stimulation of cell division. Infectious and virological synapse formation stimulates similar signaling cascades with the important exception that the signaling cascades are antigen-independent (Deng et al., 2016; Hioe et al., 2011; Len et al., 2017; Readinger et al., 2008; Schiralli Lester et al., 2013; Sol-Foulon et al., 2007; Strasner et al., 2008; Vasiliver-Shamis et al., 2009). The strength and outcome of the signaling cascades stimulated during infectious and virological synapse formation on HIV-1 replication is less clear, but recent work by the Jolly laboratory suggests that virological synapses between T cells generate TCR/CD28 signaling cascades in an antigen-independent fashion and that these cascades are important for efficient viral spread (Len et al., 2017). Len, et al. conducted phosphoproteomic analysis of T cells during HIV-1 cell-to-cell transmission and confirmed the activation of signaling molecules and transcriptional regulators downstream of TCR/CD28 including Lck, ITK, MAP kinases, NFκB and NFAT. Pathways involved in actin reorganization, Rac1 signaling and Cdc42 signaling were also observed to be activated. Interestingly, these signaling cascades took place in both the HIV-1-infected T cells and the uninfected target T cells. These studies suggests that TCR signaling cascades appear to be particularly important in HIV-1-infected T cells as cells lacking TCR and downstream signaling molecules are less efficient at generating virological synapses with uninfected cells resulting in less efficient viral transmission. How signal transduction during cell-to-cell transmission influences target cell transcriptional regulation and how changes in transcriptional regulation affect subsequent HIV-1 replication also remains unclear. The activation of AP-1, NFκB, NFAT and other transcription factors are well known to facilitate HIV-1 transcription and replication (Kaczmarek et al., 2013; Karn and Stoltzfus, 2012). Given that infectious and virological synapse formation activate these transcription factors in target cells, it seems probable that signals transduced during cell-cell contact could contribute to transcriptional changes in the target cells that in turn increase susceptibility to infection, have repercussions on cell behavior, and impact anti-viral immune responses and pathogenesis. For example, ITK-mediated signaling influences multiple steps of HIV-1 replication including proviral transcription and release of HIV-1 likely through the activity of AP-1, NFκB, and NFAT (Readinger et al., 2008; Schiralli Lester et al., 2013). Another potential contribution of cell signaling during HIV-1 cell-to-cell transmission is through the generation of latent infection.

4. Cell-to-cell transmission and the establishment of the latent HIV-1 reservoir

The study of HIV-1 cell-to-cell transmission has largely focused on investigating its contribution to viral spread. However, several laboratories, including our own, have begun investigating whether this process influences the establishment and maintenance of latent infection (Agosto et al., 2018; Evans et al., 2013; Kumar et al., 2015). Latent infection is largely found among resting memory CD4 + T cells *in vivo*

(Brenchley et al., 2004; Chomont et al., 2009; Chun et al., 1997; Cohn et al., 2018; Maldarelli et al., 2014; Ostrowski et al., 1999; Reeves et al., 2018; Wagner et al., 2014). These latently infected resting cells do not support efficient viral production due to the absence of significant levels of positive transcriptional regulators, the presence of transcriptional repressors, and repressive epigenetic modifications (Agosto et al., 2015; Karn and Stoltzfus, 2012; Siliciano and Greene, 2011). The main mechanism for the formation the latent reservoir in resting CD4 + T cells remains unclear, but one mechanism is through direct infection of resting cells despite the relative resistance of these cells to HIV-1 compared to activated CD4 + T cells (Agosto and Henderson, 2018). "Gentle" stimulation such as from the chemokines CCL19 and CCL21, and the cytokines IL-4, IL-7 have been suggested to increase the susceptibility of resting CD4 + T cells to direct infection with HIV-1 without the induction of significant T cell activation (Cameron et al., 2010; Chan et al., 2016; Dardalhon et al., 2001; Moutsopoulos et al., 2006; Saleh et al., 2007; Unutmaz et al., 1999; Verhoeyen et al., 2003).

Cell-cell contacts between infected and uninfected cells, in combination with cytokine release by the cells involved, could influence the susceptibility of a target resting CD4 + T cell to HIV-1 infection and influence the generation of latent infection. Some of the initial evidence that implicated cell-cell contact for enhancing the susceptibility of resting CD4 + T cells to infection came from experiments conducted with endothelial cells (Choi et al., 2005a, b). These experiments showed that infecting resting cells in co-culture with endothelial cells improved the susceptibility of resting CD4 + T cells and subsequent replication of HIV-1. This process was dependent on signaling through MHCII-TCR and LFA3-CD2 interactions. A prior study conducted using macrophage-resting T cell co-cultures also showed an enhancement of the susceptibility of resting cells to HIV-1 infection, but the study proposed a cell-contact independent mechanism for the increased susceptibility of resting cells including the secretion of soluble CD23 and soluble ICAM (Swingler et al., 2003). Evidence that endothelial cells not only increase the susceptibility of resting CD4 + T cells to HIV-1 infection but also mediate the establishment of latent infection was reported more recently. Two studies by Shen, et al. revealed that a proportion of resting CD4 + T cells infected in co-cultures with lymphatic endothelial cells become latently infected and implicated the secretion of IL-6 by endothelial cells as a contributing factor for increasing the susceptibility of resting cells to infection (Schilthuis et al., 2018; Shen et al., 2013).

Additional evidence for the generation of latent infection in resting cells through cell-cell contact came from experiments conducted in APC-T cell co-cultures (Evans et al., 2013; Kumar et al., 2015). Evans, et al. observed that these cell-cell interactions during infection of resting CD4 + T cells led to the upregulation of factors involved in interferon responses such as ISG15 and RIG-I and the negative regulation of the NFκB pathway through down-regulation of PRKCA. They also observed upregulation of KLF6, a factor involved in T cell quiescence and ATF3, a factor that negatively regulates AP-1. Altogether, cell-cell contacts between APCs and resting CD4 + T cells during HIV-1 infection appear to increase the susceptibility of resting CD4 + T cells to HIV-1 infection while simultaneously restrict viral replication and promote latent infection. Interestingly, these experiments showed that not all APCs are capable of generating latent infection to the same extent. The studies found that CD14+ monocytes and myeloid DC subsets were all able to generate latent infection in resting cells while B cells, CD16+ monocytes and plasmacytoid DCs were less efficient. They also found that those APCs able to generate latent infection in resting cells shared a common expression of certain cell surface molecules such as ICAM-3, CLEC-7 A, SIGLEC-10 and CD1d. Although studies conducted with endothelial cell and APC co-cultures implicate cell-cell contacts in the establishment of latent infection in resting CD4 + T cells, it was still unclear whether the process of HIV-1 cell-to-cell transmission across infectious or virological synapses contributed to the infection of target resting cells.

Our laboratory investigated HIV-1 cell-to-cell transmission across virological synapses from productively infected activated CD4 + T cells to resting CD4 + T cells and found that this process leads to the generation of latently infected cells (Agosto et al., 2018). These cell-cell interactions do not induce significant target T cell activation similar to cell-cell contacts with endothelial cells (Schilthuis et al., 2018; Shen et al., 2013), but in contrast to cell-cell contacts with APCs (Evans et al., 2013; Kumar et al., 2015). Interestingly, while a proportion of latent proviruses generated through HIV-1 cell-to-cell transmission were inducible to produce HIV-1 Gag, this proportion was smaller compared to proviruses generated by cell-free infection of resting CD4 + T cells. This observation suggests that HIV-1 cell-to-cell transmission influences the subsequent regulation and maintenance of latent infection.

5. Outcomes of cell signaling during cell-to-cell transmission on the maintenance and regulation of latent infection

Our laboratory has preliminary evidence suggesting that the strength of activating signal through the TCR plays a major role in biasing the infected cell towards either a transcriptionally latent or transcriptionally active state. The strength of signaling through the signaling domains of CD3 and CD28 at the time of HIV-1 infection directly impacts the generation of latent infection. We found that strong signaling at the time of HIV-1 infection leads to more HIV-1 expression compared to weaker signaling despite similar levels of HIV-1 integration. Furthermore, we observed that latent proviruses generated during stronger signaling were reversible compared to latent proviruses generated during weak signals suggesting that weaker signaling during HIV-1 infection promotes deep seated latent infection. It is possible that a similar principle is at play during HIV-1 cell-to-cell transmission (Gagne, et al. unpublished observations).

In preliminary experiments using APCs as HIV-1 carriers, we find that DC-mediated infection of T cells appears to reduce the signaling threshold required for generating reversible latent infection. This lowering of the signaling threshold is likely due to other signals provided by the DC in addition to signaling associated with the TCR. From this, we might hypothesize that infection mediated by APCs, such as DCs, would be more likely to establish reversible latent infection (Pedro, et al. unpublished observations). This hypothesis is consistent with the observations by Evans, et al. that latent infection generated in DC-T cell co-cultures stimulate interferon-dependent signaling cascades while simultaneously stimulating responses that promote cell quiescence (Evans et al., 2013). T cell-T cell co-cultures appear have the opposite effect compared to APC-T cell co-cultures (Agosto et al., 2018). We found that latent infection generated after transmission of HIV-1 from activated T cells to resting cells was more difficult to reverse compared to latent infection generated by cell-free infection of resting cells as determined by HIV-1 protein expression relative to the level of HIV-1 integration per cell. The mechanism behind this observation is unknown, but we hypothesize that cell-to-cell transmission between T cells generates weaker cell signaling compared to APC-T cell synapses and thus promotes deeper seated latent infection. This observation suggests that the mechanism through which latent infection is generated in resting CD4 + T cells will influence its potential to be reversed (Fig. 2) (Kumar et al., 2018; Rezaei et al., 2018). The ease to reverse latent infection generated by cell-to-cell transmission could be dependent on the specific signaling cascades activated during cell-cell contact and to unique transcriptional programs generated in target cells. Further investigation of the signaling cascades generated during HIV-1 cell-to-cell transmission and the transcriptional changes created in target resting cells will likely reveal novel factors involved in the generation and maintenance of latent infection.

6. Concluding remarks

Virus cell-to-cell transmission provides several advantages for the spread and survival of HIV-1. Active research is underway to determine

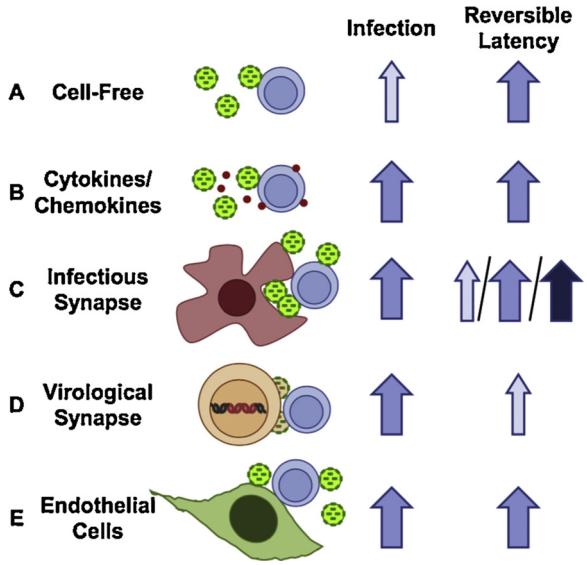

Fig. 2. The efficiency of establishing and reversing latent infection is dependent on the mechanism of resting CD4 + T cell infection. Various modes of HIV-1 infection of resting CD4 + T cells are depicted with their corresponding efficiency for establishing infection and reversible latent infection. Although no study has compared all of these mechanisms side-by-side, we estimated infection and latency reversal efficiency qualitatively based on published observations. Light blue arrows represent lower relative levels of HIV-1 infection or latency reversion and dark blue arrows correspond to higher relative levels. **A.** Cell-free infection results in lower relative levels of infection (light blue arrow) but the establishment of a moderately inducible latent population (medium blue)(Agosto et al., 2018; Lassen et al., 2012; Swiggard et al., 2005). **B.** Cell-free infections aided by chemokines, such as CCL19 and CCL21, result in increased resting cell susceptibility to infection compared to infections without added chemokines and a moderately inducible latent population (Cameron et al., 2010; Kumar et al., 2018; Saleh et al., 2007). **C.** An uninfected HIV-1-carrying cell contacts an uninfected CD4 + T cell. Virus is transmitted *in trans* via the infectious synapse. This mode of transmission promotes latent infection of resting CD4 + T cells. However, the reversion of latent infection varies widely depending on the HIV-1-transmitting cell type, indicated by the light, medium and dark blue arrows (Kumar et al., 2015). The efficiency of latency reversion also depends whether or not the target cells are proliferating during infection in APC co-cultures (Kumar et al., 2018). **D.** An infected donor cell establishes contact with an uninfected donor cell and transmits HIV-1 via a virological synapse. This is an efficient method of transmission and results in moderate levels of resting cell infection. However, although latent infection can be detected in target cells by HIV-1 DNA, viral re-expression is not readily induced (Agosto et al., 2018). **E.** The susceptibility of resting CD4 + T cells to HIV-1 infection increases when in contact with endothelial cells and enables the establishment inducible latent infection (Choi et al., 2005a, b; Schilthuis et al., 2018; Shen et al., 2013).

the degree to which this mode of viral transmission contributes to the spread and pathogenesis of HIV-1 *in vivo* and the generation and maintenance of latent reservoirs. Continued examination of HIV-1 cell-to-cell transmission is critical for a full understanding of the latent reservoir and the discovery of novel therapeutic targets for improved treatment efficacy and prognosis of people living with HIV-1 infection.

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