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Viruses exploit the tissue physiology of the host to spread in vivo

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Abstract

Viruses are pathogens that strictly depend on their host for propagation. Over years of co-evolution viruses have become experts in exploiting the host cell biology and physiology to ensure efficient replication and spread. Here, we will first summarize the concepts that have emerged from in vitro cell culture studies to understand virus spread. We will then review the results from studies in living animals that reveal how viruses exploit the natural flow of body fluids, specific tissue architecture, and patterns of cell circulation and migration to spread within the host. Understanding tissue physiology will be critical for the design of antiviral strategies that prevent virus dissemination.

Introduction

Viruses can be transmitted from infected to non-infected cells by diffusion through the extracellular space. This process is commonly referred to as cell-free transmission (Fig. 1A). Alternatively, the process where cell-surface attached viral particles are delivered to neighboring cells for infection via cell-contacts is defined as virus cell-to-cell transmission (for reviews see [1–5]). Contact-dependent transmission is further classified based on whether the donor cells are infected or not. The ability of productively infected donor cells to establish cell-cell contact with non-infected cells for infection is described by the concept of the virological synapse (Fig. 1B) [6,7]. In contrast, the ability of a non-infected donor cell to capture virus and transfer it to a permissive target cell is designated trans-infection (Fig. 1C) [8,9]. The cell-cell contact formed during trans-infection is also described as the infectious synapse [9]. Contact-dependent transmission has been observed in vitro for many enveloped viruses including the retroviruses human immunodeficiency virus (HIV), human T-lymphotropic virus (HTLV) and murine leukemia virus (MLV) [6,10–12]. The transfer of viral particles has been visualized using live cell microscopy between infected and non-infected fibroblasts, infected and non-infected T cells, between dendritic cells (DCs) and T cells, as well as macrophages and T cells [10–14]. Virological synapses and trans-infection

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events have now also been documented in living animals suggesting that both processes can contribute to viral spread in vivo [15].

Virus cell-to-cell transmission at the virological synapse

Some viruses evolved to utilize existing cell–cell contacts, such as synaptic contacts in order to spread between neurons [16,17]. Alternatively, viruses can initiate the formation of new cell-cell contacts or stabilize transient interactions between cells for transmission. Herpes simplex virus-infected cells actively attract nerve endings and induce skin cell migration for cell-contact formation and virus transmission [18,19]. Retrovirus-infected cells express the envelope glycoprotein to stabilize transient cell interactions between migratory immune cells for virus transfer [6,7,20].

Imaging techniques such as time-lapse confocal microscopy have been fundamental to characterize virus transmission across cell-cell contacts between virus-producing cells and non-infected cells [21]. Virological synapses were first described in mixed cultures of HTLV- and HIV-infected with non-infected T cells [6,7,22]. Similar cell-cell contacts have also been observed for other viruses [10,23,24]. Tight cell contacts are rapidly initiated through interactions of the virus glycoprotein with the target cell receptor leading to an accumulation of viral proteins and cellular factors at the cell-cell contact [7,10,20,25]. Similar to the supramolecular organization of immune and neuronal synapses [26,27], virological synapses of HIV-infected cells reveal a characteristic accumulation of the viral proteins Gag and Env together with the cellular receptors CD4 and CXCR4, surrounded by an adhesive contact of intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen 1 (LFA-1) [11,25,28,29]. Signaling pathways are induced in target cells that partially resemble the T cell activation seen in immunological synapses [27]. Binding of HIV gp120 to CD4 and ICAM-1 to LFA-1 partially activates T cell receptor (TCR) signaling pathways resulting in reduced cell migration and polarization [28–32]. Virus assembly and release is then polarized towards cell-cell contact sites. In the case of MLV, virus budding is polarized to areas on the plasma membrane where the clustering of Env at the cell-cell interface initiates the recruitment of Gag [12,33]. In contrast, HIV assembly is directed towards sites of cell-cell contact by polarization of the cytoskeleton and the secretory machinery [34,35], as well as spatial clustering of organelles such as mitochondria [36]. A structural analysis of the virological synapse between HIV-infected and non-infected T cells or astrocytes reveals a complex membrane organization with cell-type specific differences in the cell contact architecture and the distribution of sites for virus budding and release [37,38]. Mechanistic details of Gag polarization and virus release at the cell-cell interface comes from a recent study of the immunological synapse [39]. Electron microscopy of cell contacts between T cells and antigen presenting cells revealed the formation of numerous microvesicles at the contact center and transfer of TCR-containing vesicles. The endosomal sorting complexes required for transport (ESCRT) machinery components tumor susceptibility gene 101 (Tsg101) and vacuolar protein sorting-associated protein 4 (Vps4) were essential for cargo sorting and microvesicle scission from the plasma membrane, respectively. Strikingly, the HIV polyprotein Gag was shown to co-opt this pathway for Env-independent budding at the cell-contact site with TCR ligation-directed

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polarization. This study indicates that HIV can spread between immune cells by exploiting the fundamental properties of the immunological synapse for material transfer to other cells.

Virus transmission through trans-infection

Technological advances in microscopy, such as time-lapse confocal microscopy and electron tomography, have enabled researchers to gain insight into the organization of infectious synapses during virus trans-infection. Monocyte-derived DCs (MDDCs) were observed to bind HIV particles in vitro and subsequently form infectious synapses with virus receptor-expressing T cells [9,40]. Virus particles are attached to or internalized into virus-containing compartments by MDDCs through the interaction with C-type lectins [41,42] on immature MDDCs or the I-type lectin CD169/Siglec-1 on mature MDDCs [43–47]. CD169-dependent trans-infection of HIV and MLV has also been observed in macrophages and monocytes [15,48–50]. After the cell contact is initiated, reorientation of the virus-containing compartment to the contact site is accompanied by an accumulation of cellular receptors and cell adhesion molecules to form long-lasting contacts for virus transfer [9,41,51,52]. The cortical actin cytoskeleton and membrane sorting pathways facilitate virus transmission to target cells [40,53–55]. Sheet-like dendrites that are derived from the plasma membranes of MDDCs form a shielded cell contact region. Within this microenvironment, filopodia protrusions emanating from CD4+ T cells make contact with HIV particles within surface-accessible virus-containing compartments for infection [40,56]. Live cell microscopy confirms the highly dynamic nature of infectious synapses [51]. The distinction of virus cell-to-cell transmission into virological synapses largely observed in T cells and trans-infection routes mediated by antigen-presenting cells can also be more blurred. Certain HIV isolates are able to productively infect macrophages [57–59]. In addition, macrophages can engulf HIV-infected T cells that lead to their efficient infection and subsequent virus cell-to-cell spread [60,61].

Transmission of non-enveloped viruses

The concepts of contact-dependent virus transmission have been developed for enveloped viruses that bud from cellular membranes. The general belief that non-enveloped viruses are exclusively released as a consequence of cell lysis (Fig. 1D) has recently been challenged [62]. HepA, HepE, and poliovirus were shown to escape from intact cells by acquiring a temporary membrane (Fig. 1E) [63–66]. Older reports demonstrate the non-lytic release of poliovirus and SV40 from the apical side of polarized cells without loss of cell viability [67,68]. Mechanistically, the autophagic pathway and the ESCRT machinery have been identified to play a role in temporary membrane acquisition and non-lytic release of some non-enveloped viruses [64,66,69–71]. With the recent observations of non-lytic, polarized release, future studies should explore if contact-dependent cell-to-cell transmission plays a role in the spread of non-enveloped viruses (Fig. 1F).

Benefits of cell-to-cell transmission for virus pathogenesis

Multiple studies suggest that contact-dependent transmission provides advantages for virus spread and thus play a role in pathogenesis. Early studies demonstrated that cell contact-

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dependent transmission can be orders of magnitude more efficient than infection through cell-free virus [72,73]. A comprehensive study comparing HIV cell-to-cell and cell-free transmission shows that contact-dependent spread of HIV is the result of specific donor and target cell features [74]. Contact-dependent HIV infection has been shown to overcome multiple barriers to cell-free virus that were experimentally imposed on the donor or target cell. For example, poor virus transmission rates because of low receptor expression levels or cellular restriction factors are compensated by cell-to-cell but not cell-free infection [74–77]. Contact-dependent virus transfer across virological or infectious synapses also enables viruses to evade certain neutralizing antibodies [47,74,78–81]. Several studies found that cell-to-cell transmission of HIV resulted in a higher proviral content of infected target cells [74,82,83]. As a result, HIV-1 was able to overcome individual anti-retroviral drugs but not combinations of drugs through cell-to-cell transmission suggesting that the ability to suppress high viral multiplicity of infection is a feature of effective ART [84,85]. Interestingly, high multiplicity of infection results in bystander death through apoptosis and/or pyroptosis of the target cell, an effect that required HIV cell-to-cell transmission [86–89].

Virus transmission in vivo

In vitro studies of virus cell-to-cell transmission, discussed above, have revealed many basic insights and mechanistic details of virus transmission. However, to what extent these processes contribute to virus spread in vivo remains largely unclear. Live animal and tissue explant studies are essential for our understanding of virus spread and the development of antiviral strategies. Similar to the impact that time-lapse confocal microscopy had in visualizing virus transmission in tissue culture, intravital imaging techniques such as in vivo bioluminescence imaging and multi-photon microscopy are now opening up new avenues to follow virus dissemination directly in living animals.

Systemic virus spread by cell-free virus and migratory cells

Only few studies have started to address how viruses spread within complex tissues of living organisms. Many viruses enter the host at mucosal surfaces or skin and subsequently spread based on their cell tropism to different tissues for replication and host-to-host transmission. This systemic dissemination is closely linked to the physiology of the host as most tissues are connected through a system of extracellular fluid consisting of interstitial fluid, lymph and blood [90]. The interstitial fluid surrounds all cells of a tissue and provides essential nutrition as well as environmental cues necessary for survival. It originates from capillary-filtered blood plasma and, thus, has a similar composition. After leaving the tissue, interstitial fluid is collected in primitive vessels of the lymphatic system that become larger and more complex. The collected interstitial fluid is thereafter named lymph. Large lymphatic vessels collect lymph from various areas of the body and drain into the systemic blood circulation at the subclavian veins to close the loop.

The systemic flow and the positioning of lymphoid tissue along vessels permit tissue surveillance by the immune system to protect against pathogens and provide a network for immune cell migration. However, the continuous flow of extracellular fluid also provides an

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efficient system for viruses to spread over long distances within the host. Under experimental conditions simulating virus transmission through arthropod vectors, scratching or wounding during biting, several subcutaneously injected cell-free viruses arrived through the afferent lymph within minutes at tissue-draining lymph nodes to infect immune and neuronal cells (Figure 2A) [91–97]. Consequently, cell-free virus spread after budding from an infected cell in peripheral tissue is by all means realistic although it has not been directly shown in vivo.

An alternative pathway for virus long-distance spread is through migratory cells. Productively infected cells can function as vehicles and, thus, contribute to systemic virus dissemination. HIV-infected T cells were shown to exit peripheral lymph nodes and significantly contribute to the systemic infection of humanized mice (Figure 2A and 2B, box 4) [98]. Blocking leukocyte egress from lymphoid tissue in HIV-infected humanized mice significantly reduces virus dissemination [98]. Similarly, mouse cytomegalovirus-infected blood monocytes can disseminate virus from local infection sites to salivary glands and promote latency [99].

Finally, based on their described function in antigen delivery to draining lymph nodes [100,101], mucosal tissue DCs are suspected of transporting viruses such as HIV and varicella zoster virus to draining lymph nodes for infection of T cells [102]. A clear contribution of this pathway to virus dissemination in living animals remains to be determined.

Cell-to-cell transmission of lymph-derived virus in lymphoid tissue

Cell-free virus is transported via extracellular fluid until it reaches a susceptible cell population. Physical barriers at the fluid-tissue interface restrict virus access to target cells localized within tissues. For example, secondary lymphoid tissues such as lymph nodes are designed to efficiently filter the lymph (Figure 2A). Only small molecules (<70kDa, <5nm) can passively enter the lymph node interior through conduits for direct contact with immune cells [103–105]. Larger particles remain in the lymph or interact with immune cells at the interface. The cell sieve between the lymph node sinus and cortex is organized by a layer of tissue-specific resident macrophages and lymphatic endothelial cells that play an important role in the immune surveillance of the lymph [106,107]. Sinus-lining macrophages can capture pathogens to block their systemic spread, present immune complexes to immune cells and orchestrate immune responses by recruiting effector cells to the subcapsular sinus (SCS) floor [108]. Analogue tissue architecture is found at the marginal zone in the spleen and allows the body to similarly survey the blood [109].

Viruses have evolved mechanisms to overcome this barrier and access host tissue for the infection of permissive lymphocytes in the subjacent tissue. Fluid-derived retroviruses MLV and HIV are filtered by sinus-lining macrophages of the draining lymph node and spleen in vivo (Fig. 2B, box 1) [15]. Virus capture is mediated by the I-type lectin CD169 through the recognition of gangliosides within the retrovirus membrane [15], as previously demonstrated in vitro [43–46]. As such, retroviruses appear to exploit the inherent function of CD169+ macrophages to capture exosomes that similarly carry gangliosides [110,111]. MLV was found in deep plasma membrane invaginations of SCS macrophages in vivo as has been

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observed previously in monocyte-derived DCs and macrophages in vitro [47,51,112–114]. Using intravital microscopy, MLV transfer from SCS macrophages to B1 cells could be directly visualized [15]. After trans-infection, B cells formed Env-dependent virological synapses with susceptible cells in vivo to amplify the infection (Fig. 2B, box 3) [15,115]. These studies suggest that viruses could use fluid-based spread for long-distance travel followed by the exploitation of CD169-mediated capture of viral particles for efficient trans-infection of permissive lymphocytes for subsequent spreading in lymphoid tissues.

In addition, the complement system might facilitate virus tissue access and subsequent transport within tissue. Lymph-derived HIV particles accumulate on follicular dendritic cells in B cell follicles of lymph nodes (Fig. 2B, box 2) [116,117]. Interestingly, the transport of lymph-derived HIV particles into B cell follicles is species independent and occurs in the absence of HIV-specific antibodies [117,118]. Mechanistically, HIV was shown to fix complement factors such as C3 on its surface to mediate cell binding through complement receptor 2 (CD21) [119–122]. CD21-expressing B cells and follicular dendritic cells can bind complement-opsonized HIV for transfer to T cells in vitro [120,123,124]. Blocking of CD21 interferes with HIV accumulation on follicular dendritic cells and B cells in vitro and in vivo [123–125]. Similar transport pathways were recently described for immune complexes, vesicular stomatitis virus and soluble HIV gp120 [126–129]. After B cell-mediated transport, immune complexes are retained intact on follicular dendritic cells within a periodically cycling compartment for long-term antigen presentation [130]. Similarly, the follicular dendritic cell network in B cell follicles can store HIV particles for a long time and, thus, is considered to function as a reservoir [116–118,131]. Since follicular dendritic cells lack CD4 expression and are not infected by HIV [124], they transmit HIV to susceptible T cells via trans-infection, a process that may also occur in vivo (Fig. 2B, box 2).

Conclusions

In vitro studies of virus transmission have been fundamental to characterize the mechanism of virus cell-to-cell spread between defined cell types. Visualization of retrovirus cell-to-cell transmission helped to define the basic concepts of the virological and infectious synapse, and provided dynamic subcellular details about the individual steps of synapse formation and transfer. Importantly, the results of in vitro studies set the stage for the challenging task to study virus spreading in living animals. Initial in vivo studies have revealed how local and systemic virus transmission is critically influenced by the tissue physiology. The mechanism of virus transmission is shaped by the tissue context and influenced by physical barriers such as the fluid-tissue interfaces (lymph/lymph node, blood/spleen), local cell populations with limited exchange with the systemic cell pool or spatially restricted cell migration and cell-cell interaction. In vivo studies will be critical for the understanding of viral transmission since each tissue is a composite of specific cell subsets that depend on tissue specific cues from neighboring cells for cell development, homeostasis and function that can often not be reconstituted in vitro. Continued advances in in vivo imaging technologies together with high-resolution in vitro imaging studies will continue to provide critical insights into the mechanism of virus spread and how this knowledge can be harnessed for antiviral strategies that interfere with virus dissemination.

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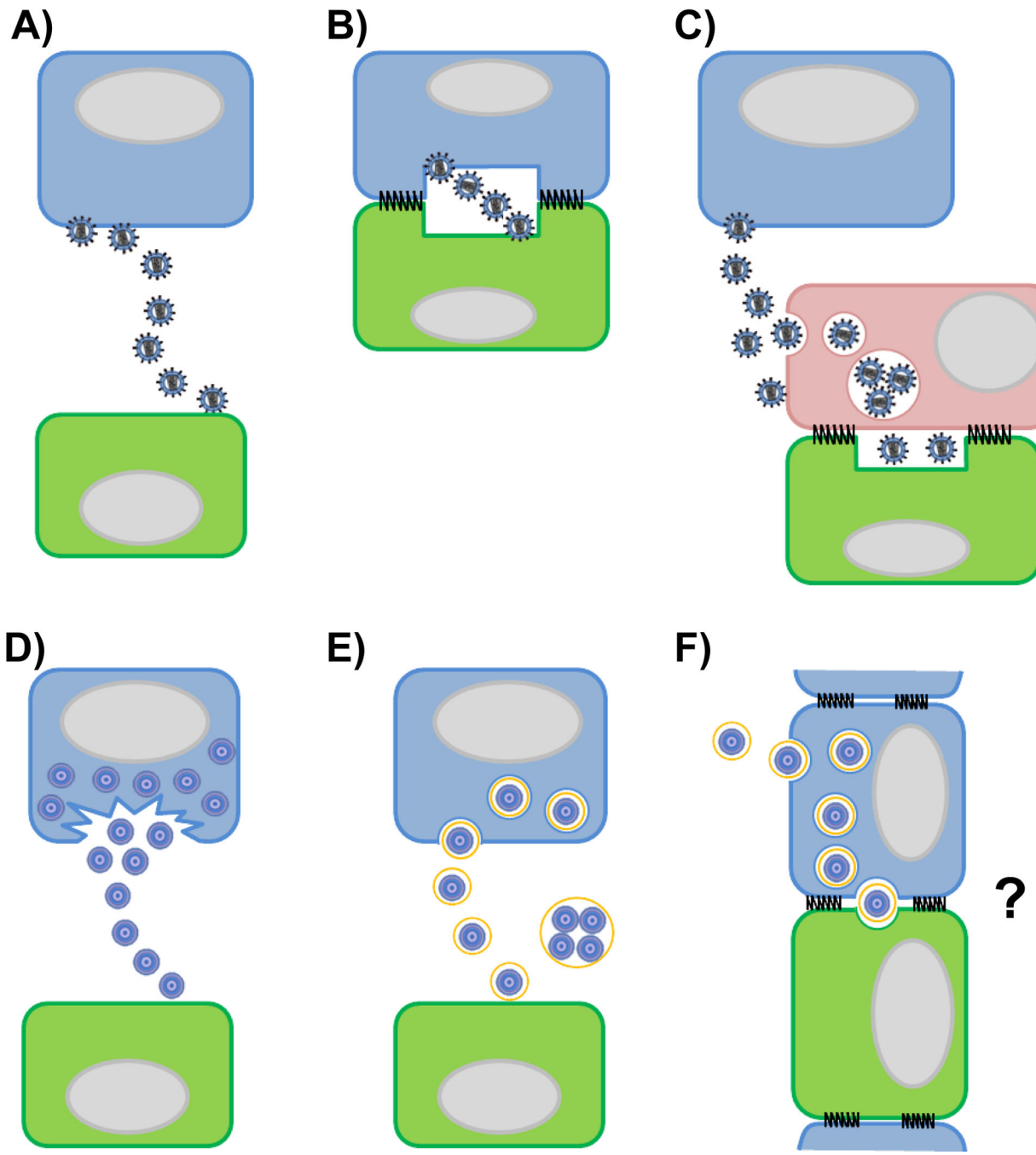

Fig. 1.

In vitro pathways of virus cell transmission. (**A–C**) Enveloped viruses have evolved with the host cell to efficiently spread from an infected cell (depicted in blue) to a non-infected cell (depicted in green). Cell-free transmission of enveloped viruses by diffusion through the extracellular environment after budding from an infected cell (A). Productively infected cell transfer virus particles across a virological synapse for cis-infection (B). For trans-infection, cell-free virus particles are captured by a cell that itself does not get infected (depicted in pink) and then presented to a target cell at a cell-cell contact designated infectious synapse

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(C). (**D–E**) Non-enveloped viruses can be released from an infected cell after cell-lysis (D) or non-lytically by acquisition of temporary host membrane to infect susceptible target cells via cell-free transmission (E). Panel (**F**) depicts a hypothesis for cell-to-cell transmission of non-enveloped viruses with acquired host membrane after polarized release at cell contact sites. Grey ovals represent cell nuclei.

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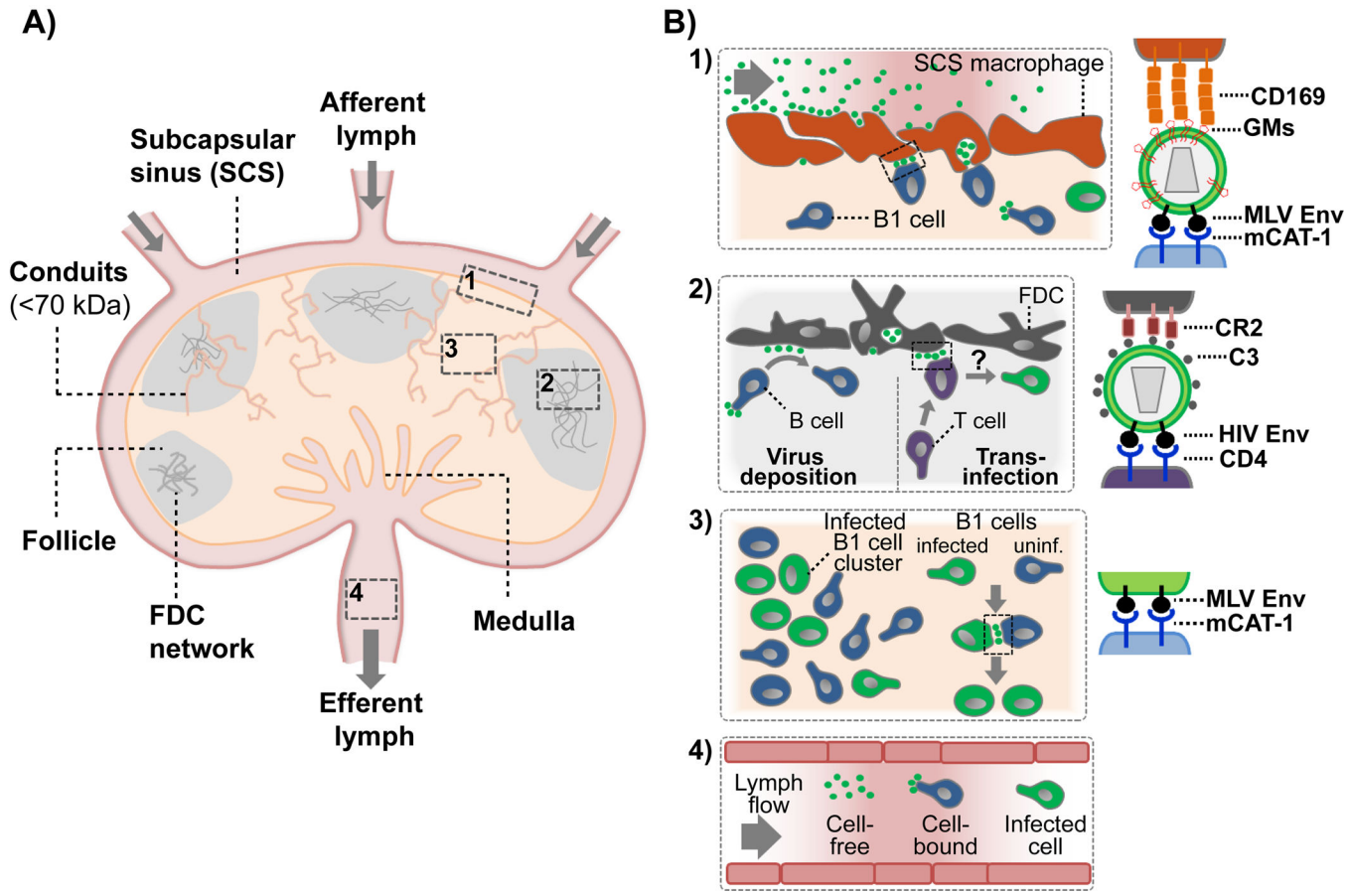

Fig. 2.

Model depicting the structural organization of a lymph node (A) and in vivo pathways of virus transmission (local tissue, systemic) (B). (**A**) Lymph arrives at draining lymph nodes through afferent lymphatic vessels and enters at the lymph node subcapsular sinus (SCS). Small molecules (<70 kDa) access the lymph node cortex via conduits for subsequent filtration by immune cells [98–100]. Sinus-lining macrophages and DCs surveil the lymph for antigen, immune complexes and pathogens. Filtered lymph is collected at the medulla and leaves the lymph node through the efferent lymphatics to enter secondary lymph nodes. B cell follicles with a stromal cell network of follicular dendritic cells (FDC) are in close contact with the SCS floor. Examples of in vivo virus transmission (Boxes 1–4) are summarized in (B). (**B**) Pathways of retrovirus transmission within lymphoid tissue and for systemic spread. (1) CD169-expressing SCS macrophages capture lymph-derived MLV and HIV by recognition of gangliosides (GMs) embedded in the virus lipid bilayer. In the case of MLV, SCS macrophages then form stable contacts with MLV receptor (mouse cationic amino acid transporter-1, mCAT-1) expressing B-1 cells to trans-infect these cells. (2) B cells can deposit HIV particles on FDCs within B cell follicles for subsequent trans-infection of T cells. Binding depends on the complement protein C3 and complement receptors 2 (CR2). (3) MLV-infected B1 cells are found in clusters within infected popliteal lymph nodes. Infected cells form mCAT1-dependent virological synapses with uninfected cells. (4)

Long-distance spread of HIV within the lymph can be mediated by either cell-free, cell-bound or migration of HIV-infected cells. Viruses are depicted as green spheres.

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