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Minireview

Nature, nurture and HIV: The effect of producer cell on viral physiology

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ABSTRACT

Macrophages and CD4-positive T lymphocytes are the major targets and producers of HIV-1. While the molecular details underlying HIV replication in macrophages and T cells become better understood, it remains unclear whether viruses produced by these target cells differ in their biological properties. Recent reports suggest that HIV virions incorporate a large number of producer cell proteins and lipids which have an effect on subsequent viral replication in newly infected cells. The identity and abundance of these incorporated factors varies between different types of producer cells, suggesting that they may influence the replication capacity and pathogenic activity of the virions produced by T cells and macrophages.

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Background

Two types of immune cells, macrophages and CD4+ T lymphocytes, are the major targets of HIV-1 in the body. Although a number of other cells, including monocytes, dendritic cells, CD8+ T lymphocytes, endothelial cells, hematopoetic stem cells, and astrocytes have been reported to harbor HIV provirus (Lunardi-Iskandar et al., 1989; Tsubota et al., 1989; De Maria et al., 1991; Langhoff et al., 1991; Langhoff and Haseltine, 1992; Steffan et al., 1992; Moses et al., 1993; Monte et al., 1992; Carter et al., 2010; Churchill et al., 2009), virus replication in these cell types is inefficient or abortive and is unlikely to contribute to viral population in vivo. Early reports divided HIV-1 phenotype into macrophage-tropic and T cell-tropic, with an underlying idea that macrophages express CCR5, but not CXCR4, and are therefore subject to infection by R5, but not X4 HIV-1 isolates, whereas most CD4+ T cell populations express CXCR4 (only memory T cells express CCR5) and are therefore sensitive to X4 HIV-1 isolates (reviewed in Mosier (2000)). These ideas started to change when it became clear that CXCR4 is expressed on macrophages (Zaitseva et al., 1997; Yi et al., 1998; Verani et al., 1998), and that macrophage tropism is determined not only at entry, but also at post-entry steps of infection (Schmidtmayerova et al., 1998; Duncan and Sattentau, 2011). Furthermore, naturally transmitted HIV-1 viruses are almost exclusively R5-tropic yet their primary targets are T cells and not macrophages (Keele et al., 2008). In fact, macrophage tropism of R5 viruses is most pronounced in a subpopulation of viruses found in CNS, where they infect and replicate in microglial cells, whereas some X4 and dual-tropic viruses in the periphery efficiently infect macrophages via CXCR4 (Gorry and Ancuta, 2011). It becomes clear now that genetically identical viruses can replicate in macrophages and T cells, although the activity of distinct viral genes can differ between host cell types due to the differing cell environment, including the spectra of host proteins, regulation of host gene expression, and size and organization of subcellular compartments. As a result, viruses produced by macrophages and T cells can be genetically identical, but they may incorporate different host cell proteins. These proteins may not only favor infection of a particular cell type, but may also determine the efficiency of viral replication and, therefore, viral pathogenesis. The role in HIV replication of host cell proteins that associate with the plasma membrane and are incorporated into HIV-1 virions as part of the viral envelope has been reviewed previously (Kolegraff et al., 2006). In this article, we will update this information, but will pay most attention to proteins incorporated from producer cell into the cores of nascent virions, focusing on the proteins that vary amongst the primary producer cells, T cells and macrophages.

Assembly pathways influence the spectrum of virion-incorporated host-cell proteins

Incorporation of host cell proteins into nascent virions occurs during virus assembly and budding. The spectrum of these proteins

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depends on the cellular compartments and organelles that the virions associate with during assembly, and on the abundance of particular proteins in these compartments. The assembly process is primarily driven by HIV-1 Gag (Ono, 2009; Accola et al., 2000) and exploits the endosomal sorting complex required for transport (ESCRT) pathway for the cellular membrane remodeling and budding of the virions ((Demirov et al., 2002; Garrus et al., 2001; von Schwedler et al., 2003; Martin-Serrano et al., 2003; Martin-Serrano and Neil, 2011; Weiss and Gottlinger, 2011), for a recent review see Meng and Lever (2013)). Whereas analysis of the virion assembly in the T lymphocytes and model epithelial cells and fibroblasts indicated plasma membrane as a primary cellular site of HIV particle assembly and budding (Perez-Caballero et al., 2004; Ono and Freed, 2004; Finzi et al., 2007), the electron microscopy and immunofluoresent microscopic studies of infected macrophages revealed accumulation of virions within intracellular compartments—the late endosomes or multivesicular bodies (MVB) (Pelchen-Matthews et al., 2003; Raposo et al., 2002; Jouve et al., 2007). In fact, the typical endosomal markers CD63, CD9, CD81 and MHC class II, as well as lysosome-associated membrane protein-1 (Lamp1), were found to co-localize with HIV-1 particles in infected macrophages (Pelchen-Matthews et al., 2003; Nguyen et al., 2003; Raposo et al., 2002; Welsch et al., 2007). These data suggested that in macrophages Gag specifically targets the endosomal membranes resulting in particle release into the lumen of late endosomes. However, later study showed that the endosomal localization of the Gag molecules and HIV-1 virions in macrophages could be a result of their secondary internalization from the plasma membrane (Jouvenet et al., 2006). Recent studies of HIV-1 infected macrophages revealed an extensive tubular network and large internally sequestered plasma membrane domains that carry late endosomal markers but are connected to the cell surface. These structures contained HIV-1 virions that were released into the extracellular space (Welsch et al., 2007; Deneka et al., 2007; Gousset et al., 2008; Bennett et al., 2009). These findings explain the contradiction between the accumulation of HIV-1 particles in intracellular membranous compartments and the primary targeting of HIV-1 particle assembly to the plasma membrane. The consensus now is that the virus particle assembly pathway is similar in both major types of natural HIV-1 target cells, CD4+ T lymphocytes and macrophages, and virus exploits the same key host proteins and protein ensembles for the assembly and release. Nevertheless, differences in the gene expression spectra between the T cells and macrophages, as well as host proteins associated with HIV-1 assembly and budding, can impact protein composition of the progeny virions.

The effect of differences between producer cell types on host cell proteins incorporated into progeny virions is illustrated by comparison of recent proteomic data (Chertova et al., 2006; Stephenson et al., 2010; Santos et al., 2012; Bregnard et al., 2013). While a large number from over a 1000 identified proteins overlap between these studies, there were also differences, most likely due to different producer cells used to prepare virions. Our analysis of the cores of HIV-1 virions produced from T lymphocytes (Sup-T1 cells) and macrophage model cells (PMA and vitamin D3 activated THP-1 cells) revealed two-fold higher amount of the vesicular trafficking-associated proteins in the macrophage-derived HIV-1 cores than in the cores of virions produced from T cells (Santos et al., 2012). This is consistent with the mode of virion assembly in macrophages, as assembly in intracellular compartments is expected to lead to more vesicular-trafficking proteins being incorporated. The cytoplasm of macrophage model cells also contained higher abundance of actin and β tubulin than Sup-T1 cells. Our data also confirmed that the amount of β tubulin in the viral cores correlated with the concentration of this protein in the producer cells, suggesting passive capturing, but not specific incorporation (Santos et al., 2012). Therefore, it appears that most cytoskeletal proteins are passively incorporated into the nascent virions. Identifying which ones actually exert an effect on the viral life cycle and alter the replication of progeny virions remains a challenging task.

A number of host cell factors interact specifically with assembling HIV particles. In this case, incorporation into the virion is less dependent on the abundance of these proteins in one or the other type of producer cell. An example of such proteins is cyclophilin A, which is packaged in association with the viral capsid into the virions produced by both primary lymphocytes and macrophages in similar amounts (Saini and Potash, 2006). Virion-incorporated CypA appears to provide only a small advantage to HIV replication (Pushkarsky et al., 2001), which is regulated mostly by target cell cyclophilin (Sokolskaja et al., 2004; Schaller et al., 2011). However, it is also possible that even host cell factors specifically interacting with assembling HIV particles must meet a certain concentration threshold to be incorporated in sufficient amounts to have physiological effect, thus contributing to differences between progeny virions from different producer cells.

Virion incorporation of Host cell proteins from HIV-1 infected T lymphocytes and macrophages and their role in the next round of infection

While many virion-incorporated host cell proteins do not contribute to host cell tropism of the progeny virus, some producer cell proteins may be involved in the post-entry stages of HIV-1 infection. As we saw in the previous section, diverse expression profiles and different localization of virion assembly units in T lymphocytes and in macrophages determine differences in the spectra of virion-incorporated proteins.

Incorporation of some host cell proteins, such as staufen 1, RNA helicase A (RHA), INI1/hSNF5 and SAP18, a component of the Sin3a-HDAC1 complex, which are involved in the virion assembly, maturation or in the next round of infection, has been demonstrated only in virus or virus-like particles produced by HEK 293T or HeLa cells (Chatel-Chaix et al., 2008, 2007; Roy et al., 2006; Bolinger et al., 2010; Xing et al., 2011; Yung et al., 2004; Sorin et al., 2009). However, for some cellular factors playing an important role in HIV-1 replication, the differences in incorporation were shown for physiologically relevant cell types, and we will describe these factors below.

Annexin II

Enrichment of myeloid cells with some cellular proteins that are not present or are low-abundant in lymphocytes determines the spectrum of cellular proteins found in HIV-1 virions derived from macrophages. It has been shown earlier that a calcium and phospholipid-binding protein annexin II involved in regulation of exocytosis and abundant in macrophages, facilitates early steps of infection in macrophages, but not in T cells (Ma et al., 2004; Wahl et al., 2006). This cytoskeleton- and membrane-associated protein directly binds to Pr55Gag, and inhibition of this interaction during the assembly stage in macrophages decreases infectivity of progeny virions. This interaction is macrophage-specific as PBLs do not express annexin II. It was demonstrated that annexin II affects replication in macrophages by organizing the specialized lipid rafts that are optimal for Gag assembly on endosomal membranes (Ryzhova et al., 2006). It should be noted here, that later studies reported that depletion of annexin II does not affect the production of virions in macrophages, but regulates infectivity of produced virions (Rai et al., 2010). Taken together, these data suggest that annexin II is specifically incorporated into virions produced by

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