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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.

Keywords

HIV-1; T lymphocytes; macrophages; virion-incorporated proteins; virion-incorporated lipids; viral replication

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 A. 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, and 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

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Author's contributions
MB conceived the manuscript and was responsible for organizing the content. SI and SS wrote the manuscript. SI was responsible for the selection of materials and structure of the manuscript. All authors read and approved the final manuscript.

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, and 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, and 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 factors incorporated from producer cell into the cores of nascent virions, focusing on the factors 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 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, and 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, and 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, and 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, and 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, and 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, and 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, due to differing concentrations among producer cells, 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 quantity 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, and 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, Chatel-Chaix et al., 2007, Roy et al., 2006, Bolinger et al., 2010, Xing et al., 2011, Yung et al., 2004, and 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, and 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 myeloid cells and is necessary for viral replication in macrophages, but is dispensable for replication in other cell types.

Nuclear Uracil DNA Glycolase (UNG2)

UNG2 comes into virions in association with Vpr (Willetts et al., 1999, and Chen et al., 2004) and integrase (Priet et al., 2003). Earlier studies showed a critical role of UNG2 in a decrease of virus mutation frequencies in target cells, but primarily in macrophages, where UNG2-mediated suppression of mutation rate was almost fivefold higher than in T cells (Chen et al., 2004). Later reports demonstrated that only the R5 virions produced from UNG2-depleted PBMCs and MDM exhibited low level of late cDNA synthesis, whereas the X4 isolates did not display dependence on the endogenous UNG2 during infection of both PBMCs and macrophages, suggesting that the UNG2 activity in reverse-transcription complexes may depend on the activation of signaling pathways in response to HIV-1 envelope-co-receptor binding (Jones et al., 2010). However, recently published data demonstrated that enforced recruitment of UNG2 from virus-producing cells into the virions similarly influenced infectivity of X4 and R5 HIV-1 strains in both transformed cell lines (293T, HeLa-CD4) and primary macrophages (Guenzel et al., 2012). Moreover, the authors showed that the decrease of a mutation rate and more efficient reverse transcription in the viruses with incorporated nuclear form of UNG2 were independent of the enzymatic activity of UNG2 (specific removal of the uracil residues from DNA). The possible mechanism of positive effect of UNG2 lies in its interaction with the p32 subunit of the replication protein A (RPA) complex, which is functional in both T cells and macrophages (Guenzel et al., 2012). Therefore, it appears that virion-incorporated UNG2 is required for HIV infectivity in both target cell types.

ERK2

Studies of another virion-associated host cell protein, ERK2, demonstrated its involvement in phosphorylation of inner nuclear lamina protein emerin (EMD) during viral replication in

non-dividing cells (Jacque et al., 1998, and Bukong et al., 2010), suggesting that ERK2 incorporation may facilitate infection of terminally differentiated macrophages and resting T cells. It should be noted that conflicting data exist regarding the role of Barrier to Autointegration factor (BAF) and other nuclear lamina proteins in HIV infection of non-dividing cells, with some groups stating their requirement, while others finding these proteins dispensable (Bukong et al., 2010, Bergamaschi and Pancino, 2010, and Mulky et al., 2008). Most likely, these contradictory data are due to different growth conditions and the proliferation status of the cells. Therefore, the effect of ERK2 expression in the producer cell on infectivity of progeny virions and possible phosphorylation targets in the newly infected cell remain to be determined.

Chaperones

Such cellular proteins as clathrin, thioltransferase, and heat shock protein 70 (HSP70), that are probably involved in organization of virion interior, regulation of viral protease activity, and correct folding of the Pol products, were found to be abundant in the highly infectious viral particles produced from infected T cell lines (CEMX174 and MT2, H9, Jurkat), whereas virions harvested from transfected HEK 293T cells displayed a lower level of packaging of these factors (Zhang et al., 2011, Davis et al., 1997, and Gurer et al., 2002). Our recent proteomic analysis revealed a higher diversity of the host proteins in the cores of T cell-derived virions, than in the core structures of viruses produced by the macrophage model cells (PMA and vitamin D3 activated THP-1) (Santos et al., 2012). Moreover, within the group of proteins detected in the cores of virions from all cells types, the incorporation rate of some factors involved in reverse transcription (RHA (Roy et al., 2006, and Xing et al., 2011)) and cDNA nuclear import and circularization (Ku70/Ku80 (Li et al., 2001, and Jeanson et al., 2002)) was higher in the viral cores from T cells than in the cores from both macrophage and monocyte model cells, and did not correlate with the abundance of these proteins in virus producing cells, suggesting their specific incorporation into the viral cores produced in T cells. These data suggest that the higher abundance and variety of host cell factors in the cores of T cell-derived viruses, as well as earlier observed cholesterol enrichment of the viral envelope (Cui et al., 2012), together facilitate higher infectivity of the T lymphocyte-derived viruses relative to viruses produced by macrophages.

Membrane proteins

Several membrane proteins (HLAs, CD80, CD86 and ICAM-1) have been shown to increase HIV-1 infectivity via enhanced attachment to the target cell (Cosma et al., 1999, Cantin et al., 1997b, Cantin et al., 1997a, and Fortin et al., 1997) reviewed in (Cantin et al., 2005), suggesting that differential incorporation of these proteins may affect HIV-1 infectivity. Of interest, one recent study of Human Discs Large (Dlg1), a scaffold protein located beneath the plasma membrane and involved in the assembly of multiprotein complexes, showed that in T cells Dlg1 binds HIV-1 Gag, and depleting Dlg1 leads to progeny virions with increased infectivity, supposedly due to re-localization of Gag to membrane structures enriched in tetraspanins CD63 and CD82 (Perugi et al., 2009). However, tetraspanin-enriched microdomains of the plasma membrane are normal sites of HIV-1 assembly and budding (Thali, 2009), and another study demonstrated that when CD63 was excluded from HIV-1 producing T cells after T cell activation, infectivity of released virions was increased (Sato et al., 2008), suggesting an inhibitory effect of this protein on HIV infectivity. Consistent with this notion, CD63 was shown to inhibit viral entry via HIV-1 Env, and this mechanism of inhibition was demonstrated across tetraspanins (CD9, CD81, CD82, CD231) (Sato et al., 2008, Krementsov et al., 2009, and Weng et al., 2009, reviewed in Thali, 2011). Of particular interest is that this inhibition appears to be strain-specific, occurring only in T-tropic viral strains of NL4-3 and IIIB, and not in the M-tropic strain of JR-FL (Sato et al., 2008). These data allowed speculation that M-tropic strains overcame this tetraspanin

inhibition, possibly due to virions' unique assembly location within macrophages. Further studies into tetraspanins' mechanism of action will probably determine precisely how these membrane proteins affect HIV infectivity, from potential virion benefits of properly assembling in tetraspanin rich microdomains to the post-attachment inhibitory mechanisms of tetraspanins seen in target cells.

Helicases

Most recently, the role of RNA helicases in HIV-1 infection has come under intense investigation, with the revelation of a multitude of helicases involved in the various stages of the HIV-1 life cycle. The best characterized functions of RNA helicases are at the stages of RNA processing and gene expression, with DDX3 and DDX1 facilitating REV export of viral RNA and UPF1 up-regulating HIV-1 expression (Yedavalli et al., 2004, Liu et al., 2011, and Ajamian et al., 2008). Some helicases down-regulate HIV-1 expression (e.g. Dicer, RIG-1, MOV10, (Christensen et al., 2007, Burdick et al., 2010, and Arjan-Odedra et al., 2012) reviewed in (Lorgeoux et al., 2012). The endogenous expression of any one or combination of these helicases would modulate the overall virion production in the producer cell and, probably, affect the next round of infection if these functionally active proteins are packaged into the virions. Given that their potential activity within the target cell is aimed at viral RNA or cDNA located within the same nucleoprotein complex, the amount of helicase molecules required to exert an effect on viral reverse transcription or integration does not need to be very large. Thus, cell-type differences in the expression of these RNA helicases and their incorporation into the virions should be looked into further for their possible roles in establishing latent or productive infections.

Mentioned briefly above, RHA plays a role in facilitating more efficient reverse transcription (Roy et al., 2006, and Xing et al., 2011). Although this effect was established only within an artificial model, it would still be interesting to understand it from a mechanistic point of view. Another RNA helicase, MOV10, has sparked some interest because of its restrictive capabilities towards HIV-1 infection within T cells. It has been shown that, similar to APOBEC3G, a well-characterized HIV-1 restriction factor that hypermutates HIV-1 cDNA during reverse transcription and is incorporated into the virions through combined action of RNA binding and interaction with NC (reviewed in (Malim and Bieniasz, 2012)), MOV-10 is incorporated into HIV-1 virions via interaction with Gag and NC (Burdick et al., 2010). However, how this RNA helicase restricts HIV-1 infection at the post-entry steps remains to be revealed.

We detected a significantly higher level of incorporation of subunits 3 and 5 of another important cellular replicative helicase, , the hexameric MCM2–7 complex, into the cores of T cell-derived virions, relative to cores of virions produced from macrophage or monocyte model cells (Santos et al., 2012). Interestingly, knockdown of MCM3 and 5 monomers in virus-producing cells resulted in generation of MCM-deficient viral particles which displayed reduced level of reverse transcription in Jurkat and Sup-T1 cells (unpublished data), suggesting that this cellular factor incorporated into the viral cores can be involved in control of viral reverse transcription.

Hijacking of cholesterol by HIV-1 virions from virus-producing T cells and macrophages determines differences in virus infectivity

Our group previously demonstrated that HIV-1 infection, through the effect of Nef protein, inhibits ABCA1 and cholesterol efflux in target cells to ensure delivery of cholesterol to nascent virions during assembly (Mujawar et al., 2006). We also showed that pharmacological stimulation of expression of ABCA1, the main cellular cholesterol

transporter responsible for the efflux of cholesterol and phospholipids to lipid-poor apolipoproteins, inhibits HIV-1 infectivity by depleting viral cholesterol (Morrow et al., 2010). An intriguing consequence of these findings is that HIV infectivity may be influenced by the natural level of ABCA1 expression in infected cells. When ABCA1 levels are compared between monocyte derived macrophages (MDM) and CD4+ T lymphocytes, significant differences can be observed. Although ABCA1 abundance in both cell types can be increased by an agonist of nuclear receptor LXR, which regulates ABCA1 transcription, there is a dramatic difference in the level of ABCA1 expression. Unstimulated peripheral blood leukocytes (PBL) have undetectable levels of ABCA1, whereas ABCA1 in MDM can be easily detected by Western blot, even without stimulation of LXR (Cui et al., 2012). Infectivity of HIV-1 produced by these cells correlated perfectly with the level of ABCA1 expression: when measured in the indicator cell line TZM-bl, infectivity of the virus produced by “high ABCA1” cell type, MDM, was about 70% lower than of the virus produced by “low ABCA1” cell type, PBL (Cui et al., 2012). Importantly, knock down of ABCA1 in MDM by siRNA brought infectivity of produced virus close to infectivity of the virus produced by PBL. Thus, differences in ABCA1 expression in host cells have a significant effect on infectivity of produced HIV virions, likely through the effect on viral cholesterol and fusogenic capacity of the virus (Morrow et al., 2010). Higher infectivity of T cell-produced virus underscores the central role of these cells as HIV-1 reservoir.

Conclusions

Incomplete and occasionally controversial data about functions of the host proteins in HIV-1 life cycle do not allow clear conclusions regarding the role of virion-incorporated cellular proteins in viral infectivity, cell specificity and efficiency of subsequent replication. Nevertheless, available information suggests that HIV-1 particles assembled in T cells are enriched in both the cholesterol and producer cell proteins relative to virions assembled in macrophages. This may contribute to higher infectivity of T cell-produced virions due to increased fusion capacity and higher efficiency of cDNA synthesis, as well as optimal PIC organization for integration. Recruitment of cellular proteins may also facilitate adaptation of HIV-1 virions to infection of cells of the same type. Indeed, within unique cellular factors identified earlier in the HIV-1 particles from monocyte-derived macrophages and macrophage cell lines, at least five proteins, GTP-binding nuclear protein Ran, importins α2, β1, β2 and transportin-SR2, were involved in the nuclear import machinery (Chertova et al., 2006, and Santos et al., 2012), which is particularly critical for HIV infection of non-dividing cells. Thus, the capacity of virus to infect the cells of a certain type is likely dependent not only on the genotype of an HIV strain, but also on the subset of host components hijacked by the virion from the producer cell (Table 1), representing a non-genetic mechanism of determination of the virus tropism.

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Highlights

- The type of virus producing cell determines the spectra of incorporated host cell proteins
- Host cell factors (proteins and lipids) incorporated into HIV virions modify viral replication capacity
- Proteins incorporated into the HIV core regulate post-entry events in viral replication and contribute to viral tropism

Table 1

Virion-associated host factors.

Factor	Role in viral replication	Enriched in (producer cell type)	Critical for replication in (target cell type)	References
Annexin II	Assists viral assembly	Macrophages	All	Ma et al., 2004, Ryzhova et al., 2006, and Rai *et al.*, 2010
*Cholesterol	Improves fusogenic capacity	Macrophages	All	Cui et al., 2012, Mujawar et al., 2006, and Morrow et al., 2010
Clathrin	Facilitates morphogenesis	T cells	All	Zhang *et al.*, 2011
Dlg1	Restricts infectivity	T cells	All	Perugi *et al.*, 2009
ERK2	Stimulates infectivity	**	Macrophages	Jacque et al., 1998, and Bukong et al., 2010
HSP70	Stimulates reverse transcription	T cells	T cells	Gurer *et al.*, 2002
Ku70/Ku80	Stimulates cDNA nuclear import and circularization	T cells	All	Santos et al., 2012, Li et al., 2001, and Jeanson *et al.*, 2002
MCM helicase	Stimulates RT	T cells	T cells	Santos et al., 2012
Mov10	Unknown, may inhibit RT	T cells	restrictive	Burdick *et al.*, 2010
RHA	Stimulates RT	T cells	All	Santos et al., 2012, Roy et al., 2006, and Xing et al., 2011
Thioltransferase	Regulates protease activity	T cells	All	Davis *et al.*, 1997
UNG2	Reduces viral mutation rate, stimulates RT	**	Macrophages	Chen et al., 2004, Priet et al., 2003, Jones et al., 2010, and Guenzel et al., 2012

*Regulated by differential expression of the host cellular protein ABCA1 within producer cells.

**Similar expression in T cells and macrophages.