frontiers | Frontiers in Virology

EDITORIAL
published: 14 June 2022
doi: 10.3389/fviro.2022.945530

Editorial: Host Immune Responses to Retroviral Infections

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Keywords: retroviruses, immune system, adaptive immunity, immune evasion, restriction factors

Editorial on the Research Topic:

Host Immune Responses to Retroviral Infections

Upon infection, retroviruses reverse transcribe their genome and integrate it into host chromosomes as proviruses; as such retroviruses are one of the greatest threats to the genetic integrity of all cellular organisms. At this point proviruses can hide inside host cells in a latent phase; however, when they are expressed and viral proteins are translated, their presence is recognized by the adaptive immune system. Thus, when inoculated into immunocompetent hosts, retroviruses can be rapidly eliminated and cause no pathology (1). To establish a long enough period of productive infection that allows interindividual transmission, retroviruses must overcome and/or evade host immune responses. Acutely transforming retroviruses overcome immune attacks by inducing rapid proliferation of infected cells, while non-acute retroviruses elaborate several different mechanisms to evade host immune responses and establish persistent infection. These mechanisms work through camouflaging viral particles, suppressing gene expression within infected cells, and inducing central and peripheral immune non-responsiveness. In this Research Topic, four groups of authors provide new insights into the different strategies that retroviruses have developed in the attempt to evade host immune responses and establish persistent infection.

It has been known for a long time that when egressing from infected cells retroviruses incorporate host cell proteins into their envelope (reviewed in 2). This process is not just passive but some particular groups of host cell proteins are selectively incorporated from the plasma membrane into budding virions through interactions with viral proteins. Immunologically relevant examples of host cell proteins that are enriched in retroviral envelopes are MHC proteins, cell adhesion molecules and complement regulating factors (2). Using newly developed technique of flow virometry, Maltseva and Langlois have shown that the incorporation of tetraspanins and lipid raft-associated Thy1.2 and CD45 into Moloney murine leukemia virus (MuLV) particles is influenced by the presence or absence of the viral accessory protein, glycosylated Gag (glycoGag). GlycoGag is unnecessary for *in vitro* replication of MuLVs but is required for their efficient proliferation and pathogenicity *in vivo*, and glycoGag-deficient MuLV revert to glycoGag-expressing ones during *in vivo* propagation and tumorigenesis (3–5). GlycoGag is also implicated in the resistance of reverse transcription to the host restriction factor APOBEC3 (6). Thus, the paper by Maltseva and Langlois suggests that glycoGag may affect MuLV replication and pathogenesis not only through resistance to restriction factors but also by modulating incorporation of host-derived proteins into budding virions.

As described above, non-acute retroviruses must evade host immune responses to establish persistent infection. Results by Higuchi et al. summarize HTLV-1's strategies for evading immune responses,

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Edited and reviewed by:
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Specialty section:
This article was submitted to Virus and Host Immunity, a section of the journal Frontiers in Virology

Received: *16 May 2022*
Accepted: *18 May 2022*
Published: *14 June 2022*

Citation:
Miyazawa M and Clerici M (2022) Editorial: Host Immune Responses to Retroviral Infections. Front. Virol. 2:945530. doi: 10.3389/fviro.2022.945530

especially those mediated by cytotoxic T-lymphocytes (CLTs). Thus, HLTV-1 lets *de novo* infected cells to proliferate through transient expression of highly immunogenic Tax, but during the persistent phase this is replaced by low-level expression of less immunogenic HBZ. Notably, the HBZ mRNA also functions as long non-coding RNA and induces nuclear signals that result in cell proliferation and anti-apoptotic effects. Even more intriguingly, HBZ induces the expression of FoxP3, thus changing the phenotype of infected $CD4^+$ T cells into that of regulatory T cells. By producing the immunosuppressive cytokine IL-10 which is also enhanced by signaling through the immune checkpoint molecule TIGIT, infected T cells evade immune elimination.

MuLVs also evade host CTL responses by inducing immune checkpoint molecules. It has been shown that in mice infected with Friend virus complex (FV), CTLs express multiple immune checkpoint molecules on their surfaces and rapidly become exhausted (7). CTL functions can be restored and the elimination of virus-infected cells facilitated when multiple checkpoints are simultaneously blocked. However, cells expressing ligands of immune checkpoint receptors and their relationship to MuLV infection are not fully understood. In this Research Topic, David et al. show that in acute FV infection granulocytes, monocytes and myeloid dendritic cells increase their cell-surface expression of PD-L1 as well as that of the newly described inhibitory ligand HVEM. Further, $CD8^+$ T cells in FV-infected animals express the HVEM receptors BTLA and CD160, and co-administration of antibodies blocking HVEM and CD160 resulted in an upregulation of viral antigen-specific $CD8^+$ T cells with a consequent reduction of viral load. These results underline the importance of the recently described checkpoint molecule HVEM in allowing immune evasion of MuLV-infected cells.

In addition to immune evasion, retroviruses can also induce central tolerance through their expression in the thymus. It has been shown that infection of immunocompetent adult mice with FV down-regulates the generation of FV-specific T cells as a consequence of thymic infection (8). Further, when expressed as proteins, endogenous retroviruses definitely serve as self-antigens and shape the repertoire of naive T cells (9, 10). Passos et al. examined the expression of human endogenous retroviruses (HERVs) in the thymus and found that developing T cell precursors express HERV mRNA in a stage-specific manner. Further, expression levels of HERVs in non-thymocyte population in the medulla are in good correlation with transcription levels of APOBEC3 restriction factors. These results may suggest unprecedented roles of APOBEC3 in influencing T-cell repertoire shaping.

Thus, papers published in this Research Topic provide new insights into interactions between host restriction factors, viral nonstructural proteins and adaptive immune responses.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.