Retroviral evasion of the immune system

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Retroviruses are unmatched at escaping immune recognition

Throughout mammalian evolution, the constant challenge of viral infection has led to the development of extraordinarily effective defense mechanisms. Some of these antiviral mechanisms are cell autonomous, whereas others depend on specialized cell types. Numerous viral evasion mechanisms have been identified through study of animal models, but it was not until pathogenic human retroviruses were first discovered in the 1980s that interest in antiretroviral immune responses was fueled. This interest is especially intense now because of the failure to develop a vaccine against HIV for almost 30 years.

The most successful vaccines are based on attenuated pathogens, as such vaccines mimic the immune recognition events occurring during natural infection. For retroviruses such as HIV, the use of attenuated strains is not an option because of the ability of retroviruses to mutate owing to their high replication and error rates. Retroviruses can also recombine, generating large genetic alterations. One immune-evasion mechanism is unique to retroviruses and relies upon proviral integration into the genome of susceptible cells. Integration into the genome of resting cells results in the establishment of a dormant infectious reservoir and, thus, indefinite virus persistence even in the face of an ongoing immune response.

Several retroviruses, known as complex retroviruses, make use of virulence factors that help them evade immune pressure [1]. Interestingly, simple retroviruses can accomplish the same goal of persistent infection while lacking obvious virulence factors. Simple retroviruses often contain as few as three genes (e.g., murine leukemia virus, which has *gag*, *pol*, *pro* and *env*) yet are able to replicate effectively and remain unrecognized by the host. How is this feat achieved with so little genomic material? We propose that the structural genes of simple retroviruses have acquired

multiple functions that contribute to their evasion strategy. Retrovirally produced structural proteins have been shown to interact with hundreds of host factors. Some of these interactions are required for successful virus replication, while others may be important for retroviral evasion of the host response. These ‘extrastructural’ roles of structural proteins could be activated/regulated in a specific manner to exhibit an immune evasion function. Post-translational modifications could, for example, result in an increased protein interactome for some retroviral proteins. Phosphorylation might change the structure of Gag to counteract a host-restriction factor in a simple retrovirus, whereas in a complex retrovirus, a new gene might be acquired to accomplish the same evasion mechanism. Endosomal acidification may cause conformational changes in viral capsid proteins enabling them to bind to host factors to withstand an antiviral response. A deeper understanding of how retroviruses utilize their genome for immune evasion will lead to the identification of overlooked evasion strategies and novel functions for viral proteins.

It is also possible that retroviruses exploit microorganisms to evade the host response. Like many pathogens, retroviruses have evolved in the context of the commensal microflora of their hosts. One can hypothesize that retroviruses may take advantage of the commensals (i.e., as adjuvant) by tolerizing the host and, thus, suppressing the antiviral immune response. Incredibly, this evasion route requires no virulence factors to achieve the intended purpose. Gnotobiotic models should be used to discern the role of normal flora in retroviral evasion.

How is retroviral infection sensed?

An adaptive immune response against a pathogen begins with recognition of pathogen-associated molecular patterns by the pattern-recognition receptors of the innate immune system [2,3].

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Pattern-recognition receptors sense replicative intermediates of viruses by recognizing structures not normally found in the host cell, such as dsRNA, or recognizing nucleic acids in a cellular compartment where they are normally absent (i.e., RNA/DNA in endosomes and DNA in the cytosol). These detection events are then translated into a pathogen-specific adaptive immune response [4]. Two observations indicate that the immune response exerts extensive pressure on retroviral replication. First, deficiencies in specific adaptive or innate immune pathways result in increased retroviral titers and, second, retroviruses have evolved numerous mechanisms to avoid immune recognition.

This raises the questions of what the retroviral pathogen-associated molecular patterns are and how they are sensed. Retroviruses are enveloped viruses with the genomic RNA packaged within a protein shell, termed the capsid [5]. Retrovirus entry is mediated through the interaction of its Env protein with a surface receptor. These events expose the virus to endosomal and cytosolic innate immune receptors. During transport to the nucleus, reverse transcription occurs in the preintegration complex, producing dsDNA molecules, which are subsequently integrated into the infected cell's genome, establishing a provirus. After integration, viral RNA molecules transcribed from the integrated provirus are translated to produce the viral proteins. As viral particles are being formed, genomic RNA and reverse transcriptase are packaged and the virus egresses from the cell. Various replication intermediates, including different nucleic acid forms, could potentially be targeted by the innate immune system as they might have physical/structural or subcellular localization differences compared

with similar forms made by the host. Clearly, we know little about the initial events that lead to host recognition of retroviral pathogens.

Conclusion & future perspective

Pathogens that cause chronic infections excel in adapting to the host in a manner that ensures long-term residence. Most viruses utilize numerous immune-evasion mechanisms, but are still eliminated or efficiently controlled by the immune system. However, infection with retroviruses rarely leads to an immune response that can prevent ongoing virus replication, suggesting that they evolved highly efficient mechanisms to escape an immune attack. Further studies should be aimed at determining mechanisms responsible for recognition of retroviral pathogens and virally evolved mechanisms to block this detection. Knowledge gained from these studies will lead to development of vaccines that could recapitulate a live-virus vaccine without using live virus, by mimicking natural detection events and subsequent adaptive immune responses. This is important for producing prophylactic vaccines, not only against HIV, but also against the future retroviruses that we are certain to encounter.

Financial & competing interests disclosure

This work was supported by PHS grant CA113784 to Tatyana V Golovkina. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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