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Mini Review

Viral evolution and Immune responses

Abstract

Antiviral responses are activated rapidly after viral infection in order to control and prevent dissemination of the virus. Different pathways are activated in the immune system, including innate and adaptive responses. On the other hand, viruses have evolved specific strategies to evade these responses. Due to the high viral evolutionary rates, escape variants can emerge and spread fast in the population. The co-evolution between viruses and their host is a constant arms race, and is of special interest to understand the viral escape mechanisms that may guide the future development of antiviral treatments and vaccines.

Introduction

A virus can be defined as an infectious agent that needs a host machinery to replicate and induce progeny. As non-living entities, viruses encounter a host, penetrate, and interact with the cellular equipment to produce new viruses. Viruses can infect all known cellular types, including archaea, bacteria, and eukaryotes (including plants and animals), although this review will focus on human viruses. Interestingly, viruses are highly specific, and will be recognized by specific cell receptors, where they will be able to attach, enter into the specific cell, and replicate. How the immune system is activated to control viral infections and understanding how viruses can escape an immune response is of special interest for the fight against many diseases. Strong immunity will suppress immune escape due to limiting transmission, while weak immunity will not allow for selection of escape variants [1]. It is important remember that viruses, due to their small genome sizes and short replication times, have high mutation rates (and evolutionary rates) that allow them to evolve and adapt fast to variable environments, and to selective pressures such as the immune system [2].

Viruses have capsids for various different activities. Firstly, capsids allow the virus to resist environmental conditions, sheltering the genome and protecting it. In addition, viral capsids will be recognized by specific cell receptors, conferring the opportunity for the virus to interact with and infect a specific cell type. For these reasons, viral capsids are under strong selective pressure and the correct packaging of the virus will be highly constrained [3]. However, capsids are exposed to the environment, and are also one of the most important parts of the virus in terms of their interaction with the immune system. For example, neutralizing antibodies can recognize specific motifs of the viral capsids that will induce the specific control of the viral infection. In case of enveloped viruses, these functions are exerted by the viral envelop. Due to the nature of the viruses, and the fact that viral populations are highly heterogeneous, viral populations are continuously evolving to try to escape immune system recognition. It is important to note that evolution has been driving viruses to develop mechanisms to avoid their recognition and their elimination by the host immune responses [4].

There are many mechanisms involved in immune evasion, including those that enable the virus to avoid recognition by the innate immune system, interfere with the cellular immune responses, and interfere with the immune effector function between others. A large spectrum of possibilities has been explored by different viruses to escape the immune response. Viral escape strategies are broad, and viruses have developed different ways to avoid being recognized by the immune system, as well to decrease the immune response by blocking specific pathways implicated in antiviral activities. Understanding viral evasion strategies to evade or antagonize host antiviral responses could help in the future design of vaccines or antiviral therapies. In this review, I am going to summarize some of the specific strategies that viruses have evolved to escape the pressure exerted by the human immune system, including innate and adaptive immune responses (Figure 1).

Immune responses to infection

After infection of a new host, at the early phase of infection, innate immune responses with an antigen independent manner will be turn on in the host to try to control the infection. This first step will mainly include macrophages, Natural Killer (NK) cells, and dendritic cells. These cells will produce inflammatory

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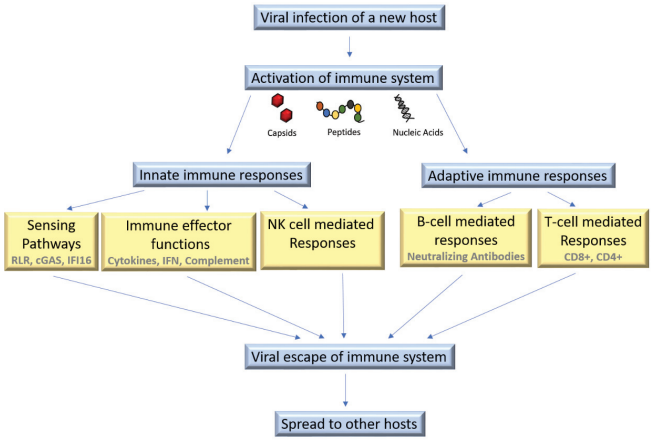

Figure 1: Schematic representation of the main responses to viral infection.

factors that will act as chemical messengers, including cytokines and chemokines. One of the most important factors is the production of interferon (IFN), which will activate the antiviral immune responses in a fast and effective manner. In a first step, Pattern Recognition Receptors (PRRs) will recognize a pathogen as a foreign particle due to the interaction with Pathogen-Associated Molecular Patterns (PAMPs). The most studied PRRs are the toll-like receptors (TLRs), which recognize microbial PAMPs. Other PRRs implicated in viral recognition are the RIG-like receptors (RLRs), the cyclic gMP-AMP synthase (cGAS), and the IFN-γ-inducible protein 16 (IFI16). The interaction of viral ligands with host receptors activates downstream signaling events that will in turn activate transcription factors, that ultimately regulate the expression of genes implicated in innate and adaptive immunity [5]. For example, if a TLR recognizes a PAMP, a cascade of signals will be activated and will induce the production of cytokines, mostly type I IFN, that will promote the maturation of dendritic cells and regulate macrophages, NK cells, and T and B cells. At this point, the efficacy of host responses will be strongly dependent on a rapid and specific recognition of the pathogen, in order to rapidly activate the first barrier response to control the infection.

At the late phase of infection, adaptive immune responses are activated. These responses are highly specific to a particular pathogen, in contrast with the innate immune ones. Furthermore, adaptive responses provide a long-lasting protection against the specific pathogen. Adaptive responses are carried out by lymphocytes, and there are two main classes of response: antibody responses, and cell-mediated immune responses. Antibody responses are mainly carried out by B cells secreting immunoglobulins, while cell-mediated immune responses are under T cell control. Adaptive immune responses are basically dependent on the major histocompatibility complex (MHC) class I and II. Adaptive immune responses are shaped by the quality of the initial innate immune responses [6].

Viral evasion of innate immune responses

Due to the short replication times in viruses, and to their high mutation rates, viruses can evolve and adapt quickly to the immune responses to evade them and continue the infection. At first, innate immune responses will be activated which are not pathogen specific. Viruses should evade the mucosal physical barrier to succeed in their entry, and this breakdown is considered a crucial event causing immune activation [7]. Viruses should also override innate responses as the complement system to increase viral spread. To favor their replication and survival, viruses should also combat IFN responses and modulate or mimic cytokines and chemokines that will allow the viruses to create a persistent infection. Finally, blocking cellular functions as pDC or NK cells are also targets for viral evasion.

Evasion of immune sensing pathways: PRRs can recognize a large number of PAMPs including lipopolysaccharide, bacterial endotoxins, flagellins, peptidoglycan, and non-self nucleic acids, among others [8]. For this reason, viral nucleic acids can be rapidly recognized as PAMPs and trigger an immune response. Many strategies used by viruses to evade innate immune responses are mediated by sensors as RLRs, cGAS or IFI16, and successful viruses need to evade or inhibit the activation of intracellular PRRs. Altering or hiding their nucleic acids are strategies to escape immune responses. Inducing the formation of specific replication compartments confined by cellular membranes, or replicating inside organelles, prevents RLRs from accessing viral nucleic acids. In addition, some viruses have evolved ways to degrade RIG-I via ubiquitylation to inhibit their signal cascade, while others encode for viral proteases that directly cleave RLRs. In the end, the IFN cascade is blocked and the production of IFNs is prevented. Another strategy is to relocalize RLRs into virus-induced structures to sequester RLRs and prevent their antiviral responses. cGAS has been recognized as an intracellular sensor that activates the IFN pathway in response to a viral infection, and again, viruses have evolved mechanisms to inhibit such a response [9].

For example, the Hepatitis C Virus (HCV) has evolved multiple mechanisms to inhibit IFN antiviral activity, and the expression of HCV proteins blocks the transcriptional response to IFN-α [10]. IFI16 has been linked, as well, to innate immunity against viruses, and can serve as nuclear or cytosolic sensor of DNA, playing a role in inducing the inflammasome [11]. Human cytomegalovirus (HCMV) has developed evasion strategies to counteract the effects of IFI16. HCMV expresses a protein that will phosphorylate IFI16, promoting its nucleo-cytoplasmic relocalization and thus removing IFI16 from the site of restriction activity. It has been also shown that HCMV incorporates IFI16 into newly formatted virions to expulse it from the cell altogether, thereby evading the IFI16 antiviral activity [12]. Influenza virus type A (IAV) is able to antagonize the innate host response by the expression of the non-structural protein 1 (NS1). NS1 is a multifunctional virulence factor that interferes with the RIG-I cascade, and also has a strong impact on gene products induced by viral infection like IFN and pro-inflammatory cytokines and chemokines [13]. Dengue virus (DENV) and West Nile virus (WNV) are able to block type I IFN expression by escaping recognition of PRRs, or by actively inhibiting PRR-mediated IFN-α/β induction. Their evasion strategies consist basically of a sequestration or modification of viral RNA, direct inhibition of PRRs or adaptor proteins, and antagonism of key signaling proteins downstream

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of PRRs [14]. Epstein-Barr virus (EBV) inhibits cellular protein synthesis in productively infected cells through global mRNA destabilization, and can affect immunological relevant proteins including TLR2 and TLR9 that are capable of sensing EBV infection. Shutoff-induced reduction in protein levels mainly prevent production of newly synthesized effector molecules, rather than reducing the levels of existing PRRs [15].

Evasion of immune effector functions: Viruses have evolved to modulate immune effector functions, including cytokines, chemokines or complement actions. For example, IL-10 is a potent immunosuppressive and anti-inflammatory cytokine. HCMV has evolved to express a homologue of IL-10 in order to decrease the immune response [16], while retaining the activities that are advantageous for the virus. Some viruses are able to express chemokine receptor homologues, implicated in viral pathogenesis sequestering chemokines, to limit effector cell activation [17,18].

Among the cytokines, IFNs have a major role in virus infection. They induce immune activation and enhance antigen presentation, and also have antiviral activity [19]. Recognition of PAMPs stimulates the activation of IFN-induced signaling pathways, leading to the production of proinflammatory cytokines and chemokines and antiviral type I IFN. Viruses have developed many strategies to alter the expression of IFN-stimulated genes, blocking multiple levels of IFN-signal transduction [19]. Some EBV gene products interfere with the function of innate effector molecules. For example, BARF1 neutralizes the effect of host cytokines, leading to reduced IFN-α secretion [20], and BZLF1 is able to downregulate the receptors for IFNs to reduce cellular responses to cytokines, as well as inducing a suppressor of cytokine signaling which again reduces IFN type I production [15]. It is interesting to note that the major sources of IFN are the plasmacytoid dendritic cells (pDCs), which play a central role in the innate immune response. Human immunodeficiency virus (HIV) inhibits the pDC counts in peripheral blood, and gp120 suppresses pDC activation and production of cytokines, inhibiting IFN production [7].

Viral interference with the complement system has been also described. The complement system, a major host defense mechanism, triggers the recruitment of inflammatory cells and induces the formation of pores in the plasma membranes of target cells. Many viruses have developed different strategies to overcome the effects of the complement and increase viral spread. Some viruses can express structural viral proteins that mimic the function of the cellular regulators of the complement activation (RCA). Others are able to incorporate host RCA into their envelope by budding through the plasma membrane or into intracellular vacuoles, and some viruses even secrete proteins that directly block complement activation [21]. Infected cells can be also lysed via antibody-dependent complement-mediated lysis. For example, the regulatory factor CD59 present in HIV prevents complement mediated neutralization of antibody bound viruses [22]. Additionally, gp41 and gp120 HIV envelope proteins interact with complement proteins, and this causes decreased complement dependent lysis of infected cells [23].

Evasion of NK cell-mediated immune response: NK cells are an important initial defense against many viral infections. NK cells release cytotoxic granules containing perforin and granzymes into infected cells to lyse them. NK cells can also bind to specific apoptosis-inducing receptors on target cells to induce cell death [24]. NK cell regulation is dependent on a fine balance between activating (Ly49D, Ly49H and NKG2D) and inhibitory (killer immunoglobulin-like receptors (KIR), immunoglobulin-like transcripts (ILT), and CD94-NKG2D) cell surface receptors [10]. These receptors bind to host MHC-I molecules and transmit inhibitory signals to the NK cell. NK cell target recognition occurs after ligation of activating receptors and repression of inhibitory receptors on the cell surface, and is activated during a wide variety of viral infections by type I IFN. Viruses have developed different approaches in order to avoid NK cell responses. Many viruses express MHC-I homologues, while others evade NK cell responses by increasing surface expression of MHC-I molecules. HIV Nef protein has been postulated as a potential regulator of NK cell cytotoxicity due to its involvement in MHC-I downregulation on CD4+ cells, conferring an additional evasion strategy against NK cells [20]. Virus-mediated inhibition of activating receptor function and production of virally encoded cytokine-binding proteins or cytokine-receptor antagonists are other approaches to circumvent the action of NK cells [24].

Viral evasion of adaptive immune responses

Adaptive antiviral immunity is activated after innate responses, and the quality of these initial innate immune responses will define the effectiveness of the adaptive responses [6]. This adaptive immunity relies on the memory-based response of virus-specific B- and T-cells. Detection and elimination of infected cells is the ultimate goal, and virus-specific T-cell responses involve the activation of CD8+ and CD4+ T-cells by interfering with the MHC-I and -II antigen presentation pathways.

Evasion of neutralizing antibodies: Neutralizing antibodies (nAbs) have specific roles in preventing, reducing, and clearing infection. Neutralization prevent viral entry into cells, mainly by recognition of specific regions of the viral capsid or envelope proteins, conformational epitopes, and glycans [25].

Many viruses display low levels of diversity at the amino acid level compared to their nucleotide diversity. Overall, capsid genes are highly constrained to maintain proper capsid folding. Furthermore, many viruses encode capsid residues by rare codons that are highly conserved and, in some cases, close to potential epitopes. This is the case for the hepatitis A virus (HAV), where only a few antigenic variants have been isolated in nature, suggesting some strong capsid constraints limiting antigenic variability [26]. For these reasons, even under immune pressure, substitutions in these specific residues is negatively selected.

Bad vaccine administration can favor the selection of variants able to escape immune system recognition, for example via escape of antibody neutralization despite their lower fitness compared to other viral variants. Due to the large

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population sizes of viruses, and despite the presence of nAbs, it has been shown that replication under restricted conditions favors the selection of resistant mutants and leads to the emergence of new serotypes, despite genomic, structural or biological constraints. In general, these mutants will have a selective advantage in the presence of nAbs, and lower fitness in permissive conditions (absence of the antibody). However, this process can have unknown consequences due to the emergence of new variants with different pathogenic properties.

One of the most studied viruses, due to previous pandemics and its rapid acquisition of resistance to anti-viral B cell immunity, is IAV. The action of NAbs against the IAV major surface protein (hemagglutinin) is one of the best studied immune responses. IAV has developed two forms of antigenic variation to escape neutralization [15]. One of them is antigenic drift, in which the introduction of point mutations in the genes encoding for the hemagglutinin and neuraminidase can produce specific mutations in the interaction sites and lead to escape variants, due to the impairment of binding of the antibody to the epitope. The error prone polymerase allows the generation of a swarm of mutants, leading to the selection of escape-mutants. The other process is known as antigenic shift, in which RNA segments are exchanged (re-assortment) between two different virus strains during double infection of one host cell, which can lead to major changes in the hemagglutinin protein and block antibody recognition of the virus [13]. This is one of the known strategies to rapidly change viral surface protein composition, and can lead to the generation of pandemic IAV strains.

Besides changes in the amino acid composition of the surface proteins, some viruses like IAV and HIV have developed post-transcriptional modifications, mainly glycosylation, that change the accessibility and function of the viral surface proteins and help with evasion of immune responses. These modifications have important implications in receptor binding, viral infectivity, and virus release. It is important to note that glycosylation can reduce viral pathogenicity if it is close to receptor-binding sites [27].

Evasion of the T-cell-mediated immune response: Cell-mediated immune responses by T cells are also a target for viral evasion. Viruses can impair activation of CD8+ and CD4+ T cells by blocking the presentation of antigen in the context of the MHC class I and II molecules, respectively. MHC-I molecules are able to present peptides that have been degraded by the proteasome in the cytosol of the cell. Proteasome degradation starts with the ubiquitylation of a protein, and is dependent on proteolytic cleavage of a specific sequence in the protein to degrade. Mutations in these specific motifs allows the virus to not cleave the protein in the correct positions, and to impair peptide presentation [28]. Studies with EBV support that changes in protein folding can block the entry to the proteasome complex [29]. In addition, phosphorylation of specific residues of HCMV proteins can also restrict the access of the protein to proteasome degradation, or divert the protein into a different degradation pathway [30]. In a second step, peptides pass the endoplasmic reticulum (ER) membrane, translocated via the transporter associated with antigen presentation (TAP), to be presented by the MHC-I complexes. HMCV expresses a protein able to inhibit TAP and retains the peptides that will not be translocated and presented by MHC-I [31]. Other viruses have developed other strategies to block the activity of TAP, like the herpes simplex virus (HSV) [32] or EBV, in which expression of BNLF2a results in a reduced CD8 + T-cell recognition through inhibition of peptide import by TAP [15].

In IAV, it has been shown that although escape mutations in MHC-I epitopes seems to occur less often than in epitopes of neutralizing antibodies, substitution in the anchor residues can lead to a loss of the binding to the respective MHC-I molecule, or decrease the avidity to the T-cell antigen receptor by mutations in the interacting residues [13]. Another strategy of EBV to inhibit T-cell recognition is the expression of BGLF5, which degrades MHC-I encoding mRNAs, reducing peptide presentation at the cell surface [15].

Other strategies reside in the prevention of MHC-I formation. HCMV is able to express a protein that will retain the MHC-I peptide complexes in the ER, which will then not be expressed at the surface of the cells [31]. Viruses such as varicella-Zoster virus (VZV) or HIV have viral products with a similar function. In addition, HCMV and human herpes virus-8 (HHV-8) express some proteins implicated in the degradation of MHC-I molecules in a proteasome-dependent manner [33,34]. EBV is able to downregulate surface MHC-I molecules by BILF1, reducing transport of MHC-I molecules from the Golgi, and also enhancing degradation via lysosomal proteases [35].

Antigenic variation also has a strong impact on T-cell responses. It has been already shown that cleavage of the peptides is sequence-dependent, and alteration of peptide binding to MHC can create unstable peptide-MHC complexes, as demonstrated in HIV or the hepatitis B virus (HBV). Finally, some viruses are able to downregulate T-cell receptors complexes in T-cells [36].

Viral peptides can also be presented by the MHC-II. In general, MHC-II is able to present antigens derived from exogenous proteins that are endocytosed, degraded in lysosomes, and then delivered to the MHC-II loading compartment [37]. Viruses like HCMV and VZV have evolved mechanisms in order to downregulate MHC-II expression, to reduce the antigen presentation. Downregulation of MHC-II inhibits Th-cell activation and, indirectly, the antibody production by plasma cells. CD4+ T-cells against lytic antigens are also found in the peripheral blood of infected individuals. For example, EBV uses entry receptor Gp42, which binds to MHC-II molecules present on B-cells, but also acts as an immune evasion molecule blocking T-cell receptors (TCRs) class II interactions, precluding activation of CD4+ T-cells. In addition, BGLF5 decreases MHC-II molecules at the cell surface via degradation of MHC-II mRNAs, as also occurs for MHC-I [15].

Finally, it is important to mention the action of the programmed cell death protein (PD-1), an immunoglobulin that regulates T cell responses. PD-1 expression is usually

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modulated by cytokines, and induced through TCRs, although it has been reported in other cells like B cells, NKs, or DCs. His role in the evasion of tumor cells has been extensively described, although also regulates antiviral immunity. Viruses have developed different mechanisms to modulate PD-1 expression, usually mediated by upregulation of PD-1 and its ligands PD-L1 and PD-L2, as has been observed during infection caused by many viruses such as HIV, HCV, or HBV. However, although PD-1/PD-L1 impact in chronic viral infections has been well described, their impact in early infections is still under study [38]. It has been shown that T cell exhaustion in chronic viral infections unable to clear the persistent infections due to the upregulation of PD-1, and recent works show the potential of PD-1 therapy to rescue T cells and control the virus [39]. Nevertheless, how viruses modulate these responses as a viral evasion mechanism, or if it represents an adaptation of the host defenses is still controversial, and further efforts in this field are mandatory to determine the nature of this interaction.

Conclusion

Viruses are constantly under immune system pressure, leading to the emergence of new variants that allow them to escape. Due to the wide range of options that the immune system has to block viral infections, viruses have evolved different mechanisms to escape from almost all the possible pathways. Understanding viral evolution and escape strategies for the specific pathways or molecules is of special interest in the development of antiviral drugs or vaccines. For example, identification of epitopes that escape rapidly to the virus-specific T-cells is of special interest for the production of epitope-based vaccines. Further efforts should be undertaken in order to better understand viral escape strategies at the molecular level, as well as how host cells evolve to thwart viral immune escape.

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