Acta Scientific Microbiology (ISSN: 2581-3226)
Volume 1 Issue 6 June 2018
Mini Review

Host Immune Responses to the Infections Caused by the Infectious Viruses

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Received: April 20, 2018; **Published:** May 10, 2018

Abstract

Evasion of host immune systems has become a norm for infectious viruses. However, host system also plays defensive games to combat and inhibit virus establishment in the body. Components of the innate immune system such as cytokines, interferon, complements, etc. act as the first and furious defense against these pathogens upon sensation. If the pathogen sustains longer, the adaptive immune system wakes up and eliminates it protecting the body. The combined actions of innate and adaptive immunity use several immune cells and components and determine the fate of an antigen.

Keywords: Viruses; Host Immunity; Evasion

Introduction

Viruses are obligate intracellular parasites that need to find a preferred way to enter into the susceptible host cell by crossing cellular membrane and exploit the usual cellular processes such as capsid destabilization, and uncoating along with the proper action of nucleic acids to initiate the infection cycle in the human body [1,2]. Furthermore, it is well known that the initial mode of viral entry is the identification and recognition of host pattern recognition receptors (PRRs), for instance, toll-like receptors (TLR) [3,4].

Human body usually responses to the viruses by activating the immune system [1,5]. After the entry of the virus into the cell, host downstream signals try to combat the virus. The process includes initiation of a cascade pathway to secrete pro-inflammatory cytokines and interferon, body's first-line defense against viral infections [3,6]. However, viruses are sometimes able to hide themselves from the adverse effects of host immune cells, and cause disease progression, especially if the host is immunocompromised [7]. On the other hand, protection to the host itself is gained by either gaining tolerance to the caused infections or through activating the immune defense mechanisms [8,9].

Actions of innate immunity to defend virus establishment

Innate immunity starts activation and defends the host to the infections as soon as after the adhesion of viral protein with the PRRs [3,4]. Different types of PRR are engaged in this recognition process [3,4]. These include TLR3, which is specific for double-stranded RNA and normally recognizes virus-infected cells in the body; on the other hand, TLR7 and TLR8, detect only single-stranded RNA and detect and bind to the viral RNA present in the infected sentinel cells; furthermore, retinoic acid inducible gene- I (RIG-I) detects and locate viruses in the cytosol of virus-infected cells [4,8]. A cascade pathway is activated by TLR producing pro-inflammatory molecules (IL-1 and IL-18) as well as three classes of interferon, firstly, interferon type I (composed of IFN-α and IFN-β), secondly, type II interferon (IFN-γ) and finally, newly reported type III interferon (IFN-λ1, IFN-λ2, and IFN-λ3) [3,10-12]. A new class of interferon, type III interferon, identified by Durbin research group [13], was found to have antiviral activity as like as type I interferon located in the mucosal surfaces, e.g., respiratory tract and gut [14-16]. However, antiviral activity of type III interferon has been documented to be limited to respiratory syncytial virus, influenza A virus and rotavirus [14].

Furthermore, several IFN-stimulated genes (ISGs) is triggered by activated interferon produced by the infected host cells, which later function to inhibit the virus replication, to promote immune systems to the antiviral state and finally to activate the adaptive immune response [3,17,18]. Some of these ISGs include viperin, a virus inhibitory protein modulating IFN-β production by activating signaling pathways, IRF3, IRF7 and PRRs (activation of this protein is distinctly induced by Sinbis virus, human cytomegalovirus, Sendai virus, etc.) [3,17,19]; tetherin, another IFN-induced protein that is composed of an unusual structure with three domains (two membrane-anchoring domains at both N-termini and C-termini, and a middle coiled domain) that act to make a link between virus and cellular membrane and thereby can capture the enveloped pathogens, for example, human immunodeficiency virus-1 [3,17,18]; another protein, SAMHD1 (sterile alpha motif and histidine-aspartic domain - 1), plays an antiviral activity by inhibiting transcriptions of both non-retroviruses and retroviruses such as herpes simplex virus type I and vaccinia virus [3,20]. Furthermore, protein kinase R, a detector protein that is capable to detect dsRNA in the cytosol, which uniquely provide signals to activate Nuclear factor (NF)-kB and thus, to inhibit the initiation of translation [21]. Defense by innate immune system of the host is not limited to the functioning proteins; however, a small portion of siRNAs and miRNAs also act to prevent virus infection [3].

Several immune cells such as neutrophils, Natural killer cells, dendritic cells, mast cells, etc. are activated to prevent the virus infections in innate system [22-24]. Neutrophils play an important role in combatting acute inflammatory infections which finally migrate to the virus infected sites rapidly [25,26]. They are activated by signals conveyed by TLRs and damage-associated molecular patterns (DAMPs) upon the infection caused by virus [26,27]. Another potent immune cell, NK cell is involved with the cellular innate immune response to viral infections [28-30]. Furthermore, NK cell functions as an effector cell possessing the both cytokine and cytotoxicity productions, and maintain a balance between the activation and inhibitory signaling [28]. For instance, during viral hepatitis, in the presence of IL-10, NK cells seem to produce less IFN-γ (anti-inflammatory cytokine) with a relatively increased cytotoxicity to the host cells [28,30].

Activation of adaptive immunity to prevent viral infections

In addition to function in allergic responses, mast cells play important role as cellular component of innate immune systems to viral infections [23,24,31]. After activation by cytokines they release pro-inflammatory cytokines, followed by stimulating other immune cells, for example, phagocytes to be recruited to the infection site [23,24,31]. Mast cells can also activate and promote adaptive immune responses by activation of T and B cell [23,31]. Additionally, another immune cell, plasmacytoid dendritic cell was documented to have antiviral response to influenza A virus [21,32]. Activation of these cells are occurred by TLR7-dependent manner and they are reported to produce type I interferon acting against the viral infection [16,21].

Adaptive immune response is essential for the inhibition of viral infections and to keep a memory to prevent the repeated infections caused by the same pathogen [33]. The activation of adaptive immune responses to viral infections needs a few days to weeks [33,34]. This activation process involves some antigen presenting cells (APC) such as neutrophils (later differentiated into muscles macrophages and dendritic cells, which act as bridges between the adaptive and innate immunity), which up regulate co-stimulatory molecules, for instance,CD80 and CD86, and pro-inflammatory cytokines, e.g., interferon (IFN), tumor necrosis factor (TNF) and interleukin (IL)-1, IL-6, IL-12 [26,33,35,36]. These induced immune components further activate other immune cells such as dendritic cells, and promote migrations to the secondary lymphoid tissues [33,35,37,38]. Peptides derived from the virus are presented on the activated cells surface by major histocompatibility complex (MHC) class II [39]. These peptides provide co-stimulatory signals to activate CD4+ T cells from the naïve state [35,39].

Differentiation of the activated CD4 + T cells results into T helper (H) 1, TH2, TH4, TH17, TFH (follicular) and regulatory T cells (Treg) cells [35,40,41]. Furthermore, these cells function differently as their nature of communications, where TH1 and TH2 produces IFN-γ and IL-4 respectively to help the macrophages activation and B cells differentiation respectively [35,42]. Additionally, TFH enter into the B cell follicles and helps to activate the B cells with interacting with CD40, which later produce specific antibody against viral infections [43,44]. On the other hand, TH17 acts against some of the deadly viruses such as vaccinia virus, influenza viruses, HSV, etc.), and Treg cells regulate the functions of other T cells and inflammatory substances from over-exuberant immune responses as well as immunopathology [35,45]. Additionally, by the help of IL-2, CD4+ T cells are activated and differentiated into cytolytic T cells (CTL) to kill viral infected cells directly [35,46,47].

On the other hand, Virus infected cells express antigens in association with MHC class I on its surface and activate CD8+ T cells [39,46]. MHC I carrying the antigenic determinant binds to the TCR (T cell receptor) and through CD80 and CD86, it provides signals to CD8+ T cells [39,46]. After receiving the signals from the infected cells, CD8+ T cells are started proliferation and differentiation into CTL and if necessary, it can lyse the infected cells by secreting perforin and granzymes, and activates cytokines like TNF-α, IL-2 and IFNγ to promote apoptosis by the macrophages [46,48,49]. At the same time, few differentiated CTLs, THs and plasma cells turn into the memory cells which further provide rapid and robust immune responses if re-infection happens [8,50].

Innate and adaptive immune systems co-stimulate each other

Both innate and adaptive immunity are the ultimate counterpart for each other and are needed to control viral infection effectively [8,51]. Innate immunity control viruses defending in the early phase infections such as virus entry, replication, and if pathogens manage to evade such responses, innate immune cells generate co-stimulatory signals to the adaptive system using pro-inflammatory molecules [8]. Then T and B cells are activated and differentiated. Furthermore, immunoglobulin that are specific to the virus infections bind and block the viral spread [8,52]. On the other hand, CTL eliminates the cells infected by viruses [8,44]. Later, some of these immune cells act as memory cells in the immune system to prevent further infections.

Conclusions

To combat the immune responses, viruses are making changes to their genome regularly which in turn upgrading their infection causing mechanisms Further studies are needed to understand the molecular mechanisms of viral evasion and the defense systems against the host immunity. Furthermore, to develop vaccines against deadly viral infections, it is essential to study the continuous modifications of virus proteins which play vital role to evade the host immunity.

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