Significance and Dynamics of Immune Responses During Viral Pathogenesis

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Abstract

Immune system is a homeostatic system which is active against numerous invading pathogens. Host immune system uses multiple immune responses (innate, adaptive, and complement system) to eliminate virus/viral particles. Additionally immune system is also well resourced with sensors that detect invading pathogens and direct responses for clearing numerous copies of virus recruits. Modern technologies help prevent pathogen emergence as well as thrust scientific improvements in understanding the viral immune responses; moreover, recent scientific advances in diagnostic virology have undeniably transformed the ability to address challenges of numerous emerging intricate viruses. The journey of diagnostic virology has started from serology, nucleic acid sequence-based amplification techniques, and genomic sequencing techniques to most advanced innovative methods (e.g., structural biology spectroscopy, NGS, microfluidics, metagenomics, CRISPR/Cas system, nanotechnology and structural biology), the world progressed way beyond with several classy diagnostic methods to help tackle the diagnosis and control of emerging viral diseases. However, the technical competencies alone are inadequate if not sustained by health promotion strategies to raise awareness of the significance of early detection and diagnosis, outbreak, and spread of virus. Yet, current outbreaks of viral diseases across the world dole out authoritative reminders to emerging viral pathogens.

Keywords

Immune system · Viruses · Diagnostic methods · Emerging viral diseases

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1.1 Introduction

Infectious diseases are reported to account for ~20% of global mortality, of which one-third of deaths are caused by viral diseases. The viral infections pose major public health risks and warrant further research and development, including surveillance and diagnostics. All the lethal viral diseases present an absurdity in mounting the pathogenesis there by killing their hosts, which is noticeably of no advantage to the virus. Viruses are infectious agents consisting of nucleic acids coated in a simple protein casing, infect, replicate in host cells, and cause acute, chronic infections. Since viral infection is an intricate and highly vibrant process, noticeably affected by the physical and chemical environment, studies into infectious viral biology ought to preferably occur in advanced research settings. Viruses replicate by hijacking the host cell's machinery and making host cells a huge virus factory and erupt as virus after… virus after… virus after… virus.

The immune system is also well resourced with sensors that detect invading pathogens and direct responses for clearing numerous copies of virus recruits. On the entry of virus, immune system of the host typically elicits both nonspecific innate and "specific" adaptive immune responses against foreign pathogens. Activation of varied immune responses, time, and the extent of response rely on how virus interacts and spreads within host cells. Host immune system uses multiple immune responses (innate, adaptive, and complement system) to eliminate virus/viral particles. The immune system employs most efficient mechanisms depending on the distinctiveness of infectious agents. Diverse actions occur during viral infections, equally toward free viral particles in addition to infected cells.

Race between virus and immune response establishes: whether the intruder will eliminate or establish a persistent infection. The host cell can also be damaged unswervingly by virus or by viral immune response. However, balance between good and bad antiviral immune response relies on the amount of viral load, chronicity of infection, and magnitude of tissues infected (Zinkernagel 1996). Therefore, a balance exists between immune activation vis-à-vis immune suppression during the setting of chronic infection. Viruses evolved numerous strategies to escape immune system to institute a chronic infection. Few viruses endure in definite cell types and hide from immune system, while some encode specific genes that target infected cells or immune system. A few viruses limit their replication, thus restricting accessibility of antigen to alert the immune system. However, a few viruses are error prone in their replication, escalating the possibility of making escape viral mutants. Nonetheless, these immune evasion strategies of virus are unprejudiced by regulation within the immune system (Finlay and McFadden 2006).

1.2 Innate Immune Responses by Virus

During early stages of infection "innate" response limits virus multiplication, which implicates synthesis of diffusible proteins called interferons, cytokines, and chemokines and stimulation of "natural killer" and dendritic lymphocytes (French and Yokoyama 2003). In order to limit viral replication, first line of defense system has

to sense the pathogens/pathogen-associated molecules (Paladino et al. 2006). This provides temporary protection against the viral onslaught. This fundamental process is accomplished by sensing virus-associated nucleic acids in infected cells using a variety of pattern recognition receptors (PRRs). PRRs recognize distinct pathogens conserved structures known as pathogen-associated molecular patterns (PAMPs). There are several classes of PRRs, namely TLRs (toll-like receptors), RLRs (retinoid acid-inducible gene-I (RIG-I)-like receptors), NLRs (nucleotide oligomerization domain (NOD)-like receptors), and many DNA and RNA sensors (Mogensen 2009). Upon interaction with cognate viral ligands, TLRs, NLRs, and RLRs stimulate production of interferons, pro-inflammatory cytokines (NF-κB-dependent response), and chemokines that limit virus replication and dissemination (Shayakhmetov et al. 2010). Infected cells produce different classes of interferons such as INF-α, INF-β, and INF-γ. Interferons mediate the most effective innate immune response during viral infection by warning nearby cells about viral presence (Haller et al. 2006). This signals neighboring cells to increase MHC class I molecules on their surfaces and to facilitate surveying T cells to identify and eliminate viral infection. Interferons also limit viral replication by the activation of NK cells which is associated with the alterations in expression of SLA by infected cells. NK cells' cytotoxic mechanism against viral infected cells is very effective and does not depend on antigen (NK cells lack TCR) (Paul and Lal 2017). However, complement activation of an alternative pathway has the effect of activating destruction of viral particle. Innate defensive mechanism generates a severe evolutionary pressure on viruses to evolve efficient mechanisms to evade and also strategies permitting for subversion of host antiviral immune systems (Finlay and McFadden 2006).

1.3 Adaptive Immune Responses by Virus

Another important second line of antiviral response is adaptive immune system that includes $CD8^+$ and $CD4^+$ T cells and neutralizing antibodies which act against viral particles and infected cells in combination. Days to weeks are essential to mount an adaptive immune response tailored for specific virus. Adaptive immune response possesses two components: humoral response (utilities virus-specific antibodies by B lymphocytes) and cell-mediated response (specific cytotoxic T lymphocytes (CTL) that kill infected cells) (Kim et al. 1999). Both the components of adaptive defense system ensue production of long-lived "memory cells" that allow much more quick response for consequent infection with similar virus (Campos and Godson 2003). Antibodies are most vital mechanisms against viral particles, while cytotoxic mechanisms are noteworthy against infected cells.

1.3.1 Humoral Immunity

Virus or virus-infected cells stimulate B lymphocytes which synthesize IgG, IgM, and IgA Abs (specific for viral antigens). Antibody neutralization is a significant mechanism by which virus occurs in huge fluid spaces (e.g., serum) or on mucous

surfaces (e.g., the gastrointestinal and respiratory tracts). Antibody can neutralize virus by (1) preventing host cell—virus interactions or (2) distinguishing viral antigens on infected cells that results in antibody-dependent cytotoxic cells (ADCC) or complement-mediated lysis (CML) (Parkin and Cohen 2001; Chaplin 2010).

1.3.2 Cell-Mediated Immunity

Viruses engage diverse strategies to restrain the presentation of virus-derived peptides. One of the important strategy entails the modulation of proteasome activity that produces peptides from full-length proteins; if there is adequate binding affinity, peptides bind to MHC class I molecules. However, a few viruses directly interact with and inhibit proteasome machinery likely for generation of peptides. Specialized immune cells, the CTL cells, recognize virus-infected cells with the help of specialized proteins (TCRs) on their surface and release cytotoxic factors to destroy infected cell and, therefore, avert survival of invading virus. The cytotoxic cells are specially armed with preformed mediators, namely perforins (forms pores in cell membranes) and granzymes (stored in and released from granules), permit entry of other factors into virus-infected cell to facilitate their destruction (Rosendahl Huber et al. 2014). Furthermore, CTL cells synthesize and release additional proteins, called cytokines, including interferon-ɤ and tumor necrosis factor-α, and transfer a signal from T cell to infected cell, or other neighboring cells, to further enhance killing mechanisms. Furthermore, cytokine signals, NK cells, act as evolutionary bridge linking innate and adaptive immunity (Belardelli and Ferrantini 2002; Sun and Lanier 2009).

It is well established that there is a mechanism for inhibiting immune response during chronic infection. In fact this mechanism is executed for two reasons: (1) To prevent immunopathology. CD8+ T-cell effector function can cause high levels of tissue damage through killing of infected cells and release of inflammatory cytokines. In reality, cytotoxicity and secretion of cytokines such as tumor necrosis factor (TNF) are often decreased if not lost in CD8+ T cells in a phenomenon known as T-cell exhaustion (Ou et al. 2008). (2) To prevent excessive proliferation of virus-specific T cells. During acute infection, virus-specific T cells can increase tenfold each day. This level of proliferation is dangerous and is therefore greatly reduced upon continued exposure to antigen (Thimme et al. 2012).

1.4 Significance

Viruses are intracellular pathogens that invade and infect host cells. Immune system is a homeostatic system which is active against numerous invading pathogens inside the body to clear infections. Propitiously, the aspects of recent modernization technologies that helped prevent pathogen emergence can also impel scientific improvements; moreover, recent scientific advances in diagnostic virology undeniably transformed the ability to address the challenges of numerous emerging intricate

viruses across the globe. Starting from serology, nucleic acid sequence-based amplification techniques, genomic sequencing techniques to most advanced innovative methods (structural biology spectroscopy, NGS, microfluidics, metagenomics, CRISPR/Cas system, nanotechnology, and structural biology), the world has progressed way beyond with more classy diagnostic methods to help tackle the detection and control of emerging viral diseases. However, the technical competencies alone are inadequate if not sustained by health promotion strategies to raise awareness of the significance of early detection, outbreak, and spread of virus. Still, current outbreaks of viral diseases across the world dole out powerful reminders of our ongoing susceptibility to emerging viral pathogens. Reflecting the diversity of viruses and viral diseases, these are notoriously difficult drug targets since they modify and adapt themselves quickly to build up resistance and emerge as new serotypes. Nonetheless, better perceptiveness of host–pathogen interactions, viral protein, and nucleic acid functions led to additional rational drug designs, resulting in important therapeutic advances against viral diseases. Furthermore, novel platforms for vaccine design, namely nanoparticles and virus-like particles, have embarked avenues for development of new vaccine targets. Treatment strategies for viral infections comprise hindering binding of virus to host cells by inhabiting on host cell receptor with an additional molecule, or use of vaccine developed for a particular virus or an analogous target of diverse viruses. Serious actions should accentuate the call for strenuous efforts to develop and execute novel interventions in viral disease diagnosis and vaccine development keeping public health perspective in view.

Dynamics of Immune Activation in Viral Diseases is an authoritative reference book in virology, which provides the current understanding of adaptive and innate immune response in viral diseases. This book also illustrates about differential regulation of each immune cells during viral pathogenesis and immune evasion. This book aims to revitalize the interaction between fields of virology and immunology in order to advance our understanding of dynamics of viral immune pathogenesis, as well as innate and adaptive immune responses elicited by host. Recent advancements in immune intervention and viral immunodiagnostics, including latest developments in vaccine research, will be discussed. It also covers new areas of immune biology where innate part of immune system helps adaptive part through cross talk with adaptive immune system. This book primarily emphasizes on the recent challenges of immune sensors, namely TLRs, DNA and RNA sensors, and other immune cells during viral infections, as it is indispensable to possess updated information on emerging viral diseases. Apart from the current understanding of immune response in human viral diseases, this book also outlines the most advanced immune techniques used in diagnostics of viral diseases and also primarily focuses on advancements of vaccine development research for emerging viral diseases.

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Conflict of Interest The author declares that he has no competing interests.

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