T Cells in Viral Infections: The Myriad Flavours of Antiviral Immunity

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Abstract

Viral diseases are a major cause of morbidity and mortality and result in a significant public health burden. T lymphocytes first identified in the chordate lineage and constitute a highly sophisticated branch of adaptive immune system. Apart from B cells, it is the only cell type that exhibits antigenic specificities; achieved by gene rearrangement. T cells are unique with respect to diversity of their subsets, which have distinct effector specificities, proliferative abilities, memory generation, and life span. T cells are impactful in viral infections by virtue of their capability to combat intracellular pathogens. The effector functions of T cells are mediated through cytokines/chemokines and by direct cytotoxicity of infected cells. T cell response can be beneficial or detrimental to host; prognosis depending on qualitative and quantitative differences in the response. Persistent viral infections are associated with functionally suboptimal, exhausted T cell responses, which are unable to clear virus. Specific subsets such as regulatory T cells (Tregs) dampen antiviral responses; thereby favouring viral persistence. However, Tregs protect the host from immunopathology by limiting perpetual inflammation. Certain other subsets such as Th17 cells may contribute to autoimmune component of viral infections. The importance of T cells is highlighted by the fact that modern vaccination and therapeutic approaches focus on modulating T cell frequencies and effector functions. This chapter emphasises the understanding how T cells influence outcomes of viral infections, modern vaccination and therapeutic strategies with thrust on T cell biology.

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9.1   Introduction

Viruses are infectious agents consists of nucleic acids coated in a simple protein casing, infects, replicates in host cells and causes acute, chronic infections. Mammals established a refined immune system to cope with several viral and bacterial infections (García-Sastre and Biron 2006). Remarkably, adaptive arm of immune responses is significant in action against virus particles and infected cells. T Lymphocytes are the key players in adaptive, cell-mediated immune responses and also in elimination of foreign pathogens by activating various immune responses. There exist many viruses for which both CD8+ and CD4+ T cells, reported to play key role in viral control viz. measles virus (Nelson et al. 2017), cytomegalovirus (CMV) (Wehrens et al. 2016), hepatitis C virus (HCV) (Sheiko et al. 2016) and HIV (Jones and Walker 2016). Typically, T_H1 cells are assumed to be efficient in antiviral T cell response. Nonetheless, many viruses can inhibit T_H1 response by downregulating interferons release from infected cells, which greatly influence outcome of virus infection (Laidlaw et al. 2016). The humoral immune response involves antibodies specific for virus to block host–virus interactions, neutralize virus and recognise viral antigens on infected cells and activates antibody-dependent cytotoxic cells (ADCC) or complement-mediated lysis to kill infected cells. However, if these antibodies are ineffective, viruses are able to infect host cells where adaptive arm acts to control viral pathogenesis (Rosendahl Huber et al. 2014).

Virus infects host cells if humoral immunity fails, viruses use protein synthesis and replication machinery of host cells for their replication and synthesis of their own proteins. Some newly synthesized proteins may degrade into peptide fragments. If these peptides have sufficient binding affinity, to class I MHC molecules they appear on cell surface of an infected cell as class I MHC–peptide complex. This complex activates CD8+ T cells and induces infected cell apoptosis by releasing cytotoxic granules and production of TNF-α and IFN-γ. Activation of CD8+ T cells also occurs in draining lymph nodes, where antigen-presenting cells (APCs) encounter naïve T cells. Priming of naïve T cells will not only occur through classical pathway via infection of cell, but also through cross-presentation of viral peptides on MHC class I molecules, taken up from extracellular sources. Priming of T cells triggers a massive expansion of antigen-specific T cells. Their progeny usually accumulate in large numbers of armed effector T cells and these normally contribute to the eradication of viral pathogens.

T cells in chronic viral infections typically exhibit strong impairments in the production of cytokines (IFN-g, TNF and IL-2) and express high levels of inhibitory receptors viz. PD-1 (programmed cell death-1) and Lymphocyte-activation gene 3 (Lag-3). These phenotypic changes along with failure of immune system to clear

pathogens in chronic infection exhaust functional T cell response. These primarily promote terminally differentiated T cells and inhibiting formation of CD8⁺ T cell memory. Furthermore, antiviral activity and CD8⁺ T cell response drastically increase when signalling through PD-1 is prevented. These observations signify that T cell immune response has ceased reversibly. However, molecular mechanisms that conserve terminally differentiated T cells in chronic infections and improvement in T cell response after checkpoint inhibition remain poorly understood of time, which still mediates certain level of virus control.

The pathogenesis of T cell also depends on processing pathogen components by Antigen Presentation Cells (APCs), and their presentation via Major Histocompatibility Complex (MHC). Antigenic diversity of peptides enhances viral pathogenesis, where diversity of MHC and TCR repertoire in viral pathogenesis is yet unexplored. The different methods are administered likewise in vivo and ex vivo to elucidate T cell responses and their mechanism in viral pathogenesis. Therefore, to explore the diversity of the viral proteins and its pathogenesis in effector T cell immune reaction and their mechanisms are important. As a result, there is a potential for designing new therapeutics to combat the viral pathogenicity. Additionally, viruses also exploit complement system for cellular entry as well as their spread.

9.2   T Cell Responses in SARS Virus

There are more than 8000 cases of respiratory diseases among which the Severe acute Respiratory Syndrome (SARS) is caused by novel coronavirus (SARS-CoV), and contributed to 10% of mortality in 2002–2003. Pro-inflammatory responses enhance disease progression. The mechanism of immune evasion is mainly characterised by poor antigen presentation by antigen presentating cells (Legge and Braciale 2003). The antigen presentation is key for activation of T cell and produces chemokines and cytokines that regulate disease progression (Seder et al. 2008). The immune evasion of novel coronavirus targets APC and suppresses T cell activation. Dendritic cell immunisation activates T cells. As a result, the production of IFN-gamma, IL-2 and TNF-alfa are released (Zhao et al. 2010). Therefore, the viral titre gets reduced as immunisation with Dendritic cells (DC) by T cell activation successfully suppressed viral pathogenesis. It can be characterised as a potent immunogen to activate immune response.

9.3   T Cell Responses in West Nile Virus

West Nile Virus is a positive sense single-stranded RNA belongs to Flaviviridae and transmitted by mosquito vectors and originated in the USA in 1999, it causes mosquito borne encephalitis. It is asymptomatic in majority of individuals and symptoms usually are arthralgia, myalgia and cephalea. The minor part of pathogenesis can be neurologic deficits and neuroinvasive in elderly people. Viral pathogenesis mainly

favours by efferocytosis activator TIM-3, which inhibits CD8$^+$ T cell activation (Lanteri et al. 2014). The viral RNA plays major role in dampening the CD8$^+$ T cell activation and it activates CD4$^+$ T cell expresses Th1 and Th17 cytokines that favours neuroinvasion (James et al. 2016). viral RNA mainly responsible in regulating T cell pathogenesis and responsible for neuroinvasion. As per study, CD8$^+$ T cell activation controls viral replication, tissue tropism and infection (Aguilar-Valenzuela et al. 2018). Despite the fact that CD8$^+$ T cell activation reaches peak expansion in the periphery of west nile virus by 7-day post infection followed by chemokine activation of CXCR3. As a result, viral clearance activated by membrane-mediated apoptosis (Shrestha and Diamond 2007) was recently evidenced to combat viral replication, novel recombinant TCR can enhance immune response (Aguilar-Valenzuela et al. 2018).

9.4   T Cell Responses in Japanese Encephalitis Virus

Japanese encephalitis virus (JEV) is an arthropod borne member belongs to family Flaviviridae, which is endemic to rural parts of South and Southeast Asia. The virus mainly infects children and it causes death. The JEV possess a single-stranded, positive sensed RNA genome and its 10 kb open reading frame (ORF) encodes four structural proteins, envelope (E), premembrane (prM), core (C) and seven non-structural (NS). The JEV viral pathogenesis mainly inhibits infiltration of T cells due to production of low levels of IFN-gamma and regulates production of IL-2 (Kumar et al. 2004). As a result, JEV is successful in disease progression. The IFN-gamma plays important role in the activation of T cells. In recent study, modes of activation of TCR by various viral epitopes and maintaining levels of IFN-gamma and increasing infiltration of activated T cells (Turtle et al. 2016).

9.5   T Cell Responses in Acute Dengue Virus

The immune evasion strategy of viruses mainly by producing diversity of viral proteins and enhances viral pathogenesis. The HLA alleles on CD8$^+$ T cell and diversity of viral protein presentation are not uniform in viral pathogenic environment makes the strong presentation of viral pathogenesis (Weiskopf et al. 2013). As a result, T cell activation is suppressed due to less polymorphism of HLA. The T cell cross-reactivity plays an important role in disease pathogenesis. Likewise, disease serotypes fail to provide immune response against later stage secondary infection of dengue virus and unresponsiveness to T memory cells to secondary infection, which are produced in primary infection and it also produces Types 1 and 2 cytokines and responsible for other pathologies (Duangchinda et al. 2011). Therefore, cytotoxic memory T cell enhances viral replication and it is considered as original antigenic sin (Mongkolsapaya et al. 2003). Therefore inorder to combat the strategy was applied to activate CD8$^+$ T cell, as a result IFN-gamma enhances immune response against DENV peptides.

9.6   T Cell Responses in Viral Hemorrhage Fever

The viral hemorrhage fever (VHF) majorly regulates T cell priming, effector T cell response and T cell activation (Dahlke et al. 2017). Early during VHF, the antigen-presenting cells produce high levels of IFN-gamma and TNF-alfa and IL-6. As a result, activation of T cells increases viremia and overproduction of IFN-gamma and TNF-alfa this results in over activation of T cells (Perdomo-Celis and Salvato 2019) This condition is termed as cytokine storm. During VHF the proportions of regulatory T lymphocytes decreases and therefore, this enhances disease pathogenicity.

9.7   T Cell Responses in Chronic and Acute Viral Infections

The chronic and viral infections effect a plethora of T cell populations drastically. The CD4^{+} T cells and CD8^{+} T cells are major players in regulating viral pathogenesis. The other differentiated T cell called regulatory T cell, which regulates immune responses and inflammatory responses. During chronic and viral infections, T reg plays important role in regulating immune responses and various cytokines (Keynan et al. 2008). As a result, it regulates effector T cells population. In chronic viral infections, depletion of Treg cells, CD8^{+} T cell proliferation (Boettler et al. 2005), IFN-gamma production and increase cytolytic activity are predominant (Haeryfar et al. 2005). In HIV infection, due to decrease in Treg population, hyper activation of CD4^{+} and CD8^{+} T cells is predominant (Oswald-Richter et al. 2004) As a result, it favours viral replication.

9.8   T Cell Responses in Human Papilloma Virus (HPV)

Human Papilloma Virus (HPV), a small DNA virus majorly infects birds, reptiles and mammals, there are 300 viral genotypes that have been discovered till now (Vande and Klingelhutz 2013). The HPV infects mucosal and/or cutaneous skin and causes benign or malignant tumours. HPV associates with cervical cancer, oral squamous carcinoma and Head and Neck cancers (Forman et al. 2012). The HPV oncoproteins, E6 and E7, majorly regulates the host immune responses and plays vital role in tumorigenesis (den Boon et al. 2015). The HPV16 viral particle involves in the host immune dysregulation by epigenetic mechanisms. The viral pathogenesis regulates the synthesis of chemokines that required for T cell activation, i.e. CXCL14 (Cicchini et al. 2016). The CXCL14 synthesis regulated epigenetically by HPV viral protein, i.e. E7. Likewise, the HPV viral protein interacts with the host DNMT1 and stimulates the methylase activation (Burgers et al. 2007) and as a result, CXCL14 is repressed. Therefore, evasion of immune responses against virus, by inhibiting the T cell activation. The HPV16 E7 suppresses the production of pro-inflammatory responses like IL-8, IL18, CCL2, CCL20 (Cho et al. 2001; Guess and McCance 2005; Huang and McCance 2002; Kleine-Lowinski et al. 2003)

Additionally, HPV16 E7 upregulates the immunosuppressive genes like IDO1 and it triggers the activation of Treg cells (Mittal et al. 2013). Strikingly, the HPA18 E6 and E7 proteins jointy dysregulate the T cell activation by binding directly to the proteins involved in non-receptor tyrosine kinase signalling pathway (Li et al. 1999). As result, it downregulates the IFN-alfa and other cytokines like IL-6 and IL12. The HPV proteins regulate the IFN signalling for its major mechanism in evading the host T cell responses. The MHC restriction is a typical immune escape used by the HPV protein E5 by downregulating the MHC-I complex (Ashrafi et al. 2005, 2006). Hence HPV hinders the activation of CD8+ T cell and evasion of host responses are dysregulated by viral proteins and favours for the tumour progression.

9.9   T Cell Responses in Hepatitis B Virus

There are more than 350 million people infected with the Hepatitis B virus. The virus mainly infects liver and causes chronic and acute pathology. The infection carried commonly by mother to child during birth. The one in all among the viruses, which is a non-retroviruses that uses the host RNA polymerase for its transcription and as a result, the closed circular DNA gets transcribed and involved in the host disease pathogenesis. The adaptive immunopathogenesis plays important role in the disease progression. The liver residing APC plays an important role in the activation of naïve CD4 T and CD8 T cells via cross-priming and facilitates the persistence of the virus (Lan et al. 2016). The downregulation of the TLR-7 and TLR-9 in plasmacytoid dendritic cell and as a result, the IFN signalling is inactivated and cytokines are inhibited (Seeger and Mason 2000). The NK cells are also major cells providing immune to the HBV by expressing death ligand and inactivating the CD4 T cells Bertoletti and Ferrari 2016). The CD8 T cells exhaustion is the major episode in the disease pathology by expressing death receptors such as TIM-3, PD-1 and 2B4, poor proliferative signal, IL-2 and IFN-gamma (Raziorrouh et al. 2010). The CTL apoptosis of CTL by upregulation of various apoptotic genes likewise, Bim and TRAIL-R2. Due to downregulation of T-bet results in exhaustion of the T cells.

9.10   T Cell Responses in Zika Virus

Zika virus is mainly infected by mosquito borne flavivirus and it has unexpected links with microcephaly and Guillain–Barre syndrome. It is hypothesised as the infection resultant to the testis damage. The Zika viral infection results in the expression of TIM-4, which is one of the phagocytic markers and facilitates viral replication (Osuna et al. 2016; Zhang et al. 2018). The population of lymphocyte subsets are reduced in the period of infection. The virus getting successfully evading the host immune responses. The current study in combatting the viral immune evasion

mainly on designing the RNA vaccines and T cell epitope tetramer for activation of T cells, recombinant vector-based vectors (Zang et al. 2018).

9.11   Future Perspectives and Conclusions

Acquired immunity plays an important role to eliminate the pathogen by activating APC, CD4 T and CD8 T cells. The APC presentation by MHC and the presented processed peptide activates the TCR and CD4 and CD8 associated with MHC stabilises the TCR activation. The TCR activation supported by the co-stimulatory molecules like CD28/B7 activates the T cell proliferation. As a result, the IL-2 and other cytokines and chemokines are released. The TLR's are the receptors which activates the innate immunity and as a result, the activation of chemokines and cytokines are upregulated and various proliferative signals are activated with the response to the PAMP's. The naïve T cells, as aresult differentiates into CD4 and further has different subsets like, Th1, Th2, Th17 and T reg. The other CD8 T and memory T cells are prominent cells in elimination of disease. The virus infection evades the acquired immunity and immune responses by various mechanisms. The viral antigen manipulates the host immune responses by inhibiting the proliferative signals, expressing exhausting receptors, MHC restriction and various anti-inflammatory cytokines. The viral proteins upregulate apoptotic genes and inhibits immune responses of T cells. Due to high diversity of viral proteins, the HLA polymorphism is restricted, hence the MHC restriction and MHC cross presentation makes more significant in the viral persistence. The TLR-7 and TLR-9 are majorly downregulated in the HBV and provide immune to the viral propagation. The differentiation of the CD4 Th cells into Regulatory T lymphocytes hinders the immune activation and provide immune-resistance to the virus. In few viral serotypes, the T memory cells fail to respond to the secondary infection. In VHF, the overexpression of cytokines like TNF-alfa, IFN-gamma and IL-6 are responsible for 'cytokine storm' and increase viremia and favour in disease progression. The NK cell-mediated immune evasion in cancer causing viruses is unique by causing exhaustion of T cell and therefore, inhibiting immune responses.

There are vast potential targets to design the therapeutic and diagnosing markers for the virus. Recently, immunotherapy is a novel application for treating various virus pathogenicity by PD-1/PD-L1, this infers the overcoming the exhaustion of T cells (Pauken and Wherry 2015). The active T cell induces immune responses against viral titre and resolving the immune evasion of viruses. The tcf1 can be a potential biomarker for the chronic viral infections. The acquired immunity is a potential target to combat against the viral infection. The RNA-based Next-generation sequencing play an imperative role in transplanting the γδ T cell antigen receptors from the human cohort (Utzschneider et al. 2016). Ex vivo application of IFN-gamma is also a potential therapeutic activation of viral immune responses (Turtle et al. 2016). Immunisation of acquired immune responses by activating the DC cells viral peptide and evade the anergic condition (Zhao et al. 2010). The maintenance of antiviral peptides from the healthy infected individuals is the potential strategy for combatting the immune evasion.

Conflict of Interest The authors declare that they have no competing interests.

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