Immune Checkpoints in Viral Infections

Subjects: Zoology

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As evidence has mounted that virus-infected cells, such as cancer cells, negatively regulate the function of T-cells via immune checkpoints, it has become increasingly clear that viral infections similarly exploit immune checkpoints as an immune system escape mechanism. Although immune checkpoint therapy has been successfully used in cancer treatment, numerous studies have suggested that such therapy may also be highly relevant for treating viral infection, especially chronic viral infections. However, it has not yet been applied in this manner. Here, we reviewed recent findings regarding immune checkpoints in viral infections, including COVID-19, and discussed the role of immune checkpoints in different viral infections, as well as the potential for applying immune checkpoint blockades as antiviral therapy.

Keywords: immune checkpoint ; virus ; chronic infection ; immunotherapy

1. Introduction

Viral infections, especially chronic viral infections, are still a major threat to global health. Currently, the world is facing the serious challenge of a viral pandemic (coronavirus 2019; COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has infected over 28,000,000 people and resulted in nearly 930,000 deaths globally. Additionally, more than 325 million people worldwide are infected with chronic hepatitis B [1] and about 1.2 million people worldwide die each year from acquired immune deficiency syndrome (AIDS) and related diseases [2]. In chronic viral infections, the virus escapes elimination by the immune system and establishes a persistent infection by modulating or regulating the host immune response [3]. Many chronic viral infections result in T-cell exhaustion, which is the main source of host difficulty in eliminating such infections [3][4]. As a negative regulatory signal for the activation and proliferation of T-cells, the immune checkpoint pathway is involved in the immune escape of many viruses [5][6].

Immune checkpoint molecules are negative regulatory receptors expressed on immune cells. Under normal physiological conditions, they function as a brake for the immune system, maintaining self-tolerance and preventing immunopathology in the body [7]. However, these molecules have also been shown to participate in the mechanism of immune escape by causing T-cell dysfunction in a variety of diseases, such as cancer and infection. The expression of immune checkpoint molecules on suppressor cells, such as regulatory T- (Treg) and regulatory B (Breg)-cells, could affect the function and cytokine secretion of these cells. Although the concept of immune checkpoints was first proposed in 2006 [8], research on the checkpoint receptors began much earlier. Allison discovered cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) in 1995 and began studying the therapeutic effect of anti-CTLA-4 antibody on tumors [9][10], and Honjo discovered programmed death-1 (PD-1) in 1992 [11]. Since then, additional immune checkpoint molecules, such as T-cell immunoglobulin and mucin domain-containing-3 (TIM-3) and lymphocyte activation gene-3 (LAG-3), have been discovered [12][13]. To date, at least six immune checkpoints have been found to be involved in viral infections.

Conventional antiviral therapy is usually incapable of eliminating chronic infection [14]. However, recent advances in cancer immunotherapy may be applicable as antiviral therapy for chronic viral infections. Seven immune checkpoint inhibitors (ICIs) targeting CTLA-4, PD-1, or programmed death-ligand-1 (PD-L1) have been approved for the treatment of certain cancers and have shown positive therapeutic outcomes in patients [15][16]. Moreover, as a new approach for effective T-cell activation, combination therapy targeting multiple immune checkpoints or applied with other therapeutic modalities such as vaccines are currently being tested in clinical trials [17]. Here, we reviewed the recent findings regarding immune checkpoints in viral infection. We also discussed the role of immune checkpoints in different viral infections and the potential of applying immune checkpoint blockades as antiviral therapy.

2. Immune Checkpoints and Their T-cell Inactivation Pathways

The immune checkpoint coinhibitory network acts by inhibiting T-cell activation through various mechanisms and signaling pathways.

PD-1 is preferentially expressed on the surface of activated T-cells and B-cells. Its expression has also been observed on the surface of other immunocyte subsets, such as natural killer (NK) cells, monocytes, and dendritic cells (DCs) [18][19]. The cytoplasmic tail of PD-1 has an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). When it binds to its ligand PD-L1/PD-L2, PD-1 translocates to T-cell receptor (TCR) microclusters and recruits SH2 domain-containing tyrosine phosphatase 2 (SHP2) by phosphorylating tyrosine residues in the ITSM [20]. Subsequently, the dephosphorylation of Zap-70 and LCK by SHP2 leads to inhibition of the Ras–MEK–MAPK pathway and interference with CD28 costimulatory signaling [21][22]. Additionally, SHP2 recruitment blocks the activation of phosphoinositide 3-kinase (PI3K) by completely binding to the phosphorylation kinases, then inhibits downstream Akt activation, which ultimately downregulates the activation of T-cells. A recent study suggested that the immune inhibitory function of PD-1 may occur via an SHP2-independent pathway [23]. PD-1 also can inactivate T-cells by promoting microcluster formation and degrading TCR on the surface of T-cells [22].

CTLA-4 is an important co-inhibitory receptor on T-cells that downregulates T-cell activation and induces tolerance [24]. It is transiently expressed following T-cell activation and blocks the costimulatory effect of constitutively expressed CD28 by competing with CD28 for CD80 binding [25]; it then inhibits Akt activation by recruiting PP2A [26][27]. Based on work in murine T-cells, CTLA-4 engagement results in T-cell suppression by limiting nuclear factor (NF)-κB and AP-1 transcriptional activity [28][29]. Recent research found that CTLA-4 expression induces high levels of the proapoptotic protein Bim in $CD8^+$ T-cells and promotes Bim-dependent apoptosis in T-cells [30].

TIM-3 is selectively expressed on $CD4^+$ T helper (Th)1 or Th17 cells [31], $CD8^+$ T cytotoxic 1 (Tc1) cells, and Treg cells, and this expression can lead to inhibition of the Th1 response and apoptosis of antigen-specific cells. Under normal circumstances, the molecular adaptor human leukocyte antigen B (HLA-B)-associated transcript 3 (Bat3), which binds to the intracellular tail of TIM-3, protects Th1 cells from TIM-3-mediated cell death or exhaustion. When galectin-9 (Gal-9) binds to TIM-3, Bat3 is released from TIM-3, allowing TIM-3 to bind to the SH3 domain-containing TCR-associated intracellular kinase LCK and then to mediate downregulatory signals that inhibit Th1 responses [32]. Some research has suggested that TIM-3 suppresses T-cell activation by suppressing the nuclear factor of activated T-cells (NFAT) dephosphorylation and AP-1 transcription [33][34].

T-cell immunoglobulin and ITIM domain (TIGIT) is typically expressed on activated human T-cells, human NK cells, memory T-cells, and Treg cells. When TIGIT binds to CD155 (PVR) or CD112 (PVRL2 or Necl5) expressed on antigen-presenting cells (APCs), an inhibitory signal for T-cell activation is directly transmitted via the cytoplasmic tail of TIGIT [35]. The phosphorylated ITT-like motif in the TIGIT cytoplasmic tail binds the cytosolic adapter growth factor receptor bound protein 2 (Grb2) and then recruits SH2-containing inositol phosphatase-1 (SHIP-1), which further inhibits the PI3K and MAPK signaling pathway [31]. Additionally, TIGIT can also indirectly improve the negative regulation function of DCs and Treg cells [36][37].

LAG-3 is not expressed by naive T-cells, but its expression is induced upon T-cell activation. Compared with PD-1, LAG-3 displays a moderate immunosuppressive activity. LAG-3 can transmit inhibitory signals via the KIEELE motif in its cytoplasmic tail, the FXXL motif in its membrane-proximal region (PR), or its C-terminal EX repeat [38]. However, the molecular mechanism by which LAG-3 inhibits T-cell activation is still largely unknown.

B and T lymphocyte attenuator (BTLA) is selectively expressed on Th1 cells and has been identified as an immune checkpoint receptor. Upon BTLA binding to herpesvirus entry mediator (HVEM), the BTLA cytoplasmic domains ITIM and ITSM bind to and activate the tyrosine phosphatases SHP-1 and SHP-2, which leads to the inhibition of lymphocyte-specific protein tyrosine kinase (LCK)-dependent T-cell activation [39][40]. Additionally, the third domain Grb-2-recognition motif in BTLA can recognize the Grb-2 protein, subsequently recruiting the PI3K protein subunit p85, stimulating the PI3K signaling pathway, and finally promoting cell proliferation and survival. Unlike other immune checkpoint regulators, BTLA can both positively and negatively co-stimulate T-cell regulation [41].

3. Immune Checkpoints in HIV

Human immunodeficiency virus (HIV) infects mainly T-cells. HIV infection destroys the host immune system and makes the infected individual increasingly more vulnerable to a range of infections, cancers, and other diseases. Recent research has shown that immune checkpoints extensively participate in HIV infection via their role in inhibiting T-cell function; the two main ways in which they act are by causing T-cell exhaustion and helping to establish HIV-latency reservoirs [42][43].

4. Immune Checkpoints in Hepatitis Virus

Chronic infection caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) is the main cause of liver cancer. Around 15%–40% of HBV-infected individuals are predisposed to cirrhosis or hepatocellular carcinoma (HCC) [44]. In Japan, HCV infection is the major risk factor for HCC (80%–90%) [45]. Three-quarters of HCV infections develop into chronic hepatitis. Fortunately, highly effective direct acting antivirals (DAA) targeting NS3 protease, NS5A polymerase, or NS5B polymerase can cure over 95% of HCV-infected individuals [46]. HBV is a small, enveloped, DNA virus. During HBV infection of hepatocytes, the relaxed circular DNA genome (rcDNA) of HBV is transported into the nucleus and converted into covalently closed circular DNA (cccDNA) to serve as a viral persistence reservoir [47], which is refractory to current antiviral therapies [48]. Life-long nucleoside/nucleotide analogue (NA) therapy can achieve long-term suppression of viral replication, but it cannot eliminate cccDNA. Consequently, the withdrawal of NA therapy poses the risk of viral rebound [49].

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