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REVIEW

immunology
Insights into immunity in health and disease

New sights of low dose IL-2: Restoration of immune homeostasis for viral infection

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Abstract

Viral infection poses a significant threat to human health. In addition to the damage caused by viral replication, the immune response it triggers often leads to more serious adverse consequences. After the occurrence of viral infection, in addition to the adverse consequences of infection, chronic infections can also lead to virus-related autoimmune diseases and tumours. At the same time, the immune response triggered by viral infection is complex, and dysregulated immune response may lead to the occurrence of immune pathology and macrophage activation syndrome. In addition, it may cause secondary immune suppression, especially in patients with compromised immune system, which could lead to the occurrence of secondary infections by other pathogens. This can often result in more severe clinical outcomes. Therefore, regarding the treatment of viral infections, restoring the balance of the immune system is crucial in addition to specific antiviral medications. In recent years, scientists have made an interesting finding that low dose IL-2 (ld-IL-2) could potentially have a crucial function in regulating the immune system and reducing the chances of infection, especially viral infection. Ld-IL-2 exerts immune regulatory effects in different types of viral infections by modulating $CD4^+$T subsets, $CD8^+$T cells, natural killer cells, and so on. Our review summarised the role of IL-2 or IL-2 complexes in viral infections. Ld-IL-2 may be an effective strategy for enhancing host antiviral immunity and preventing infection from becoming chronic; additionally, the appropriate use of it can help prevent excessive inflammatory response after infection. In the long term, it may reduce the occurrence of infection-related autoimmune diseases and tumours by promoting the restoration of early immune homeostasis. Furthermore, we have also summarised the application of ld-IL-2 in the context of autoimmune diseases combined with viral infections; it may be a safe and effective strategy for restoring immune homeostasis without compromising the antiviral immune response. In conclusion, focusing on the role of ld-IL-2 in viral infections may provide a new perspective for regulating immune responses following viral infections and improving prognosis.

KEYWORDS
IL-2, immunomodulatory, infection, low-dose IL-2 therapy, virus

INTRODUCTION

Viral infections have always posed a significant threat to human health. Not only are new viruses continually being discovered, but known viruses also undergo constant mutation, making diagnosis and treatment a great challenge. The pathophysiological mechanism of viral infections is complex, and it often leads to secondary bacterial infections, which are associated with more severe clinical outcomes. The immune response plays a more crucial role than the direct effects of virus replication during viral infection. Viral infections are prone to severe infection or sepsis, leading to excessive inflammation and immunosuppression at different stages, resulting in a significantly increased mortality rate [1, 2]. Especially for patients with immunosuppression, it is particularly important to promptly restore immune homeostasis and enhance the ability to respond to infections. It is crucial to regulate the disordered and dysfunctional immune systems in a timely manner for improving clinical outcomes.

In addition to the replication of the virus, viral infection also triggers a series of intricate and complex immune responses. The infected individuals must have a robust and well-coordinated immune response to eliminate the viruses. An inappropriate immune response can result in chronic infection, histopathological damage and even excessive inflammatory response or autoimmune diseases. There are still many gaps in our understanding of the pathogenic mechanism and treatment of viral infections. Uncontrolled viral replication and excessive inflammation are the main causes of death in virus-infected hosts. Due to the variation of the virus and its ability to evade the immune system, the options for antiviral therapy are currently very limited. It is important to consider both the use of specific antiviral drugs and the restoration of immune system balance in a timely manner for treat viral infections. Therefore, it is of great value to explore safe and effective immunomodulators in infection.

Endogenous IL-2 has been shown to be effective in enhancing the antiviral response by promoting cell proliferation and production of IFN-γ, as demonstrated in studies conducted several years ago [3]. In recent years, there has been a lot of research using low dose IL-2 (ld-IL-2) as a therapy for various autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and Type 1 diabetes (T1D) [4, 5]. Interestingly, researchers have found that ld-IL-2 can help regulate the immune response and clear viral infections [6, 7]. Studies have also focused on IL-2 complexes that target distinct immune subsets based on their expression of the IL-2 receptor (IL-2R) [8–10].

In our review, we aim to summarise the current research progress on the effects and immune mechanisms of IL-2 or IL-2 complexes in viral infections. We discussed the role of IL-2 in different types of viral infections and its specific mechanism on different immune subsets. Additionally, we explored the potential of ld-IL-2 in autoimmune diseases combined with viral infections. Our goal is to provide insights and ideas for immune regulation strategies in viral infections, with the aim of improving prognosis and reducing mortality (Figure 1).

THE IMMUNOLOGY OF VIRUS INFECTION

The immune response to viral infections involve a series of complex processes that work together to protect the host. Different types of viruses trigger different immune responses based on their unique characteristics. However, in general, both the innate and adaptive immune systems are involved in fighting against viruses.

Innate immune response

The innate immune response is the first line of defence against viral infections. It includes physical barriers, such as the skin, as well as various types of cells like phagocytes, cytokines and interferons (IFNs). This response is rapid but not specific. Viruses often enter the host by disrupting these physical barriers. For example, influenza A viruses (IAVs) primarily infect cells in the airway and lungs [11], whereas Epstein–Barr virus (EBV) infects oral epithelial cells and B cells in the tonsils [12]. Human immunodeficiency virus (HIV) initially infects mucosal tissues and then spreads to lymphoid organs within days [13]. In some respiratory virus infections, airway epithelial cells, natural killer (NK) cells, alveolar macrophages and dendritic cells (DCs) play key roles in eliminating the virus and limiting its spread. DCs also help establish the connection between the innate and adaptive immune responses during a viral infection. Additionally, DCs also can exert cytolytic activity. NK cells have multiple mechanisms to fight against viruses, such as releasing cytotoxic granules and producing cytokines. However, viruses have evolved strategies to evade the NK immune response, including the expression of specific viral proteins that can decrease the antiviral activity of NK cells [14]. Type I and type III IFNs are crucial for the antiviral response, and autoantibodies against certain IFNs have been observed in some patients with severe COVID-19 [15]. Fox example, autoantibodies directed

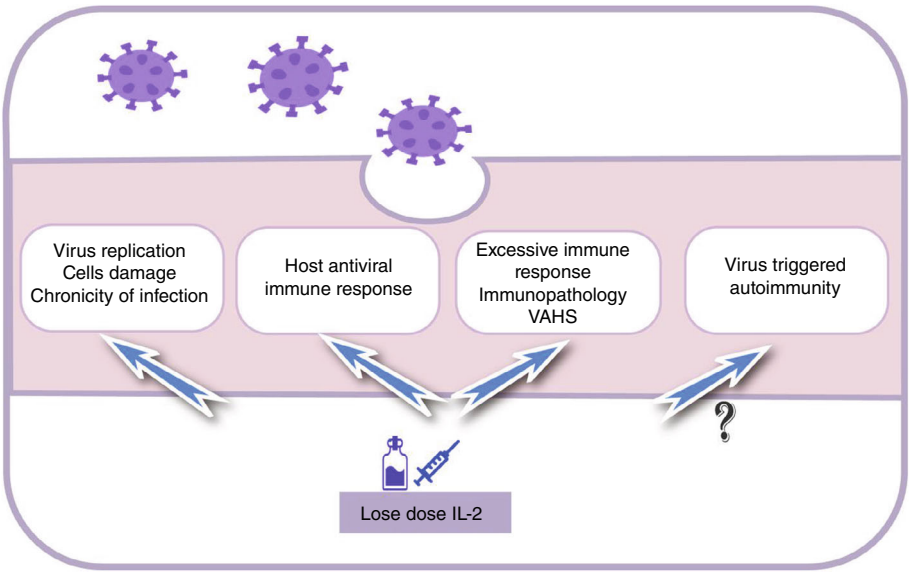

FIGURE 1 The potential role of low dose-IL-2 in viral infections. Low-dose IL-2 may act through several mechanisms: (1) enhance host antiviral immunity and prevent infection from becoming chronic; (2) avoid excessive immune response, such as immunopathology, VHAS, and so on; (3) may prevent the occurrence of virus-induced autoimmune diseases and tumours. VAHS, virus-associated haemophagocytic syndrome.

against IFN α2 and IFN ω were observed in some patients with life-threatening COVID-19 [16]. It is of great significance that recent research has discovered that commensal microbiota can regulate the response of IFNβ and IFN-I. This role has been found to enhance the body's resistance against virus infections [17].

Adaptive immune response

T cells, specifically $CD4^+$ and $CD8^+$ T cells, and B cells play key roles in the adaptive immune response against viruses. Viruses lack their own biosynthetic or metabolic machinery and replicate inside infected cells. They can be cleared by antibodies before entering cells, but once inside, they can only be eliminated by destroying or modifying the infected cells. $CD8^+$ T cells can transform into cytotoxic T cells, which play a crucial role in immune defence. These cells release three types of cytotoxic proteins, namely granzymes, perforin and granulysin, to effectively eliminate viruses. Additionally, cytotoxic T cells can induce apoptosis in target cells and release cytokines to inhibit viral replication. One of the main immune dysfunctions in chronic hepatitis B virus infection is the impairment of HBV-specific $CD8^+$ T-cell responses. Lymphocytic choriomeningitis virus (LCMV) infection also triggers a strong response from $CD8^+$ T cells.

Naïve $CD4^+$ T cells have the capability to differentiate into various subsets, including Th1, Th2, Th17, Tfh, Treg cells and more. HIV replication primarily affects $CD4^+$ T cells and leads to a wide array of immunological abnormalities [13]. Among these $CD4^+$ T subsets, Th1 cells produce antiviral cytokines like IFN-γ, TNF and IL-2 [18]; these cytokines then activate alveolar macrophages regulate the differentiation of $CD8^+$ T cells to effectively clear viruses [19, 20]. Th2 cells secrete IL-4, IL-10 and IL-13, which enhance cell proliferation, activate antibody production and facilitate the switching of antibody classes. Furthermore, Tfh cells primarily release IL-21, which plays a role in mediating B cell immune responses [21]. Some researches have confirmed the existence of Th1 and Th2, Treg and Th17 imbalance in some types of viral infections [22, 23]. Tfh cells play a crucial role in the seroconversion of hepatitis B virus envelop (HBe) and hepatitis B virus surface (HBs) antigens [24].

B cells are essential for initiating the immune response against viral infections. However, memory B cells and plasma cells are necessary for a protective immune response and the development of vaccines. Antibody-dependent cell-mediated cytotoxicity (ADCC) also helps in killing target cells and clearing viruses. Some viruses, like EBV, can easily infect B cells with long incubation periods and enter the memory B lymphocytes.

Immunopathology

$CD8^+$ T cells perform precise cytotoxic functions that only target infected cells, sparing normal adjacent cells. This precision helps minimise tissue damage while eliminating infected cells. However, when this regulation is disrupted, $CD8^+$ T cells can contribute to immunopathology. An excessive immune response can lead to severe tissue destruction. Virus-triggered immunopathology is observed in LCMV infection mouse models [25]. Interestingly, studies suggested that impaired immune responses, rather than exaggerated immune responses, may be the

primary cause of immunopathology [26, 27]. This leads to ongoing stimulation of $CD8^+$ T cells and eventually results in persistent inflammatory response and the development of chronic immunopathology [28]. Therefore, there is often a state of low immune response rather than high inflammation in some viral infections. Under the circumstances, strengthening the immune response instead contributes to the restoration of immune homeostasis, thereby interrupting the vicious cycle of immunopathology.

Accordingly, the combination of antiviral therapy and enhanced immune therapy is helpful to the recovery of some viral infection. It also suggests that the transformation of our concept from immunosuppression to immune regulation may bring us new ideas for treatment.

Virus-associated haemophagocytic syndrome

Haemophagocytic syndrome, also known as haemophagocytic lymphohistiocytosis (HLH), is a severe and life-threatening hyperinflammatory syndrome. It can be divided into primary and secondary forms [29]. Secondary HLH is primarily caused by infection, malignant tumour, autoimmune disorders and immunosuppression [30]. HLH secondary to SLE, juvenile idiopathic arthritis and other rheumatic disease is often used to be called macrophage activation syndrome [31]. Virus infection is a common cause of secondary HLH caused by infection. Here, we are focusing on virus-associated haemophagocytic syndrome (VAHS). Recent research has shown that several types of viruses, including EBV [32, 33], CMV [34], HIV [35], parainfluenza virus [36], human herpesvirus Type 6 (HHV-6) [37] and other types of viruses [38] can trigger HLH. Among VAHS, EBV is major cause of HLH, and EBV-HLH is associated with a high risk of death and multi-organ failure. CMV reactivation leading to HLH often occurs in individuals with pre-existing autoimmune disorders [39, 40], immunosuppression or co-infection with other pathogens [41]. In such cases, it is crucial to promptly confirm CMV infection. In healthy individuals, cytolytic cells are able to induce activated macrophages and T cells apoptosis to control inflammatory response when virus infections occur. However, once the cell lysis function is impaired or defective, the immune system will be overactivated. Dysfunction of NK cells and cytolytic $CD8^+$ T cells leads to pro-inflammatory cytokine cascades [42]. Cytokine storm leads to macrophage activation, haemophagocytosis and multi-organ failure [31]. Even cytokine storm and immune cell dysfunction create a vicious cycle of mutual influence. In the setting of VAHS, early diagnosis and timely treatment are essential. Additionally, antiviral elimination therapy to eliminate the precipitating factors, appropriate targeted immune cell such as activated macrophages and T cells therapy also plays a vital role in treatment. Moreover, virus infections can often be accompanied by secondary infections caused by other pathogens. Therefore, it is essential to address these coexisting infections and identify other potential triggers of HLH. Despite the availability of treatment strategies for patients with VAHS, the prognosis remains less than ideal, and the current methods often have significant side effects. Due to the life-threatening nature of the condition, it is necessary to explore new strategies that minimise side effects and improve the prognosis.

Virus-trigged autoimmunity

Virus have been always considered as main environmental factors to triggering the occurrence of autoimmunity diseases, including SLE, T1D, RA, multiple sclerosis and so on. Currently, viruses that have been confirmed to be related to autoimmunity include EBV, CMV, IAV, rotavirus, parvovirus B19 and so on [43]. In addition, since the COVID-19 pandemic, some infected patients have been clinically observed to develop some confirmed autoimmune diseases or associated autoimmune syndromes secondary to infection, such as RA, SLE and Guillain-Barrė syndrome [44–47]. These findings provide substantial evidence that viral infections can trigger autoimmunity. At present, the confirmed mechanisms of virus-associated autoimmunity are mainly related to antigen mimicry, amplification of type I IFN response, immune tolerance to destruction antibody production, superantigen and inhibition of apoptosis of infected cells [48, 49]. There are some differences in the mechanisms and characteristics of autoimmunity triggered by different types of viruses. But in fact, after viral infection, the host will coordinate antiviral immunity and autoimmunity, maintain the homeostasis of immune tolerance and induce autoimmunity only in the case of partial errors or immunity dysregulation. Contrarily, recent studies have provided some evidence suggesting a protective role of viral infection against autoimmunity, mainly by inducing regulatory immune responses after viral infection to prevent the occurrence of autoimmunity [50]. So, to some extent, the host's coordinated processes between the virus and autoimmunity may even help to mitigate autoimmunity. While the seemingly opposite effects of viruses and autoimmunity may not be contradictory, the dual effects of the host immune response in different circumstances may be related to a number of factors that are not yet fully understood.

Virus-associated cancers

It had been discovered that some types of virus infections are related to the occurrence of cancers [51]. For example, we all know that EBV infection is closely related to the occurrence of lymphoma, nasopharyngeal carcinoma and a subset of gastric cancers [52].

Hepatitis B virus infection and high-risk human papillomavirus infections are related to the occurrence of liver cancer and cervical cancer. Additionally, Human T-cell lymphotropic virus, Type-1 (HTLV-1), Merkel cell polyomavirus, HHV-6, CMV and so on have also been found to have a possible carcinogenesis [53, 54]. The primary mechanism of direct carcinogenesis in most viruses is associated with the continuous expression and insertional mutation of specific oncogenes carried by cancer-causing viruses. Additionally, indirect carcinogenesis can occur through chronic inflammation and immunosuppression in infected cells, as long-term chronic inflammation can lead to the accumulation of DNA damage [54]. Identifying and characterising viruses that may have carcinogenic effects is the first step in preventing virus-related tumours. For known oncogenic viruses, vaccines and specific antiviral treatments are crucial and effective to reduce the incidence of virus-associated cancers. For example, the currently developed vaccines against hepatitis B and human papillomavirus can effectively prevent the occurrence of virus-related tumours. However, there is no specific vaccine for EBV, so it is important to prevent such virus-associated tumours by early screening and treatment, and by focusing on the recovery of immune homeostasis after infection.

BIOLOGICAL CHARACTERISTICS OF IL-2

IL-2 was first identified as an activity present that promote T cell growth and proliferation in 1976 [55]. It is now widely recognised as a pleotropic cytokine with potential therapeutic effects for various diseases. IL-2 is primarily produced by active $CD4^+$ T cells, but it is also secreted to a lesser extent by $CD8^+$ T cells, NKT cells and DCs [56]. IL-2Rs are divided into three classes according to the composition of three polypeptide chains. The low-affinity receptor only included IL-2Rα, intermediate affinity receptors contained IL-2Rβ and IL-2Rγ, and high affinity receptors contained IL-2Rα, IL-2Rβ and IL-2Rγ [9]. Intermediate affinity receptors are mainly expressed on the surface of resting NK and $CD8^+$T cells, whereas high- and low-affinity receptors are mainly expressed by activated lymphocytes. Especially, Treg cells constitutively express the high-affinity receptor, which makes them more sensitive to IL-2, and even ld-IL-2 can support the development and function Treg cells [9, 56]. Based on the different expression of IL-2R on the cell surface, IL-2 can play pleiotropic effects effect on different immune cells. Such as, IL-2 can promote the differentiation of Th1, Th2, Th9 and Treg, but suppresses the differentiation of $CD4^+$ T cells into Th17 and Tfh cells. Moreover, IL-2 can support the terminal differentiation of $CD8^+$ T cells, and mainly stimulates the proliferation and enhance the function of NK cells [57]. IL-2 combined with IL-2R exerted its biological effects mainly through the activation of the Janus kinase (JAK)–STAT, extracellular signal-regulated kinase and phosphoinositide 3-kinase pathways [56].

In the early stage, IL-2 was mainly clinically used in malignancies immunotherapy, but its clinical application in tumour was limited by its vascular toxicity, instability in vivo and the expansion of Treg cells. In recent years, ld-IL-2 has been used in many autoimmune diseases because it selectively activates suppressive Treg cells. But there is also a risk of activating effector T cells. Ld-IL-2 selectively targeted on Treg cells to maintain immune tolerance, it has high application value in autoimmune diseases [57, 58], but there are still some challenges, such as its short half-life and the risk of activating effector T cells. Therefore, there are many studies focused on manipulating the ability of IL-2 to target specific subsets as needed [59–61].

THE ROLE OF IL-2 AND EFFECT OF IL-2 THERAPY IN VIRAL INFECTION

Hepatitis virus

In a preliminary study, it was found that administering ld-IL-2 treatment can enhance the immune response to the hepatitis B vaccine in patients with end-stage kidney disease who did not respond well to the vaccine. The findings suggest that ld-IL-2 might be an effective approach to stimulate specific immune responses in patients with certain immune deficiencies [62]. In addition, ld-IL-2 therapy can improve immune function and clinical outcomes in patients with chronic hepatitis B who did not respond to standard treatment, and sequential IL-2 treatment can promote the loss of HBeAg [63]. Hepatitis C virus (HCV) can induce the incidence of vasculitis, some researched observed that the decrease of marginal-zone B cells and the improvement of symptoms of vasculitis in refractory HCV-induced vasculitis received ld-IL-2 treatment. Importantly, it did not affect the anti-viral immune response and increase viral loads [64] (Figure 2).

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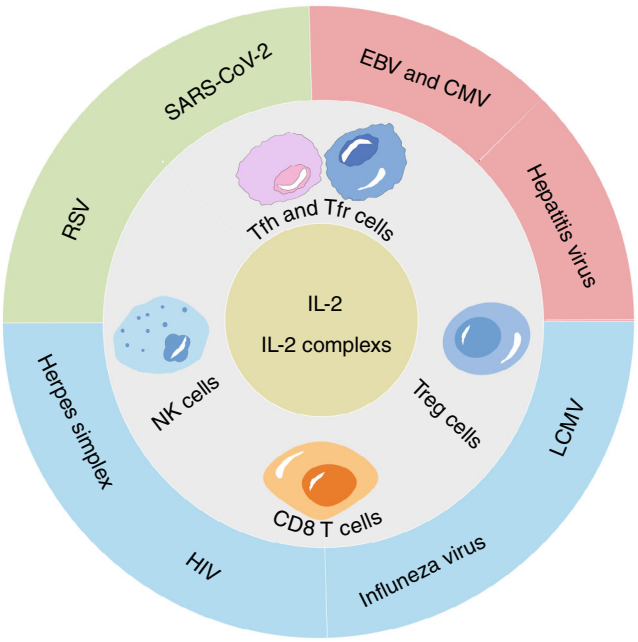

FIGURE 2 The immune regulation of IL-2 and IL-2 complex in virus infection. IL-2 plays an immune regulatory role in various virus infections by regulating the expression and function of Treg, Tfh, Tfr, $CD8^+$ T and NK cells. CMV, cytomegalovirus; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; LCMV, lymphocytic choriomeningitis virus; NK, natural killer; RSV, Human respiratory syncytial virus.

Lymphocytic choriomeningitis virus

LCMV is an ancient virus that serves as a valuable research tool for scientists investigating the underlying mechanisms of innate and specific immunity. LCMV primarily infects rodents, such as mice [65]. While natural LCMV infection does not typically cause obvious lesions, it may lead to classic lymphocytic choriomeningitis, immune-complex glomerulonephritis and vasculitis. In the mouse model of acute LCMV infection, IL-2 therapy improves the differentiation and cytolytic function of $CD8^+$ T cells [7]. However, it also worsens the immunopathology caused by $CD8^+$ T cells. On the other hand, a study investigating the combination of PD-1 blockade and IL-2 cytokine therapy found that it can enhance virus control by increasing LCMV-specific $CD8^+$ T cells [66] (Figure 2).

Epstein–Barr Virus/Cytomegalovirus

EBV is a gamma-herpesvirus with a high global infection rate of 95% that persists for life after the acute phase of infection [67]. CMV is a double-stranded DNA virus that also belongs to the herpesvirus family. Both are the common viruses infecting humans [68]. Opportunistic infections are common complication of connective tissue diseases (CTD), such as EBV and CMV viremia. Our previous study found that ld-IL-2 treatment can restore imbalance between Th17 and Treg cells in dermatomyositis (DM) patients with EBV/CMV viremia, the viral load of some patients decreased; in the meantime, there are no obvious abnormal laboratory indicators during the treatment. In summary, ld-IL-2 treatment may be beneficial for regulating immune balance in CTD with EBV or CMV infection without exacerbating existing infections [6] (Figure 2).

Influenza virus

Influenza viruses have the ability to infect humans and are a common cause of respiratory infections in humans [69]. These viruses have a high mutation rate, which makes them susceptible to escaping the immune system [70]. Zhou et al. found that IL-2 treatment can promote the generation and enhanced the cytotoxic functions of effector $CD8^+$ T, leading to the clearance of influenza virus [7]. This suggests that ld-IL2 can enhance the immune response to influenza virus infection. IL-2 complexes made with the antibody clone JES6-1A12 (JES6) have been found to selectively activate Treg cells expressing CD25, resulting in anti-inflammatory effects [71]. Another kind of complexes made with the Ab clone S4B6 can preferentially excite expressing those cells that express high CD122, predominantly $CD8^+$ T and NK cells [71, 72]. Many studies support that memory $CD4^+$T cell-derived IL-2 may be vital to fight off IAV infection [73, 74]. Then to test this possible hypothesis, a team of researchers unexpectedly found IL-2 secreted from memory $CD4^+$ T cell instead accelerated early inflammatory response especially in the lung during acute IAV infection murine model. In the proof-of-mechanism experiments, it was found that IL-2 complexes (S4B6) therapy led to a strong expression of inflammatory cytokines in the lung and serum, resulting in accelerated acute death. This effect was related with the involvement of NK cells [75]. On the other hand, treatment with JES6 IL-2Cs also promoted the release of inflammatory mediators, but had opposite survival outcomes. JES6 IL-2Cs improved lung immunopathology and promoted the formation of $CD4^+$ T cell memory during IAV infection. It was also shown that the different outcomes of the two IL-2 complexes in IAV infection were due to the distinct, but partially overlapping, patterns of inflammatory response they induced [76]. In brief, these findings suggest that while IL-2 or its complexes may contribute to virus control and immune regulation during viral infection, the tissue inflammatory environment in

which IL-2 or engineered IL-2 acts must be carefully evaluated to prevent tissue damage and excessive inflammatory response. (Figure 2).

Herpes simplex virus

Herpes simplex viruses are highly prevalent pathogens worldwide [77]. The mucosa or skin is the most common site of primary infection, and conditions such as herpes and keratitis may occur after infection. HSV infection is usually mild, but in some immunocompromised patients, it can lead to meningitis, pneumonitis and hepatitis [78]. Recombinant IL-2 combined with anti-IL-2 (clone S4B6) therapy has been shown to decrease virus levels and reduce the severity of lesions in the model of HSV-1 infection [79] (Figure 2).

Human immunodeficiency virus

HIV infection can lead to the development of Acquired Immune Deficiency Syndrome (AIDS), a life-threatening infectious disease that attacks the immune system and impairs its function [80]. $CD4^+$ T cells are the primary target of HIV. A clinical trial has discovered that intermittent IL-2 treatment can significantly increase $CD4^+$ T cells in HIV-infected patients, indicating that the increased $CD4^+$ T cells are derived from peripheral expansion rather than the thymus [81]. In the Friend Retrovirus model, which is used to study retroviruses, it has been observed that the IL-2 mAb S4B6 complex can effectively reduce viral loads [82]. (Figure 2).

Human respiratory syncytial virus

Human respiratory syncytial virus (RSV) primarily causes severe respiratory tract diseases in infants under 6 months old, and upper respiratory tract infections such as rhinitis and colds in older children and individuals with weakened immune systems [83]. A study has demonstrated that $CD4^+$ T cells produce a significant amount of IL-2, which may promote the increase of Group 2 innate lymphoid cells (ILC2) in the lungs during RSV infection. Furthermore, ILC2 and their secreted cytokines can greatly exacerbate airway inflammation, particularly during the early phase of RSV infection [84]. This suggests that IL-2 may mediate the aggravation of the inflammatory response during RSV infection. Tfh cells are essential for producing protective antibodies against secondary infection in a murine model of RSV infection, but increased IL-2 inhibit the generation of Tfh cells, thereby limiting antibody-mediated immunity after early-life infection [85]. However, one study found that the co-expression of mIL-2 by recombinant RSV can moderately reduce virus growth and enhance the response of pulmonary $CD4^+$ T cells. Additionally, the level of antibody induced by it was comparable to that of wild-type RSV [86]. There are still conflicting results regarding the role of IL-2 in RSV, and further studies are necessary to explore whether IL-2 could be a novel immunomodulatory strategy in RSV infection (Figure 2).

SARS-CoV-2

In the past few years, the COVID-19 caused by the virus SARS-CoV-2 had become a global pandemic, its respiratory symptoms range from mild to severe forms [87]. The immune mechanisms involved in COVID-19 infection are complex. Now in the post-COVID-19 period, more attention is focused on prognosis rehabilitation of the post-COVID condition [88]. Post-COVID syndrome is accompanied by a series of immune disorders [89]. The latest research suggests that recombinant human IL-2 contributes to the immune recovery of post-COVID syndrome patients with low levels of NK cells, which is undoubtedly essential for the prevention of secondary infections [90]. However, a randomised controlled clinical trial found that ld-IL-2 was safe, but its clinical improvement was ineffective for COVID-19 [91]. (Figure 2).

Other types viruses

Polyoma BK virus (PBK) is a virus that specifically infects the human urinary system and is a member of the polyomavirus family. It is associated with the occurrence of a variety of diseases. BK virus is usually dormant, but it can become active and cause kidney-related diseases, especially after immunosuppression [92]. A systematic review of published studies has suggested that IL-2 plays a protective effect in PBK reactivation during immunosuppression in renal transplantation [70]. Furthermore, IL-2 also has a function in regulating the immune response to certain uncommon viruses, such as Tick-borne encephalitis virus [93].

IMMUNE REGULATION MECHANISM OF IL-2 AND LOW-DOSE IL-2 THERAPY IN VIRUS INFECTIONS

Treg cells

IL-2 is indispensable for the development and suppressive function maintenance of Treg cells. The role of Tregs

in infection has been debated, as their suppressive function of antigen-specific T-cell responses may hinder the immune response against viruses [94, 95]. But actually, Treg cells are for preventing immune hyperactivation and reducing tissue damage during infection. They can also decrease the risk of viral infection-related immune dysfunction and autoimmunity by resisting virus infection-induced apoptosis [96].In HIV infection, Treg cells can limit potential targets for HIV infection and minimise the pathological effects [97, 98]. Additionally, HIV itself can directly infect Tregs [99]. Based on these observations, using ld-IL-2 as a strategy to modulate the immune system and target Treg may be a promising approach to restore immune balance during viral infections. A previous study showed that ld-IL-2 can improve HCV-induced vasculitis by increasing the number of Treg cells without activating effector T cells or worsening viremia [64]. Besides, severe RSV infection in infants maybe associated with a decrease in circulating Treg cells. Interventions with exogenous IL-2 have been found to increase Treg cell frequency in RSV-infected infants, although their response to IL-2 may be limited compared to healthy controls, possibly due to soluble CD25 [100]. More interestingly, Treg depletion during influenza infection will impair influenza-specific GC responses and the Tfh differentiation [101]. This certainly suggests that Treg are essential for the promotion of influenza-specific GC responses, the main mechanism of its action is to mediate the availability of IL-2, through by preventing excessive increase of IL-2 to inhibit Tfh cells differentiation. In addition, our preliminary clinical observations have shown that ld-IL-2 treatment can significantly increase the levels of Treg cells, helping to rebalance the Th17 and Treg populations [6]. We also did not observe an exacerbation of viral infection. Th17 cells are also increased after treatment, but DM patients with viral infection are often in a low-response state of immunosuppression. In this case, the increase of Th17 cells may be beneficial to the antiviral immune response.

Tfh and Tfr cells

Follicular regulator T (Tfr) cells, which localised in germinal centre (GC), express Foxp3, CXCR5 and Bcl6, the latter two are normally expressed by Tfh cells [102]. Tfh cells are a special type of $CD4^+$ T cells, which are involved in B cell proliferation, GC formation and the differentiation of memory B cells and long-living plasma cells [103]. During the peak of the infection, when IL-2 levels are high, IL-2 promotes the expression of Blimp-1 and inhibits the expression of Bcl-6, thus limiting the development of Tfr cells. However, once the infection is cleared and IL-2 levels decrease, the differentiation of Treg cells into Tfr cells is promoted. This helps prevent the accumulation of reactive B cells [104]. Importantly, excessive IL-2 will suppress Tfh cells differentiation by inhibiting Bcl-6 expression through STAT5; therefore, in environments with high IL-2 levels, the response of Tfh cells is limited, However, IL-2 consumption by Treg cells can contribute to the formation of virus-specific Tfh cells during influenza virus infection [101]. Besides, one study has identified that intrinsic IL-6 can help maintain IL-2 hyporesponsiveness through negative regulate CD122 expression in an influenza infection model [105]. Collectively, we recognised that the flexible regulation of Tfr and Tfh cells by IL-2 during influenza infection is a key link in the immune response and thus contributes to the resolution of influenza infection. However, we observed some variations in RSV infection. As we have mentioned above, early life mice infected failed to generate RSV-specific antibody response was associated with the limited differentiation of Tfh cells. Mechanistically, IL-2 secretion by $Foxp3^-CD4^+$ T is increased in early life, which activates STAT5 signalling to inhibit Tfh cells [85]. More importantly, the expression of Foxp3 is unstable and delayed in early life [106], this may account for the reduced IL-2 consumption by Tregs in early life, creating an IL-2 high environment. These studies suggested that the effects and mechanisms of IL-2 may be different in different types and timing of virus infection. Therefore, further research is needed to understand the specific mechanisms and personalised exploration of IL-2 in viral infections.

$CD8^+$ T cells

CD8 regulates the immune response through a variety of mechanisms and plays an important role in viral clearance and recovery of infection. Resting $CD8^+$ T cells express moderate affinity IL-2Rs on their surface, activated $CD8^+$ T cells can express the high-affinity IL-2R, so IL-2 as a pleiotropic cytokine has a regulatory effect on $CD8^+$ T cells. One early research demonstrated that supplementary IL-2 expression by recombinant adenovirus could improve the state of immunosuppression by enhance the development and effector function of $CD8^+$ T cells during RSV infection to improve the clinical income [107]. This strongly suggested that IL-2-mediated enhancement of beneficial immune responses maybe play a useful role in viral infection or even prevent the aggravation of immunopathology. A study explored the role of sequential ld-IL-2 treatment in non-responder patients after IFN-α therapy. The results found ld-IL-2 therapy promote the expression of $CD8^+$ T cells-related molecules such as CD38 and IFN-γ, and also increases the frequency of HBV-specific $CD8^+$ T cells. The level of HBV-

specific $CD8^+$T subsets were correlated negatively with HBeAg levels. Additionally, the IL-2 exposure primarily activated STAT1 but not STAT5 [63]. These findings indicated that sequential IL-2 therapy-mediated $CD8^+$ function may be a potential approach to enhance antiviral immunity response in some refractory viral infections. In a model of familial haemophagocytic lymphohistiocytosis using LCMV to induce inflammation in perforin-deficient mice, it was observed that limited IL-2 production by $CD4^+$ T cells and increased sCD25 release by $CD8^+$ T cells resulted in preferential binding of IL-2 by $CD8^+$ T cells compared to Treg cells. Additionally, Treg homeostasis is also defective in this condition, and these are related to the manifestation of high inflammation in HLH [108]. Based on this, it is not difficult to see that the availability of IL-2 by different immune subsets is crucial for the immune response in HLH. Therefore, it is efficacious to explore the immune balance treatment strategy based on IL-2 to avoid $CD8^+$ T cells over-activation and recover Treg homeostasis for the treatment of HLH. In a mouse model of influenza virus infection, ld-IL-2 has been found to promote the differentiation of $CD8^+$ T cells and enhance their cytotoxic function by increasing the secretion of IFN-γ and granzyme B. As a result, the clearance of the virus is accelerated [7]. Also in that study, IL-2 therapy accelerates virus clearance in acute LCMV infection by a similar mechanism. However, it is worth noting that CD8 also mediates the occurrence of LCMV induced-immunopathology, then the antiviral effect of IL-2 was absent in the absence of $CD8^+$ T cells [7]. In the context of virus infection, it is necessary to consider the competition for IL-2 binding between $CD8^+$ T cells and other subsets such as Tregs. Additionally, the immunopathology caused by excessive activation of $CD8^+$ T cells should be taken into account. It is also worth mentioning that IL-2 complex can enhance the cytolytic activity of $CD8^+$ T cells and provide protection against virus infection [79].

NK cells

NK as the key components of innate immune cells play a pivotal role in the antiviral immune response. They have an intermediate-affinity IL-2R on their surface, which allows them to respond to ld-IL-2, although not as strongly as Treg cells. In a study involving patients with chronic hepatitis B, mononuclear cells were isolated from liver biopsies and stimulated with IL-2 in vitro. This led to a significant increase in the frequency of IFN-γ^+ NK cells, $CD38^+$ NK cells and $NKp30^+$ NK cells [63]. Similarly, in chronic HIV-1 infection, IL-2 was found to promote the activation and enhance the ADCC response of NK cells [109]. The level of mature and cytotoxic NK cells was decreased and the $CD56^{dim}$ immature NK was increased in post-COVID syndrome patients. Then, treatment with rhIL-2 could restore peripheral blood NK cell count and function. However, it should be noted that pro-inflammatory NK cells also increased after IL-2 treatment [90]. Recent research has highlighted the importance of metabolic pathways in regulating the activation and function of NK cells. O-GlcNAcylation, a post-translational modification, has been found to be associated with the cytotoxic function of NK cells. In vitro stimulation with IL-2 has been shown to increase the protein level of O-GlcNAcylation [110]. However, there is limited research on the regulation of IL-2 on NK cells through metabolic pathways during viral infections. Interestingly, IL-2 can be as medium a key mediator of the adaptive T cells to help NK cells against infection. Studies have shown that IL-2 after re-exposure to human cytomegalovirus (HCMV) can enhance the activity of NK cells in response to HCMV-infected target cells [111]. The use of IL-2 complex treatment can prevent Treg cells from consuming IL-2 and stimulate the antiviral activity of NK cells, which is an important mechanism of its antiviral effect [82]. For example, treatment with IL-2 complex (clone S4B6) significantly increases the expression of early activation marker CD69 and the maturation marker KLRG1, as well as the frequency of terminally differentiated NK cells during acute retroviral infections, ultimately helping to reduce viral loads [101].

To conclude, we have summarised several immune regulatory mechanisms involving IL-2 in viral infection. It is worth noting that IL-2 not only regulates the immune response in the mentioned contexts, but also has an impact on innate lymphoid cells [112], B cells [64, 113, 114] and other immune subsets. More interestingly, it has been found that ld-IL-2 can induce the changes of intestinal microbiota [115, 116], the interaction between microbiota and local immune cells in the intestine may also be a vital mechanism for the immunomodulatory effects of IL-2. However, their specific roles in viral infection have not been extensively studied. Further investigation into the regulation of IL-2 on various cell types and the interplay between different subsets could potentially lead to more targeted and effective treatments for virus infections.

THE REGULATORY EFFECT OF LOW-IL-2 ON IMMUNE HOMEOSTASIS IN VIRAL INFECTION

Ld-IL-2 is helpful to enhance host antiviral immunity and prevent infection from becoming chronic

During various viral infections, ld-IL-2 not only controls the activity of many types of immune cells such as NK

cells, $CD8^+$ T cells and Tfh cells, but also has a significant impact on Treg cells, which are cells that play a crucial role in regulating the immune response. Interestingly, this regulatory role is usually not in conflict with the immune response during most viral infections, and in fact, ld-IL-2 and Treg cells may even work together synergistically at different stages of the infection to help the body clear the viruses in a timely manner. Although the exact mechanisms and comprehensive studies of how ld-IL-2 regulates the immune response during viral infections are still lacking, as well as research results in humans, some existing studies suggested that ld-IL-2 may contribute to the antiviral immune response and help in the timely clearance of the virus, potentially reducing the adverse consequences of chronic infections.

Ld-IL-2 plays a role in mitigating excessive inflammatory responses and minimising pathological damage

After viral infection, a dysregulated immune response can easily induce an inflammatory cascade, leading to the occurrence of cytokine storm, VAHS and even multiple organ dysfunction. Intervening with ld-Il-2 at the appropriate time can help facilitate a smooth transition of the immune response and disrupt the vicious cycle of inflammatory cascades. Furthermore, ld-IL-2 therapy may be beneficial in patients who experience immune suppression after viral infections, as it can enhance the immune response and protect against secondary infections. However, it is important to note that an excessive immune response can also result in immunopathology, where $CD8^+$ T cells and NK cells may play crucial roles. Animal studies with LCMV have shown that ld-IL-2 can enhance the function of $CD8^+$ T cells in fighting against the virus, but it can also worsen CD8-related immunopathology and lead to accelerated death. However, there is currently no available evidence of ld-IL-2-induced immune pathology in humans based on preliminary observational studies.

Ld-IL-2 may prevent the occurrence of virus-induced autoimmune diseases and tumours

Viral infections are closely related to the occurrence of autoimmunity diseases and cancers. In summary, part of the mechanism is related to the structural characteristics of the virus itself, and the other important generalised mechanism is the disorder of the body's immune system caused by viral infection. After the occurrence of viral infection, on the basis of timely specific antiviral therapy, combined with immunomodulatory therapy to restore immune homeostasis, more importantly, to maintain immune tolerance, this may help to reduce the likelihood of virus-related autoimmune diseases and tumours in the long term. Although there is currently no evidence in evidence-based medicine, ld-IL-2 is a promising option for safe and effective treatment based on this study. Long-term treatment follow-up and rigorous animal studies are necessary in this area, as they have important clinical implications for improving the long-term prognosis of viral infections.

THE ROLE OF LD-IL-2 IN AUTOIMMUNE DISEASES COMBINED WITH VIRUS INFECTION

Infection is one of the common complications and causes of death in many autoimmune diseases. Additionally, infection, particularly viral infection, has the potential to disrupt immune tolerance and contribute to the development of autoimmune diseases. Recent research suggested that ld-IL-2 could serve as a novel immunomodulatory strategy for treating autoimmune diseases complicated by infection. This approach aims to restore immune homeostasis without increasing the risk of infection [117]. Autoimmune diseases are often characterised by the destruction of immune tolerance mediated by the reduction of Treg cells, it is commonly observed that suppressive Treg cells are increased during most infections. However, the specific immune function status of autoimmune diseases complicated with infection is highly heterogeneous with different disease states and different infection types. The clinical effectiveness and mechanism of using ld-IL-2 in autoimmunity diseases combined with virus infection is not completely understood. There are some studies that give some preliminary evidence. For example, one study conducted in our hospital examined SLE patients with infections who received short-term ld-IL-2 treatment. The study found that the levels of $CD8^+$ T cells, NK, Th1, Th17 and Treg cells all significantly increased compared to the baseline. This suggests that IL-2 may be an effective strategy for restoring immune tolerance in SLE patients with infections [118]. However, the study did not specify the specific type of infection or evaluate the specific outcome of the infection after treatment. Nonetheless, it does provide evidence that ld-IL-2 can restore immune balance in SLE patients with co-infections. Another noteworthy study retrospectively analysed a large group of SLE patients and

discovered that the incidence of infections, including viral infections, was significantly reduced in patients treated with IL-2. Additionally, the mechanism was discussed in animal models, suggesting that it is primarily related to the response of effector $CD8^+$ T cells [7]. As mentioned earlier, our research group found that Ld-IL-2 treatment can significantly increase the number of total T, $CD4^+$, $CD8^+$ T cells and Th1, Th17, Treg of $CD4^+$T subsets. It also helped reduce measures of disease activity and did not worsen infection [6]. Besides, some studies have confirmed that IL-2 or IL-2 complexes can improve some virus-induced autoimmune diseases such as chikungunya virus-induced chronic arthritis [119], HCV-induced vasculitis [64] and so on. In summary, these initial studies have provided some evidence suggesting that ld-IL-2 may be a safe and effective strategy for restoring immune homeostasis in the context of autoimmune diseases combined with viral infections, without compromising the antiviral immune response. However, it is worth conducting in-depth research on the specific diseases and types of infections, as well as the timing and mechanism of treatment in the specific application.

PROSPECTS FOR THE APPLICATION OF LOW DOSE-IL-2 IN VIRAL INFECTIONS

In recent years, ld-IL-2 has shown promising outcomes in treating various autoimmune diseases. It works by increasing the number and enhancing the function of Treg cells, which helps to reduce disease activity. Additionally, there have been some studies indicating its potential use in viral infections, although more robust evidence is needed to determine the exact mechanism and application. On one hand, ld-IL-2 may assist in reducing the viral load during acute viral infections, thereby decreasing chronicity and tissue damage. On the other hand, it primarily regulates different aspects of the immune system to restore immune balance in various inflammatory environments, reducing excessive inflammatory responses and improving immunosuppression. Furthermore, although there is no direct evidence, it is speculated that ld-IL-2 may also decrease the occurrence of autoimmune syndromes or diseases that arise as a result of viral infections. However, its primary function remains centred around comprehensive immune response regulation. Therefore, it is crucial to explore combination therapies to maximise the beneficial clinical effects, both in cases of viral infection alone and in cases of other diseases accompanied by viral infection.

CONCLUSION

Over the years, several researchers have studied the role of IL-2 in viral infections. It has been discovered that ld-IL-2 may be a safe and effective way to modulate the immune system and aiding the virus clearance. However, there are also reports that suggest IL-2 could worsen immune inflammation and immunopathology. Therefore, the exact mechanism by which IL-2 shapes inflammatory responses is not well understood. To better understand its effects, more researches are needed to determine the optimal dose, duration and timing of IL-2 treatment. Additionally, it is important to explore how IL-2 interacts with other immune cells, as well as the influence of tissue structure, inflammatory environments and local flora distribution. Since IL-2 is produced and secreted in limited concentrations and acts in both autocrine and paracrine ways, therefore, the specific utilisation mechanism in virus infection of IL-2 secreted by the body and exogenous intervention of IL-2 is still unclear. The absence of appropriate pre-clinical models for studying autoimmune or tumour co-infection poses a challenge for further research. In addition to solely using IL-2, it would be valuable to investigate the development and utilisation of combination therapy or engineered IL-2. It is important to explore a specific strategy that can maintain the normal functions of $CD8^+$ T, NK and Treg cells, while also preventing immunopathology and excessive inflammation, in order to sustain appropriate antiviral immunity.

AUTHOR CONTRIBUTIONS

R. S. wrote the article and drew illustrations. T. Z, H. W, G. Y, R. W. and X. Z provided contributions to discussions of the content. All authors reviewed and/or edited the manuscript before submission. C. W. conceived the topic of this review. C. G. and X. L. critically revised the content of the manuscript. All authors approved the publication of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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