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Review Article

IL-10: A Multifunctional Cytokine in Viral Infections

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The anti-inflammatory master regulator IL-10 is critical to protect the host from tissue damage during acute phases of immune responses. This regulatory mechanism, central to T cell homeostasis, can be hijacked by viruses to evade immunity. IL-10 can be produced by virtually all immune cells, and it can also modulate the function of these cells. Understanding the effects of this multifunctional cytokine is therefore a complex task. In the present review we discuss the factors driving IL-10 production and the cellular sources of the cytokine during antiviral immune responses. We particularly focus on the IL-10 regulatory mechanisms that impact antiviral immune responses and how viruses can use this central regulatory pathway to evade immunity and establish chronic/latent infections.

1. IL-10 and the Complex Interplay between Its Cellular Sources and Targets

Antiviral immune responses ideally eliminate replicating virus and viral reservoirs without host damage. However, in many infections, severe complications could occur due to excessive immune activation. To prevent host tissue damage, immunoregulatory cytokines control the magnitude of these immune responses. IL-10 is a key component of this cytokine system that regulates and suppresses the expression of proinflammatory cytokines during the recovery phases of infections and consequently reduces the damage caused by inflammatory cytokines [1, 2]. IL-10 binds IL-10R, a dimeric receptor composed of a high affinity IL-10R1 chain predominantly expressed on leukocytes and unique to IL-10 recognition, and an ubiquitously expressed IL-10R2 chain involved in the recognition of other cytokines from the IL-10 family (IL-22, IL-26, IL-28A, IL-28B, and IL-29) [3, 4]. The interaction of IL-10 with IL-10R triggers the Jak-STAT signaling pathway, leading to STAT1, STAT3, and, in some instances, STAT5 activation. STAT3 is critical for IL-10 effects on immune cells [5–7].

As its specific receptor (IL-10R1) expression indicates, IL-10's broad spectrum of cellular targets includes virtually all leukocytes. IL-10 is considered a master negative regulator of inflammation. Blockade in the IL-10 pathway typically results in prolonged and exaggerated immune responses to antigens that can lead to immunopathology. Initially identified as a Th1 inhibitory factor secreted by Th2 cells [8], IL-10 is now known to be produced by a variety of innate and adaptive immune cells, including macrophages, dendritic cells (DCs), natural killer (NK) cells, CD4, CD8, $\gamma\delta$ T cells, and B cells (reviewed in [4, 9, 10]). Untangling the complex interplay between IL-10 sources and target cells during immune responses remains an outstanding challenge. For instance, systemic administration of IL-10 for autoimmune therapy proved to be paradoxically proinflammatory [11, 12], whereas localized IL-10 delivery usually proves to be therapeutic [13–15]. Spatial delivery of IL-10 signaling is therefore crucial to its effects.

Autoimmune disease models in IL-10-deficient mice have helped elucidate the role of this cytokine in T cell homeostasis in the periphery. They also highlight the complex link between IL-10's source and its role. IL-10-deficient mice develop spontaneous enterocolitis typically driven by microbial insult and dependent on T cell responses [16–18]. When these mice are bred in pathogen-free environments or when MyD88 (a key component for pathogen recognition receptor (PRR) signaling) is also knocked out, colitis does not occur implicating the gut microflora as a causal agent [16–20]. IL-10 thus maintains T cell tolerance to commensal

microflora in the gut. Treg cells are critical in the prevention of spontaneous colitis in this model [21, 22]. When IL-10 deficiency is restricted to the Treg cell compartment, mice develop colitis [22]. Although Treg cells are the source of IL-10 that maintains peripheral tolerance, they also need to sense IL-10 to provide protection, as IL-10R-deficient Treg cells cannot impair disease development [23]. Restricting IL-10 deficiency to myeloid cells does not cause colitis which confirms that macrophages are not the main source of protective IL-10 in this model [24]. IL-10 produced by macrophages could however partly contribute to colitis protection, as it triggers Treg cell protection when anticommensal T cells are adoptively transferred into a sensitive host [25]. Importantly, deficiency in IL-10R signaling in macrophages leads to colitis development [24, 26]. IL-10 signaling appears necessary for macrophages to trigger their anti-inflammatory functions. Macrophages thus act as intermediates in the maintenance of tolerance. IL-10 produced during the initial inflammation in the gut probably drives IL-10 production by Treg cells, which in turn limits macrophage-induced activation of anticommensal T cells, maintains peripheral T cell tolerance, and controls immunopathology.

This well-studied autoimmune model shows how IL-10 produced locally acts as a natural negative feedback mechanism that controls inflammation and maintains immune homeostasis in the periphery. Indeed, IL-10 deficiency aggravates several experimental autoimmune disorders [27–29], illustrating the central role of this cytokine in immune regulation.

IL-10 is also important in controlling viral immunity. Studies using lymphocytic choriomeningitis virus (LCMV) infections with strains that provoke either acute or persistent infections have helped understand the role of IL-10 in viral infections. IL-10 acts as an immunoregulator, inhibiting proinflammatory responses from innate and adaptive immunity and preventing tissue damage due to exacerbated adaptive immune response. However, viruses have evolved mechanisms that exploit the immunoregulatory function of IL-10 for immune evasion, suppression, and tolerance, promoting their own survival. As a result, viruses can persist for life in infected hosts possessing otherwise competent immune responses. The effects of pleiotropic IL-10 during the course of infection are nonetheless multiple and the subtle IL-10-governed mechanisms that balance inflammation and immunoregulation are still subject to plenty of attention. In this review, we will discuss the role of IL-10 in immune cells during acute infections and the IL-10-dependent mechanisms that viruses use to drive viral persistence.

2. IL-10 in Acute Viral Infection

2.1. Early IL-10 Induction and Effects on Innate Immunity. During the early phase of infections, viruses typically trigger PRR engagement after pathogens-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) recognition (reviewed in [30]). PAMP and DAMP recognition drives the antiviral state in antigen-presenting cells (APC) and type I IFN production that initiate the innate immune response. Concomitant to the proinflammatory first line of defense triggered by PRR signaling, the immunoregulatory cytokine IL-10 is induced in DCs and macrophages (Figure 1) [31–37]. The regulation of IL-10 production in APC is complex and depends on cell type [37] and the integration of secondary activation signals such as type I IFN [34, 38], PGE_2 [39], or CD40 ligation [40] that synergize with PRR signals. Moreover, IL-10 production in APC can be antagonized by the presence of IFN-γ [34, 41]. In macrophages, IL-10 production can be maintained through an autocrine IFN-β feedback loop [36]. In DC, IL-10 production depends on subtype-specific preprogrammed cytokine patterns [37, 40]. Kinetic studies indicate that IL-10 could be produced in late activation phase in APCs [33, 34], which suggests that IL-10 balances the proinflammatory signals induced by viral PAMPs. Early IL-10 production by APCs probably limits excessive inflammation and thus potential tissue damage.

NK and NKT cells are an essential effector arm of innate immunity that participates in the control of viral infections [42–45]. IL-10 has been shown to promote NK cell proliferation, cytokine production, and cytotoxicity in vitro [46–50], although in some in vivo settings it could modulate NK cell activity [51, 52]. IL-10 acts as a prosurvival factor in activated NK cells by inhibiting activation-induced cell death [53]. The cytokine thus appears to promote activated NK cell effector function. Interestingly, NK cells are also a source of IL-10 upon synergistic activation with IL-2 and IL-12 (Figure 1) [54–57]. IL-10-producing NK cells can control liver inflammation in acute murine cytomegalovirus (MCMV) infection [58] and therefore limit immunopathology in some organs. IL-10-producing NK cells could serve as an early control for excessive inflammation during the initiation of the immune response [59, 60], while their viremia-controlling effector functions are maintained. IL-10 produced in the early phase of antiviral innate immunity by APCs and NK cells is probably a counterbalance to proinflammatory signals that protect from tissue damage. Although in most cases IL-10 derived from innate immune cells is unlikely to affect the development of antiviral immunity, this source of IL-10 can be induced by some viruses to evade immunity, as described later.

2.2. IL-10 and Antiviral Cellular Responses. To eliminate intracellular pathogens like viruses the immune system typically uses cytotoxic $CD8^+$ T lymphocytes (CTL), whose functions are armed by Th1 cells. $CD8^+$ T cells are critical in antiviral immunity, since they can kill infected cells through the recognition of viral peptides presented on MHC I molecules. Th1 cells also recognize viral peptides presented by APC on MHC-II molecules. Th1 cells provide the "license to kill" to the virus-specific $CD8^+$ T cells to differentiate into effector CTLs using professional APC as intermediates [61, 62]. This central mechanism of antiviral immunity can be modulated by IL-10 at different levels. High IL-10 levels act as a regulatory trigger that initiate the resolution of the acute phase of infection in which antiviral T cell populations contract [63].

2.2.1. IL-10 Production by Antiviral T Cells. Currently it is well established that virtually all T cell subsets can produce

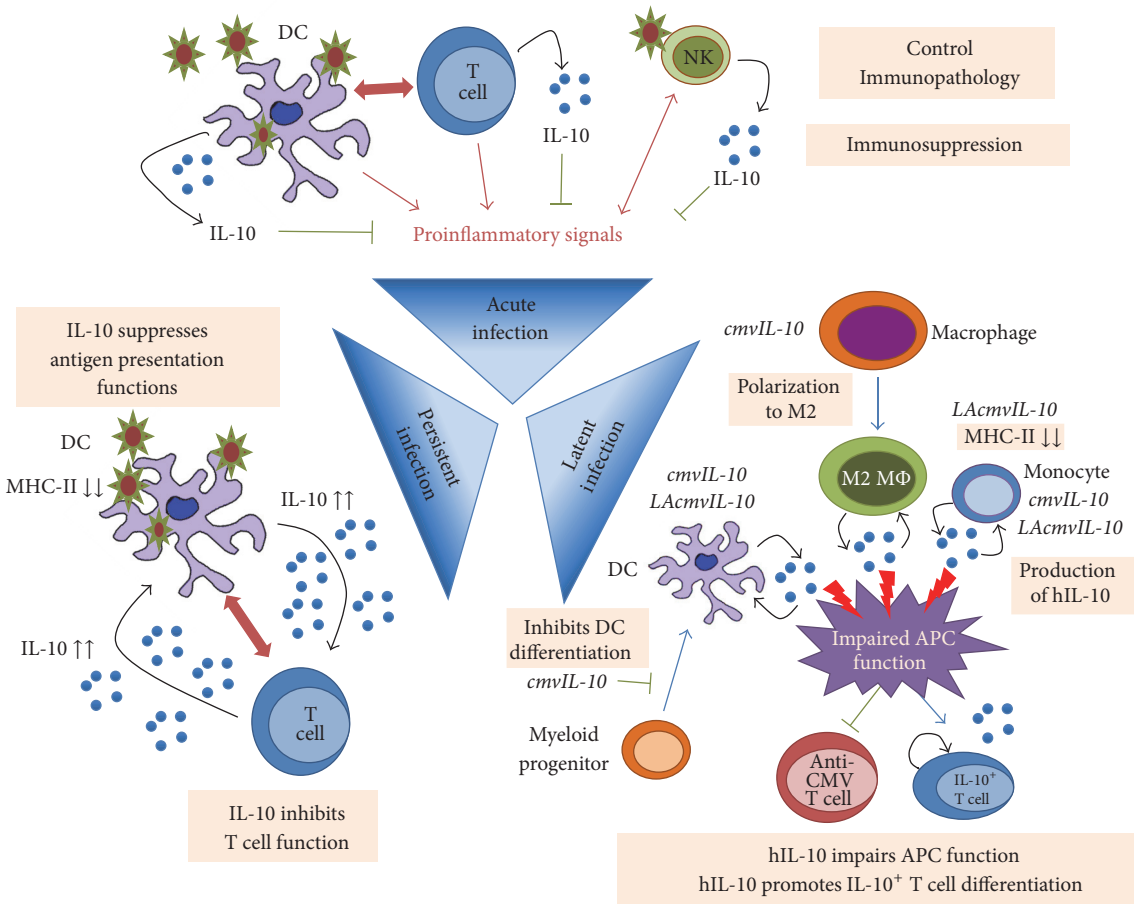

Figure 1: IL-10 role in viral infections. During acute infections, proinflammatory signals are produced by DCs after recognition of pathogen patterns. In parallel, NK cells recognizing pathogen patterns and/or stimulated by proinflammatory signals further enhance inflammation. In this proinflammatory context, DC can promote antiviral T cell responses that clear the infection. Activation of DC, T cells, and NK cells also results in the production of the immunoregulatory cytokine IL-10 to balance inflammation. In this context, IL-10 expression controls immunopathology and leads to the resolution of the inflammation and T cell responses once the pathogen is cleared. During persistent infections, the virus exploits the production of IL-10 by DCs to exhaust antiviral T cells. High IL-10 levels produced by DCs suppress their antigen presenting capacity and lead to inefficient T cell activation. Chronic antigen presence further exhausts T cells and induces IL-10 production. T cells therefore become "tolerant" to viral antigens and infection persists. To establish chronicity and latent infections, the virus produces viral IL-10 homologs that favor anti-inflammatory responses. In human cytomegalovirus infection, cytomegalovirus-encoded IL-10 (cmvIL-10) and latency-associated cytomegalovirus-encoded IL-10 (LAcmvIL-10) are produced in myeloid cells and impair their function. cmvIL-10 induces hIL-10 production in DCs, macrophages, and monocytes, impairs DC differentiation, and promotes M2 polarization of macrophages. LAcmvIL-10 also promotes hIL-10 production in DCs and monocytes and impairs monocyte presenting capacity. IL-10 viral homologs induce human IL-10 (hIL-10) production in myeloid cells that contributes to impairment of their antigen presenting cell (APC) function. This in turn probably limits anti-CMV T cells responses and promotes IL-10^+ T cell development. Impaired APC function permits chronic infections, while IL-10^+ T cells allow latent infections to persist.

IL-10 (reviewed in [64, 65]). IL-10 production appears thus to be embedded in the activation program of T cells. Indeed, at the height of the inflammatory response and once cellular immune responses are mounted, antiviral $CD4^+$ and $CD8^+$ T cells become the main sources of IL-10 (Figure 1) [66–72]. Th1 cells can produce IL-10 [73] in response to intracellular protozoan [74, 75], LCMV [72, 76], MCMV [77–79], or influenza [68] infections among others. IL-10 production in Th1 cells is driven by TCR engagement but is not directly regulated by T-bet, the master transcription regulator of Th1 cell programming [80, 81]. IL-27 (a proinflammatory cytokine belonging to the IL-12 family) is a potent inducer of IL-10 in Th cells [82–85]. Type I IFN can also induce IL-10 expression in $CD4^+$ T cells [86, 87]. IL-10 production in Th cells therefore depends on secondary environmental signals upstream of STATs (such as IL-10 itself [5–7] and proinflammatory cytokines [88]) or SMADs (such as TGF-β [89]). It should be noted that chronic antigen stimulation results in IL-10-producing Th1 cells [72, 90, 91] unable to respond to pathogens. This natural regulatory mechanism that maintains T cell homeostasis in the periphery can be used to establish chronic infection as discussed later.

Effector $CD8^+$ T cells can produce IL-10 during the acute phase of influenza virus [67, 68], respiratory syncytial

virus [70], coronavirus infection [69], paramyxovirus simian virus 5 [71], or vaccinia [66] infections. The transcription factor BLIMP-1 is essential for IL-10 production in effector and memory $CD8^+$ T cells [92]. BLIMP-1 is induced in $CD8^+$ T cells through T cell help and can be sustained by proinflammatory signals (IL-27), T cell growth factors (IL-2) [92], and antiviral signaling like type I IFN [67]. It thus appears that antiviral and inflammatory signals elicited during viral infections trigger activated T cells to produce IL-10 as a feedback regulatory mechanism that limits excessive inflammation.

2.2.2. IL-10 Uses APC as Intermediate to Modulate T Cell Responses. Although T cells become the main IL-10 produ cers during the acute phase of infection, IL-10 effects on T cell function are usually mediated through paracrine activity on DCs and macrophages (reviewed in [1, 9]). IL-10 recognition by APC skews their response towards a noninflammatory protissue repair phenotype [93–99]. IL-10 is a major regulator of the potent APC-derived inflammatory cytokine IL-12 [100] and promotes expression of its own mRNA in a positive feedback loop [101]. Exposure to IL-10 also leads to down-regulation of costimulatory and MHC molecules on APCs [4, 102, 103] which limits the amount of antigen exposure T cells can receive. IL-10 also restricts the production of proinflammatory cytokines and chemokines that permit APC trafficking to the lymph nodes, thereby interrupting Th1 differentiation of naïve T cells [103, 104]. These elevated IL-10 levels impair de novo Th1 stimulation [105, 106] and trigger the resolution of the acute phase of infection in which antiviral T cell populations contract [63]. IL-10 therefore acts as a switch on APC that controls inflammation and ultimately interrupts T cell responses once pathogens are cleared.

2.2.3. IL-10 Effects on Antiviral T Cells. Through its effects on APC, IL-10 can alter antiviral T cell function, although its effects on Th1 cells and CTLs are very different. Acute and chronic LCMV infection models have been essential to comprehend IL-10's crucial role in controlling antiviral T cell responses. IL-10 limits cytokine production and proliferation in antiviral Th1 cells [2, 104, 107]. When IL-10 regulatory action is removed (through IL-10R blockade or IL-10 deficiency), antiviral Th1 responses can prevent chronic LCMV infection [2, 31, 104, 107, 108]. IL-10 blockade increases the amount of Th1 cells in germinal centers [104], promotes Th1 priming [106], and enhances Th1 effector function and memory development [104, 107]. IL-10 thus appears central to the regulation of antiviral Th1 cell responses. Removal of the IL-10 "brake" on Th responses can lead to immunopathology following viral infection as illustrated by the increased neurologic disease detected in IL-10-deficient mice during fatal alphavirus encephalomyelitis [109]. This general regulatory mechanism prevents host immunopathology and controls the amplitude of Th1 cell responses during acute viral infections. This mechanism can nonetheless be exploited by viruses to promote chronic and persistent infections as discussed later.

In contrast to Th1 cells, $CD8^+$ T cell effector functions (e.g., cytokine production and cytotoxicity) can be enhanced by IL-10 addition in vitro [4]. IL-10 blockade prior to LCMV infection only results in a modest increase in LCMV-specific $CD8^+$ T cells 8 days after infection [104, 107], which indicates that IL-10 does not greatly alter antiviral $CD8^+$ T cell priming. Nonetheless, IL-10 blockade/deficiency facilitates virus clearance by $CD8^+$ T cells in chronic LCMV infections [2, 31, 104, 107], which confirms that secondary $CD8^+$ T cell responses are regulated by IL-10 [105]. It should be noted that the effects of IL-10 on $CD8^+$ T cells could also depend on the strength of the antigenic signal, as $CD8^+$ T cells recognizing different LCMV epitopes appear to have different IL-10 inhibition thresholds [104].

IL-10 has also been linked to $CD8^+$ T cell memory differentiation [110, 111]. Recently IL-10 produced by Treg cells was shown to promote $CD8^+$ T cell memory differentiation in LCMV infections by insulating a portion of $CD8^+$ T cells from inflammatory signals during the resolution phase of the immune response [112]. Other reports have nonetheless indicated that IL-10 could impair $CD8^+$ T cell memory development in the same infection [104], while others found no difference in the quality and quantity of $CD8^+$ T cell memory development after IL-10 blockade [107]. These contradictory results obtained through different approaches (IL-10/IL-10R antibody blockade, IL-10-deficient mice, or adoptive transfer of IL-10-sufficient Treg cells) hint at a very delicately regulated system for CD8 memory development that could be controlled by T cell signal strength as well as spatial and temporal IL-10 delivery. This raises the intriguing possibility for a new facet in IL-10 biology whereby IL-10 dampening of $CD8^+$ T cell responses could facilitate the differentiation of a portion of these cells into memory.

2.3. IL-10 and Antiviral Humoral Response. B cell-produced antibodies represent the other major arm of the adaptive immunity involved in virus clearance [113]. Most clinically effective vaccines not only require the induction of cellular immunity but also the production of neutralizing antibodies [114, 115]. Nonneutralizing antibodies can also participate in antiviral immunity as shown in LCMV infections where virus-specific nonneutralizing antibodies participate in virus clearance alongside $CD4^+$ and $CD8^+$ T cells [108]. The importance of B cell responses in viral immunity is also exemplified by the interference of viruses with humoral immunity. For instance, Bluetongue virus can affect antiviral antibody titers early in infection [116], and human immunodeficiency virus (HIV) can continuously mutate its antigenic determinants, a phenomenon known as antigenic drift, to evade neutralization by antibodies [117, 118].

Since IL-10 regulates B cell survival and differentiation [4], it could potentially control B cell responses to virus. IL-10 favors B cell effector function by stimulating plasma cell differentiation at the expense of B memory cells [4, 119]. Autocrine IL-10 production promotes B cell survival and Ig class switch [120–122]. In LCMV-infected mice, IL-10 however does not control B cell differentiation in the priming phase [104]. Moreover IL-10 blockade does not affect follicular Th cell numbers, a subpopulation of Th cells involved in B cell help and necessary for the generation of high affinity antibodies [104]. It thus appears that IL-10 may

not directly affect B cell responses, although this has not been widely studied.

B cells could nonetheless be a source of IL-10 that could modify antiviral responses. IL-10 expression in B cells can be triggered by TLR engagement [123–125] and increases when B cells are activated in a context mimicking T cell and DC help, that is, through anti-Ig antibody, anti-CD40 antibody, and IL-12 [126]. Type I IFN that are typically produced during antiviral responses can also enhance TLR-induced IL-10 production in B cells [127, 128]. These reports indicate that IL-10 production is an integral part of B cell activation programming. However, the factors driving IL-10 production in B cells during immune responses are not fully understood.

A B regulatory cell population (Breg) has been described [129, 130] and can be a principal source of IL-10. No precise Breg cell markers have so far been defined (reviewed in [131, 132]), but these cells are potent inhibitors of autoimmune inflammation through their IL-10 production [133, 134]. Breg cells can suppress *Listeria monocytogenes* [135] or *Salmonella typhimurium* [136] clearance. These cells can therefore also modulate responses to infections. The observation that Breg cells can be therapeutic in allergy [137] indicates that IL-10 produced by Breg cells could have systemic activity. IL-10-producing Breg cell numbers increase in coxsackie virus-induced acute myocarditis model [138]. In MCMV murine infections, IL-10 expression in B cells can suppress MCMV-specific $CD8^+$ T cells responses [139, 140]. Moreover, IL-10-producing Breg cells could promote chronic MCMV brain infection [141]. In HIV patients, IL-10-producing Breg cells are elevated in peripheral blood of untreated patients and can suppress virus-specific $CD4^+$ and $CD8^+$ T cell activity in vitro [142]. Similarly, in chronic hepatitis B virus (HBV) patients, IL-10-producing B cells are elevated in the periphery and suppress HBV-specific $CD8^+$ T cell responses [143]. IL-10-producing B cells have therefore the capacity to create an immunoregulatory milieu unsuitable for cellular immunity. The localized effects of IL-10 on T cells however suggest that B cell-derived IL-10 would probably affect effector T cell activity in specific settings. Further work will be required to clarify both how B cell-derived IL-10 influences antiviral responses and how IL-10 modulates antiviral B cell responses.

2.4. IL-10 and Virus Clearance. Although IL-10 acts as an immune brake on inflammation, its overall effects on antiviral immune responses can be complex and depend on the virus, site of infection, timing of the antiviral immune response, and so forth. For instance, high IL-10 plasma levels could be protective in early responses to HIV but become detrimental during acute infection as they promote virus persistence [144].

In some settings, IL-10 expression can contribute to virus clearance. In influenza infections, coproduction of IL-10 and IFN-γ facilitates anti-influenza antibody accumulation in the lung mucosa [145]. Thus IL-10 not only limits immunopathology in this case but also supports adaptive immunity. In cutaneous vaccinia virus infections, IL-10-producing T cells have been linked to lesion control [66], which suggests that local IL-10 effects may be multiple and depend on the organ and microenvironment.

IL-10's supportive role for effective virus clearance is very apparent in CNS infections. Virus-induced encephalitis results from an excessive immune-induced inflammation designed to control viral infection. IL-10-deficiency aggravates this immunopathology in *Flavivirus* or *Coronavirus* infections with CNS tropism [63, 146–149]. In these CNS infections, IL-10 usually improves virus control, although this outcome probably results from direct and indirect effects of the cytokine. In CNS immune responses to the coronavirus mouse hepatitis virus, $CD4^+$ T cells and $CD8^+$ T cells are the initial sources of IL-10 [63]. Once the viral load is controlled, IL-10-producing $CD8^+$ T cells diminish while IL-10-producing $CD4^+$ T cells remain [63]. IL-10 produced during the immune response peak could enhance CD8 activity while limiting APC-driven inflammation. During this resolution phase, natural $CD4^+$ $CD25^+$ Treg cells are the main source of IL-10. However transition in the IL-10 source from natural Treg cells to T regulatory 1- (Tr1-) like $CD4^+$ $CD25^-$ cells could be a sign of CNS viral persistence [63] and indicate chronic antigen stimulation. In infection with the *Flavivirus* Japanese Encephalitis virus, IL-10-producing $CD4^+$ $Foxp3^+$ natural Treg cells improve survival in a murine model probably by controlling the immunopathology [148]. In other organs, modulation of immunopathology by IL-10 during infection is not solely reliant on Treg cell activity. In MCMV acute infection, NK cells are the main IL-10 source that modulates immunopathology in liver [58], while IL-10-producing Breg cells probably participate in neuroinflammation control [141]. IL-10 regulatory mechanisms are therefore essential to control severe inflammatory responses produced by viral infections and can thereby, albeit indirectly, be essential for virus clearance.

In an adequate acute immune response, IL-10 presence should not affect virus clearance; however sustained expression during immune priming or secondary responses can favor persistence or chronic infections. This fine balance between the inflammatory response crucial to virus clearance and the IL-10-mediated immune regulation necessary for T cell homeostasis and host tissue protection can be subverted by viruses to allow replication and spreading.

3. IL-10 in Chronic Viral Infections

Persistent or chronic viral infections are not cleared by the host immune response and result in long-term equilibrium between the host and the virus. Several factors can contribute to this persistence such as viral immune evasion mechanisms, impaired viral clearance facilitated by the host-regulated immunosuppression, or, as for herpesviruses, manipulation of the host immune environment to enable persistence (latency). We will next review different mechanisms used by viruses to induce chronicity or persistence, in which either host IL-10 is involved as a regulating cytokine or viruses have evolved mechanisms that mimic IL-10 function, such as IL-10 viral homologs.

3.1. Persistent Viral Infections. Persistent infections such as those established by hepatitis C virus (HCV), HBV, and HIV are of particular interest in human health due to their

high rates of morbidity and mortality as well as the lack of efficient therapies. Impaired viral clearance can result from viral evasion of the immune response or be assisted by the host-regulated immunosuppression. More precisely, $CD4^+$ T cells and $CD8^+$ T cells lose their effector functions and are unable to control viral infections, a phenomenon called T cell exhaustion [150] (Figure 1). $CD8^+$ T cells lose the ability to produce antiviral cytokines, to kill infected cells, and to proliferate in response to antigen stimulation [151]. Similarly, $CD4^+$ T cells show impaired cytokine production and lack of proliferation [90]. This loss of T cell function has been described in persistent infections with HCV, HBV, HIV, and LCMV, suggesting that a conserved mechanism of immunosuppression may downregulate T cell function. These mechanisms produce gene expression changes in T cells, including inhibitory receptor induction [152, 153], production of soluble factors such as TGF-β [154], or elevated systemic IL-10 levels [2, 155, 156]. The programmed death-1 (PD-1)/PD-ligand(L)1 inhibitory pathway actively suppresses T cell responses and can also participate in the establishment of persistent infections [106, 152]. Although PD-1 contributes to T cell exhaustion, a common characteristic of these persistent infections is elevated IL-10. This has been described for HCV and HIV infections in which high IL-10 levels in the early/acute phase are associated with progression to persistence [157–160], which suggests that this is an evolutionarily conserved mechanism in persistent viral infections with clinical relevance.

Studies on LCMV persistent infection have helped elucidate the mechanisms by which IL-10 can mediate persistent infections. Infection of adult mice with Armstrong (Arm) LCMV strain results in acute infections that are efficiently cleared within 7–10 days by anti-LCMV $CD8^+$ CTLs. By contrast, the LCMV clone 13 (Cl13) induces a persistent infection that suppresses cellular and humoral responses. Cl13 infection of DCs results in cell loss in this compartment during the first week of infection and plays a relevant role in establishing persistence [161–163]. Among the different host factors that play a role in immunosuppression in Cl13 infections, it has been documented that IL-10 production is highly increased in serum. Neutralization of IL-10 activity by treatment with anti-IL-10R antibody rescues T cell responses and consequently virus clearance occurs [2, 31]. Similarly, Cl13-infected IL-$10^{-/-}$ mice show increased T cell function and viral clearance [2, 31]. Thus, IL-10 induces immunosuppression that leads to viral persistence.

IL-10 mechanism of action in viral persistence involves complex cellular cross-talks and interplay between the cytokine source and its target. IL-10^+ DCs increase in frequency during the acute phase of Cl13 infection and then decline with time [164]. Thus during the acute phase and up to the time that T cell exhaustion is initiated, DCs are the main cellular source of IL-10. Increased IL-10 production by DCs has also been reported during HIV, HCV, and foot-and-mouth disease virus infections, specifically inducing loss of T cell responses [165–170]. Within the DC populations, IL-10 production is higher in $CD8\alpha^-$ DCs and those expressing high CCR7 levels, a receptor required for DC migration to T cell areas in secondary lymphoid tissues [171]. IL-10 production in these DCs therefore increases the likelihood for IL-10 exerting its regulatory influence on T cells. A similar scenario has been described for HIV in which IL-10-induced immune dysfunction has been related to the modification of DC populations able to gain access to areas where the quality of adaptive immune responses can be profoundly modulated [167]. This mistimed virus-induced IL-10 production by DCs therefore promotes persistent/chronic infections by affecting the inflammatory balance necessary to mount effective T cell responses.

In later stages of chronic Cl13 infection in mice (i.e., from day 8 after infection and throughout the course of disease), NK cells and virus-specific T cells also play a large role in producing IL-10 [72]. In the T cell compartment, virus-specific $CD4^+$ T cells become the main IL-10 overproducers. These data are in line with data from other nonviral infections such as *Leishmania* [172], malaria [74], or *Toxoplasma* [75], in which IL-10 produced by T cells has a high impact on disease outcome.

This induction of IL-10 production in $CD4^+$ T cells is probably a homeostatic mechanism that limits Th-induced inflammation [173]. IL-10 is induced in Th1 cells obtained from LCMV-nonchronically infected mice after antigen reexposure [72], and chronic antigen exposure can lead to the differentiation of IL-10-producing self-regulatory Th1 cells [90, 91, 174]. Repeated antigen exposure could thus convert virus-specific Th cells into IL-10-producing self-regulatory Th1 cells, a mechanism that could further feed LCMV chronic infections. These self-regulatory Th1 cells can prevent DC maturation and suppress Th1 cell differentiation [102]. This negative feedback mechanism can thus be used by LCMV to suppress Th1 effector function. Similar to self-regulatory Th1 cells, Tr1-like cells have been identified as the main IL-10 producers in HIV infections [175]. Tr1-like cells can also be generated through repeated TCR stimulation in the presence of IL-10 [176], but only when APC are present in the culture [177]. The DC-T cell cross-talk in the presence of high IL-10 levels can thus give rise to IL-10-producing T cells that limit T cell immunity. Hepatitis C virus (HCV) chronically infected patients show an increase in IL-10 production by NK cells [158]. In this case, IL-10-producing NK cells could produce a DC-NK cell cross-talk that impairs adaptive immune response and contributes to chronic infections. It is thus apparent that chronic viral infections often use the regulatory role of IL-10 on T cells and APC to cause T cell exhaustion and deactivate antiviral T cell immunity. Blockade of IL-10R with antibody treatment rescues T cell function and contributes to clearance of persistent infections, suggesting that therapeutic strategies that neutralize IL-10 activity could help control persistent infections, such as HCV, together with other molecular therapies.

3.2. Viral IL-10 Homologs in Chronic and Latent Infections. Latency is a mode of persistent or chronic infection in which the viral genome is retained in the host cell, but with a profound restriction on gene expression that results in the production of few viral antigens and no viral particles (reviewed in [178]). Under appropriate conditions, the expression of the

viral genome can be induced and infectious particles are produced. To establish latency, viruses have developed immune evasion mechanisms that allow for persistence. Among these mechanisms, large DNA viruses encode for protein homologs of cytokines and chemokines or express viral factors that alter host cytokine production [179, 180]. Members of the representative latency-inducing Herpesviridae family, such as human cytomegalovirus (HCMV) [181], Epstein-Barr virus (EBV) [182], ovine herpesvirus 2 [183], and equine herpesvirus 2 [184], encode for IL-10 homologs. Among the best-characterized IL-10 homologs are the cytomegalovirus-encoded IL-10, termed cmvIL-10, and the latency-associated cmvIL-10, termed LAcmvIL-10 [181, 185] (Figure 1). HCMV is a β-herpesvirus that infects a majority of the world's population. Following primary infection, HCMV establishes a lifelong latent infection in cells of the myeloid lineage from where it can later be reactivated to produce infectious progeny [186]. HCMV success in infecting host's cells and causing disease relies partially on a number of virally encoded proteins that are homologs of cellular cytokines, chemokines, and their receptors [181], in which the IL-10 homolog plays an important role. During productive infection cmvIL-10 transcripts are expressed from the gene UL111A [185, 187]. This gene also encodes for the splice variant LAcmvIL-10, which has been associated with latency [188]. cmvIL-10 protein shares 27% amino acid identity with hIL-10 but retains the ability to bind the hIL-10 receptor [187]. Therefore, cmvIL-10 mediates immunomodulatory functions similar to hIL-10 such as inhibiting proinflammatory cytokine production, decreasing MHC-I and MHC-II expression in monocytes [189], and impairing monocyte-derived DCs maturation [190].

Another immunomodulatory mechanism of action for cmvIL-10 resides in its ability to alter macrophage polarization. Depending on the signal they received, monocytes and macrophages become polarized to either M1 proinflammatory or M2 anti-inflammatory subsets [191]. M1 macrophages have a proinflammatory effect with a relevant role in defense against intracellular pathogens. By contrast, M2 macrophages show increased phagocytic activity and suppress proinflammatory cytokine production. cmvIL-10 modulates macrophage polarization and promotes an M2 phenotype [192] characterized by downregulation of MHC-II, upregulation of molecules associated with anti-inflammatory functions, and poor activation of $CD4^+$ T cells.

Viral IL-10 homologs probably shape the immune response in the early phase of infection by promoting anti-inflammatory signals. cmvIL-10 induces the upregulation of hIL-10 in monocytes, macrophages, and DCs, thereby amplifying IL-10-mediated immunosuppression and favoring chronicity [193]. Viral Rhesus CMV IL-10 homolog is critical for establishing chronic infections, yet during latent phase a better correlation was observed with cell-derived IL-10 levels than with viral homolog [194]. IL-10-producing $CD4^+$ T cells are also linked to HCMV and MCMV persistence [77, 79, 195]. These data indicate that CMV mostly uses endogenous IL-10 signaling to maintain persistence. Taken together these mechanisms enhance the ability of HCMV to establish a primary productive infection and contribute to productive chronic infection.

By contrast, the function of LAcmvIL-10 is much more limited. While both cmvIL-10 and LAcmvIL-10 suppress MHC-II expression on monocytes, LAcmvIL-10 does not impair DC maturation nor does it suppress proinflammatory cytokine production [196, 197]. LAcmvIL-10 can also upregulate hIL-10 in latently infected myeloid cells, although it probably uses a different activation mechanism to cmvIL-10, as LAcmvIL-10 and cmvIL-10 interact differently with the IL-10 receptor and trigger distinct signaling events [196].

Another well-known example of herpesvirus encoding an IL-10 homolog is EBV. EBV is a γ-herpesvirus carried by a high percentage of the human population. EBV infections are mostly asymptomatic, but in some cases EBV induces mononucleosis or B cell and epithelial-cell malignancies [198]. One of the strategies used by EBV to establish latent infections is to produce a viral IL-10 (vIL-10) encoded by the BCRF1 gene, classified as a late gene but expressed in B cells early after infection [199]. vIL-10 has been shown to bind to and signal through the human IL-10 receptor, similarly to cmvIL-10 [200], although its affinity for the IL-10 receptor is 1000-fold lower than that of hIL-10 [201]. The lower receptor affinity of vIL-10 compared to hIL-10 does not allow vIL-10 to stimulate the proliferation of thymocytes or mast cells [202, 203], but it retains the capacity to suppress proinflammatory cytokine production and enhance B-cell viability. During EBV infection vIL-10 seems to play a role only during acute infection, during which it protects infected B cells by altering cytokine production, inhibiting CD4 and NK cell responses, and ultimately facilitating EBV dissemination [199, 204].

4. Concluding Remarks

IL-10's main function is to prevent immunopathology during inflammatory responses. IL-10 can be produced by virtually all immune cells and in turn IL-10 can modulate the response of these cells. Untangling the complex interactions of this pleiotropic cytokine remains an outstanding challenge for immunologists. IL-10 is so central to immune response regulation that viruses exploit this pathway to evade immunity and establish persistent/latent infections. IL-10 effects in the course of viral infections depend on its spatial and temporal delivery. IL-10 can impair T cell priming in the early stages of adaptive immunity, a mechanism that viruses use to promote their persistence by infecting APC and inducing IL-10 production. The effects of IL-10 on the immune response during acute infections are more subtle. The cytokine is produced in high amounts by antiviral effector T cells at this stage. IL-10 prevents tissue damage in this phase while probably not affecting effector function of antiviral $CD8^+$ T cells. IL-10 does however negatively regulate Th1 responses by downmodulating antigen presenting capacity of APC. This regulatory mechanism promotes inflammation resolution when the pathogen clears. Mistiming of IL-10 production at this stage can impair antiviral T cell responses, favoring an early resolution phase that can lead to chronic infection. Chronic antigen exposure in this phase can exhaust antiviral

T cells and switch their phenotype to IL-10-producing cells unable to reactivate when presented again with the antigen.

IL-10 blockade, an attractive therapy to treat chronic infection, should be approached with caution since, for instance, IL-10 can be necessary for virus clearance in CNS infection where it controls immunopathology. IL-10 could also play a role in antiviral $CD8^+$ T cell memory development; thus IL-10 blockade could prove detrimental to establish long-term $CD8^+$ T cell memory. Targeting the fine balance between inflammation and resolution controlled by IL-10 will therefore require spatial and temporal refinement of delivery approaches. A better understanding at the basic level of IL-10 sources and IL-10 effects on the different components of immunity during infections will allow for precise therapeutic targeting of this pathway.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] W. Ouyang, S. Rutz, N. K. Crellin, P. A. Valdez, and S. G. Hymowitz, "Regulation and functions of the IL-10 family of cytokines in inflammation and disease," *Annual Review of Immunology*, vol. 29, pp. 71–109, 2011.

[2] D. G. Brooks, M. J. Trifilo, K. H. Edelmann, L. Teyton, D. B. McGavern, and M. B. A. Oldstone, "Interleukin-10 determines viral clearance or persistence in vivo," *Nature Medicine*, vol. 12, no. 11, pp. 1301–1309, 2006.

[3] Y. Liu, S. H.-Y. Wei, A. S.-Y. Ho, R. De Waal Malefyt, and K. W. Moore, "Expression cloning and characterization of a human 11-10 receptor," *Journal of Immunology*, vol. 152, no. 4, pp. 1821–1829, 1994.

[4] K. W. Moore, R. De Waal Malefyt, R. L. Coffman, and A. O'Garra, "Interleukin-10 and the interleukin-10 receptor," *Annual Review of Immunology*, vol. 19, pp. 683–765, 2001.

[5] J. K. Riley, K. Takeda, S. Akira, and R. D. Schreiber, "Interleukin-10 receptor signaling through the JAK-STAT pathway. Requirement for two distinct receptor-derived signals for anti-inflammatory action," *Journal of Biological Chemistry*, vol. 274, no. 23, pp. 16513–16521, 1999.

[6] M. A. Meraz, J. M. White, K. C. F. Sheehan et al., "Targeted disruption of the Stat1 gene in mice reveals unexpected physiologic specificity in the JAK-STAT signaling pathway," *Cell*, vol. 84, no. 3, pp. 431–442, 1996.

[7] A. S.-Y. Ho, S. H.-Y. Wei, A. L.-F. Mui, A. Miyajima, and K. W. Moore, "Functional regions of the mouse interleukin-10 receptor cytoplasmic domain," *Molecular and Cellular Biology*, vol. 15, no. 9, pp. 5043–5053, 1995.

[8] D. F. Fiorentino, M. W. Bond, and T. R. Mosmann, "Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones," *Journal of Experimental Medicine*, vol. 170, no. 6, pp. 2081–20095, 1989.

[9] K. N. Couper, D. G. Blount, and E. M. Riley, "IL-10: the master regulator of immunity to infection," *Journal of Immunology*, vol. 180, no. 9, pp. 5771–5777, 2008.

[10] P. Shen and S. Fillatreau, "Suppressive functions of B cells in infectious diseases," *International Immunology*, vol. 27, no. 10, pp. 513–519, 2015.

[11] H. Tilg, C. Van Montfrans, A. Van den Ende et al., "Treatment of Crohn's disease with recombinant human interleukin 10 induces the proinflammatory cytokine interferon γ," *Gut*, vol. 50, no. 2, pp. 191–195, 2002.

[12] F. N. Lauw, D. Pajkrt, C. E. Hack, M. Kurimoto, S. J. H. Van Deventer, and T. Van der Poll, "Proinflammatory effects of IL-10 during human endotoxemia," *Journal of Immunology*, vol. 165, no. 5, pp. 2783–2789, 2000.

[13] D. J. Cua, B. Hutchins, D. M. LaFace, S. A. Stohlman, and R. L. Coffman, "Central nervous system expression of IL-10 inhibits autoimmune encephalomyelitis," *Journal of Immunology*, vol. 166, no. 1, pp. 602–608, 2001.

[14] E. Bettelli, M. P. Das, E. D. Howard, H. L. Weiner, R. A. Sobel, and V. K. Kuchroo, "IL-10 is critical in the regulation of autoimmune encephalomyelitis as demonstrated by studies of IL-10- and IL-4-deficient and transgenic mice," *Journal of Immunology*, vol. 161, no. 7, pp. 3299–3306, 1998.

[15] F. J. Barrat, D. J. Cua, A. Boonstra et al., "In vitro generation of interleukin 10-producing regulatory CD4+ T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines," *Journal of Experimental Medicine*, vol. 195, no. 5, pp. 603–616, 2002.

[16] L. R. Leon, W. Kozak, and M. J. Kluger, "Role of IL-10 in inflammation—studies using cytokine knockout mice," *Annals of the New York Academy of Sciences*, vol. 856, pp. 69–75, 1998.

[17] R. K. Sellon, S. Tonkonogy, M. Schultz et al., "Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice," *Infection and Immunity*, vol. 66, no. 11, pp. 5224–5231, 1998.

[18] R. Kühn, J. Löhler, D. Rennick, K. Rajewsky, and W. Müller, "Interleukin-10-deficient mice develop chronic enterocolitis," *Cell*, vol. 75, no. 2, pp. 263–274, 1993.

[19] S. Rakoff-Nahoum, L. Hao, and R. Medzhitov, "Role of toll-like receptors in spontaneous commensal-dependent colitis," *Immunity*, vol. 25, no. 2, pp. 319–329, 2006.

[20] N. Hoshi, D. Schenten, S. A. Nish et al., "MyD88 signalling in colonic mononuclear phagocytes drives colitis in IL-10-deficient mice," *Nature Communications*, vol. 3, article no. 1120, 2012.

[21] H. H. Uhlig, J. Coombes, C. Mottet et al., "Characterization of Foxp3+CD4+CD25+ and IL-10-secreting CD4+CD25+ T cells during cure of colitis," *Journal of Immunology*, vol. 177, no. 9, pp. 5852–5860, 2006.

[22] Y. P. Rubtsov, J. P. Rasmussen, E. Y. Chi et al., "Regulatory T cell-derived interleukin-10 limits inflammation at environmental interfaces," *Immunity*, vol. 28, no. 4, pp. 546–558, 2008.

[23] A. Chaudhry, R. M. Samstein, P. Treuting et al., "Interleukin-10 signaling in regulatory T cells is required for suppression of Th17 cell-mediated inflammation," *Immunity*, vol. 34, no. 4, pp. 566–578, 2011.

[24] E. Zigmond, B. Bernshtein, G. Friedlander et al., "Macrophage-restricted interleukin-10 receptor deficiency, but not IL-10

deficiency, causes severe spontaneous colitis," *Immunity*, vol. 40, no. 5, pp. 720–733, 2014.

[25] M. Murai, O. Turovskaya, G. Kim et al., "Interleukin 10 acts on regulatory t cells to maintain expression of the transcription factor foxp3 and suppressive function in mice with colitis," *Nature Immunology*, vol. 10, no. 11, pp. 1178–1184, 2009.

[26] D. S. Shouval, A. Biswas, J. A. Goettel et al., "Interleukin-10 receptor signaling in innate immune cells regulates mucosal immune tolerance and anti-inflammatory macrophage function," *Immunity*, vol. 40, no. 5, pp. 706–719, 2014.

[27] A. M. Beebe, D. J. Cua, and R. De Waal Malefyt, "The role of interleukin-10 in autoimmune disease: systemic lupus erythematosus (SLE) and multiple sclerosis (MS)," *Cytokine and Growth Factor Reviews*, vol. 13, no. 4-5, pp. 403–412, 2002.

[28] H. Hata, N. Sakaguchi, H. Yoshitomi et al., "Distinct contribution of IL-6, TNF-α, IL-1, and IL-10 to T cell-mediated spontaneous autoimmune arthritis in mice," *Journal of Clinical Investigation*, vol. 114, no. 4, pp. 582–588, 2004.

[29] X. Bai, J. Zhu, G. Zhang et al., "IL-10 suppresses experimental autoimmune neuritis and down-regulates TH1-type immune responses," *Clinical Immunology and Immunopathology*, vol. 83, no. 2, pp. 117–126, 1997.

[30] S. Tartey and O. Takeuchi, "Pathogen recognition and Toll-like receptor targeted therapeutics in innate immune cells," *International Reviews of Immunology*, pp. 1–17, 2017.

[31] M. Ejrnaes, C. M. Filippi, M. M. Martinic et al., "Resolution of a chronic viral infection after interleukin-10 receptor blockade," *Journal of Experimental Medicine*, vol. 203, no. 11, pp. 2461–2472, 2006.

[32] S. S. M. Ng, A. Li, G. N. Pavlakis, K. Ozato, and T. Kino, "Viral infection increases glucocorticoid-induced interleukin-10 production through ERK-mediated phosphorylation of the glucocorticoid receptor in dendritic cells: potential clinical implications," *PLOS ONE*, vol. 8, no. 5, Article ID e63587, 2013.

[33] R. Samarasinghe, P. Tailor, T. Tamura, T. Kaisho, S. Akira, and K. Ozato, "Induction of an anti-inflammatory cytokine, IL-10, in dendritic cells after toll-like receptor signaling," *Journal of Interferon and Cytokine Research*, vol. 26, no. 12, pp. 893–900, 2006.

[34] M. Javad Aman, T. Tretter, I. Eisenbeis et al., "Interferon-α stimulates production of interleukin-10 in activated CD4+ T cells and monocytes," *Blood*, vol. 87, no. 11, pp. 4731–4736, 1996.

[35] E. Y. Chang, B. Guo, S. E. Doyle, and G. Cheng, "Cutting edge: involvement of the type I IFN production and signaling pathway in lipopolysaccharide-induced IL-10 production," *Journal of Immunology*, vol. 178, no. 11, pp. 6705–6709, 2007.

[36] M. J. Pattison, K. F. MacKenzie, and J. S. C. Arthur, "Inhibition of JAKs in macrophages increases lipopolysaccharide-induced cytokine production by blocking IL-10-mediated feedback," *Journal of Immunology*, vol. 189, no. 6, pp. 2784–2792, 2012.

[37] A. Boonstra, R. Rajsbaum, M. Holman et al., "Macrophages and myeloid dendritic cells, but not plasmacytoid dendritic cells, produce IL-10 in response to MyD88- and TRIF-dependent TLR signals, and TLR-independent signals," *Journal of Immunology*, vol. 177, no. 11, pp. 7551–7558, 2006.

[38] A. Howes, C. Taubert, S. Blankley et al., "Differential Production of Type I IFN Determines the Reciprocal Levels of IL-10 and Proinflammatory Cytokines Produced by C57BL/6 and BALB/c Macrophages," *The Journal of Immunology*, vol. 197, no. 7, pp. 2838–2853, 2016.

[39] K. F. MacKenzie, K. Clark, S. Naqvi et al., "PGE_2 induces macrophage IL-10 production and a regulatory-like phenotype via a protein kinase A-SIK-CRTC3 pathway," *Journal of Immunology*, vol. 190, no. 2, pp. 565–577, 2013.

[40] A. D. Edwards, S. P. Manickasingham, R. Spörri et al., "Microbial recognition via toll-like receptor-dependent and -independent pathways determines the cytokine response of murine dendritic cell subsets to CD40 triggering," *Journal of Immunology*, vol. 169, no. 7, pp. 3652–3660, 2002.

[41] X. Hu, P. K. Paik, J. Chen et al., "IFN-γ suppresses IL-10 production and synergizes with TLR2 by regulating GSK3 and CREB/AP-1 proteins," *Immunity*, vol. 24, no. 5, pp. 563–574, 2006.

[42] M. G. Brown, A. O. Dokun, J. W. Heusel et al., "Vital involvement of a natural killer cell activation receptor in resistance to viral infection," *Science*, vol. 292, no. 5518, pp. 934–937, 2001.

[43] H. E. Farrell, K. Bruce, C. Lawler et al., "Type 1 interferons and NK cells limit murine cytomegalovirus escape from the lymph node subcapsular sinus," *PLOS Pathogens*, vol. 12, no. 12, Article ID e1006069, 2016.

[44] C. Lawler, C. S. Tan, J. P. Simas, P. G. Stevenson, and R. M. Longnecker, "Type I interferons and NK cells restrict gammaherpesvirus lymph node infection," *Journal of Virology*, vol. 90, no. 20, pp. 9046–9057, 2016.

[45] O. Chijioke, A. Müller, R. Feederle et al., "Human natural killer cells prevent infectious mononucleosis features by targeting lytic epstein-barr virus infection," *Cell Reports*, vol. 5, no. 6, pp. 1489–1498, 2013.

[46] C. Qian, X. Jiang, H. An et al., "TLR agonists promote ERK-mediated preferential IL-10 production of regulatory dendritic cells (diffDCs), leading to NK-cell activation," *Blood*, vol. 108, no. 7, pp. 2307–2315, 2006.

[47] S. Mocellin, M. Panelli, E. Wang et al., "IL-10 stimulatory effects on human NK cells explored by gene profile analysis," *Genes and Immunity*, vol. 5, no. 8, pp. 621–630, 2004.

[48] G. Cai, R. A. Kastelein, and C. A. Hunter, "IL-10 enhances NK cell proliferation, cytotoxicity and production of IFN-γ when combined with IL-18," *European Journal of Immunology*, vol. 29, no. 9, pp. 2658–2665, 1999.

[49] W. E. Carson, M. J. Lindemann, R. Baiocchi et al., "The functional characterization of interleukin-10 receptor expression on human natural killer cells," *Blood*, vol. 85, no. 12, pp. 3577–3585, 1995.

[50] Y. Shibata, L. A. Foster, M. Kurimoto et al., "Immunoregulatory roles of IL-10 in innate immunity: IL-10 inhibits macrophage production of IFN-γ-inducing factors but enhances NK cell production of IFN-γ," *Journal of Immunology*, vol. 161, no. 8, pp. 4283–4288, 1998.

[51] B.-C. Chiu, V. R. Stolberg, and S. W. Chensue, "Mononuclear phagocyte-derived IL-10 suppresses the innate IL-12/IFN-γ axis in lung-challenged aged mice," *Journal of Immunology*, vol. 181, no. 5, pp. 3156–3166, 2008.

[52] M. J. Scott, J. J. Hoth, M. Turina, D. R. Woods, and W. G. Cheadle, "Interleukin-10 suppresses natural killer cell but not natural killer T cell activation during bacterial infection," *Cytokine*, vol. 33, no. 2, pp. 79–86, 2006.

[53] M. A. Stacey, M. Marsden, E. C. Y. Wang, G. W. G. Wilkinson, and I. R. Humphreys, "IL-10 restricts activation-induced death of NK cells during acute murine cytomegalovirus infection," *Journal of Immunology*, vol. 187, no. 6, pp. 2944–2952, 2011.

[54] J. H. Bream, R. E. Curiel, C.-R. Yu et al., "IL-4 synergistically enhances both IL-2- and IL-12-induced IFN-γ expression in murine NK cells," *Blood*, vol. 102, no. 1, pp. 207–214, 2003.

[55] M. Bodas, N. Jain, A. Awasthi et al., "Inhibition of IL-2 induced IL-10 production as a principle of phase-specific immunotherapy," *Journal of Immunology*, vol. 177, no. 7, pp. 4636–4643, 2006.

[56] M. J. Loza and B. Perussia, "The IL-12 signature: NK cell terminal CD56+high stage and effector functions," *Journal of Immunology*, vol. 172, no. 1, pp. 88–96, 2004.

[57] L. R. Grant, Z.-J. Yao, C. M. Hedrich et al., "Stat4-dependent, T-bet-independent regulation of IL-10 in NK cells," *Genes and Immunity*, vol. 9, no. 4, pp. 316–327, 2008.

[58] P. J. Gaddi, M. J. Crane, M. Kamanaka, R. A. Flavell, G. S. Yap, and T. P. Salazar-Mather, "IL-10 mediated regulation of liver inflammation during acute murine cytomegalovirus infection," *PLoS ONE*, vol. 7, no. 8, Article ID e42850, 2012.

[59] S.-H. Lee, K.-S. Kim, N. Fodil-Cornu, S. M. Vidal, and C. A. Biron, "Activating receptors promote NK cell expansion for maintenance, IL-10 production, and CD8 T cell regulation during viral infection," *Journal of Experimental Medicine*, vol. 206, no. 10, pp. 2235–2251, 2009.

[60] A. Maroof, L. Beattie, S. Zubairi, M. Svensson, S. Stager, and P. M. Kaye, "Posttranscriptional regulation of Il10 gene expression allows natural killer cells to express immunoregulatory function," *Immunity*, vol. 29, no. 2, pp. 295–305, 2008.

[61] R. Maldonado-López and M. Moser, "Dendritic cell subsets and the regulation of Th1/Th2 responses," *Seminars in Immunology*, vol. 13, no. 5, pp. 275–282, 2001.

[62] D. Y. Ma and E. A. Clark, "The role of CD40 and CD154/CD40L in dendritic cells," *Seminars in Immunology*, vol. 21, no. 5, pp. 265–272, 2009.

[63] S. S. Puntambekar, C. C. Bergmann, C. Savarin et al., "Shifting hierarchies of interleukin-10-producing T cell populations in the central nervous system during acute and persistent viral encephalomyelitis," *Journal of Virology*, vol. 85, no. 13, pp. 6702–6713, 2011.

[64] M. Saraiva and A. O'Garra, "The regulation of IL-10 production by immune cells," *Nature Reviews Immunology*, vol. 10, no. 3, pp. 170–181, 2010.

[65] C. L. Maynard and C. T. Weaver, "Diversity in the contribution of interleukin-10 to T-cell-mediated immune regulation," *Immunological Reviews*, vol. 226, no. 1, pp. 219–233, 2008.

[66] S. S. Cush, G. V. Reynoso, O. Kamenyeva, J. R. Bennink, J. W. Yewdell, and H. D. Hickman, "Locally produced IL-10 limits cutaneous vaccinia virus spread," *PLOS Pathogens*, vol. 12, no. 3, Article ID e1005493, 2016.

[67] L. Jiang, S. Yao, S. Huang, J. Wright, T. J. Braciale, and J. Sun, "Type I IFN signaling facilitates the development of IL-10-producing effector $CD8^+$ T cells during murine influenza virus infection," *European Journal of Immunology*, vol. 46, no. 12, pp. 2778–2788, 2016.

[68] J. Sun, R. Madan, C. L. Karp, and T. J. Braciale, "Effector T cells control lung inflammation during acute influenza virus infection by producing IL-10," *Nature Medicine*, vol. 15, no. 3, pp. 277–284, 2009.

[69] K. Trandem, J. Zhao, E. Fleming, and S. Perlman, "Highly activated cytotoxic CD8 T cells express protective IL-10 at the peak of coronavirus-induced encephalitis," *Journal of Immunology*, vol. 186, no. 6, pp. 3642–3652, 2011.

[70] J. Loebbermann, C. Schnoeller, H. Thornton et al., "IL-10 regulates viral lung immunopathology during acute respiratory syncytial virus infection in mice," *PLoS ONE*, vol. 7, no. 2, Article ID e32371, 2012.

[71] E. M. Palmer, B. C. Holbrook, S. Arimilli, G. D. Parks, and M. A. Alexander-Miller, "IFNγ-producing, virus-specific CD8+ effector cells acquire the ability to produce IL-10 as a result of entry into the infected lung environment," *Virology*, vol. 404, no. 2, pp. 225–230, 2010.

[72] I. A. Parish, H. D. Marshall, M. M. Staron et al., "Chronic viral infection promotes sustained Th1-derived immunoregulatory IL-10 via BLIMP-1," *Journal of Clinical Investigation*, vol. 124, no. 8, pp. 3455–3468, 2014.

[73] A. O'Garra and P. Vieira, "T_H1 cells control themselves by producing interleukin-10," *Nature Reviews Immunology*, vol. 7, no. 6, pp. 425–428, 2007.

[74] A. P. F. Do Rosário, T. Lamb, P. Spence et al., "IL-27 promotes IL-10 production by effector Th1 $CD4^+$T cells: a critical mechanism for protection from severe immunopathology during malaria infection," *Journal of Immunology*, vol. 188, no. 3, pp. 1178–1190, 2012.

[75] D. Jankovic, M. C. Kullberg, C. G. Feng et al., "Conventional T-bet^+Foxp3^- Th1 cells are the major source of host-protective regulatory IL-10 during intracellular protozoan infection," *Journal of Experimental Medicine*, vol. 204, no. 2, pp. 273–283, 2007.

[76] K. Richter, G. Perriard, R. Behrendt et al., "Macrophage and T cell produced IL-10 promotes viral chronicity," *PLoS Pathogens*, vol. 9, no. 11, Article ID e1003735, 2013.

[77] I. R. Humphreys, C. De Trez, A. Kinkade, C. A. Benedict, M. Croft, and C. F. Ware, "Cytomegalovirus exploits IL-10-mediated immune regulation in the salivary glands," *Journal of Experimental Medicine*, vol. 204, no. 5, pp. 1217–1225, 2007.

[78] S. Redpath, A. Angulo, N. R. J. Gascoigne, and P. Ghazal, "Murine cytomegalovirus infection down-regulates MHC class II expression on macrophages by induction of IL-10," *Journal of Immunology*, vol. 162, no. 11, pp. 6701–6707, 1999.

[79] M. Clement, M. Marsden, M. A. Stacey et al., "Cytomegalovirus-specific IL-10-producing $CD4^+$ T cells are governed by type-I IFN-induced IL-27 and promote virus persistence," *PLOS Pathogens*, vol. 12, no. 12, p. e1006050, 2016.

[80] S. Rutz and W. Ouyang, "Regulation of interleukin-10 expression," in *Regulation of Cytokine Gene Expression in Immunity and Diseases*, vol. 941 of *Advances in Experimental Medicine and Biology*, pp. 89–116, Springer, Dordrecht, Netherlands, 2016.

[81] M. Kubo and Y. Motomura, "Transcriptional regulation of the anti-inflammatory cytokine IL-10 in acquired immune cells," *Frontiers in Immunology*, vol. 3, article 275, 2012.

[82] A. Awasthi, Y. Carrier, J. P. S. Peron et al., "A dominant function for interleukin 27 in generating interleukin 10-producing anti-inflammatory T cells," *Nature Immunology*, vol. 8, no. 12, pp. 1380–1389, 2007.

[83] M. Batten, N. M. Kljavin, J. Li, M. J. Walter, F. J. De Sauvage, and N. Ghilardi, "Cutting edge: IL-27 is a potent inducer of IL-10 but not FoxP3 in murine T cells," *Journal of Immunology*, vol. 180, no. 5, pp. 2752–2756, 2008.

[84] D. C. Fitzgerald, G. X. Zhang, M. El-Behi et al., "Suppression of autoimmune inflammation of the central nervous system by interleukin 10 secreted by interleukin 27-stimulated T cells," *Nature Immunology*, vol. 8, no. 12, pp. 1372–1379, 2007.

[85] G. Murugaiyan, A. Mittal, R. Lopez-Diego, L. M. Maier, D. E. Anderson, and H. L. Weiner, "IL-27 is a key regulator of IL-10 and IL-17 production by human $CD4^+$ T cells," *Journal of Immunology*, vol. 183, no. 4, pp. 2435–2443, 2009.

[86] L. Zhang, S. Yuan, G. Cheng, and B. Guo, "Type I IFN promotes IL-10 production from T cells to suppress Th17 cells and Th17-associated autoimmune inflammation," *PLoS ONE*, vol. 6, no. 12, Article ID e28432, 2011.

[87] M. K. Levings, R. Sangregorio, F. Galbiati, S. Squadrone, R. De Waal Malefyt, and M.-G. Roncarolo, "IFN-α and IL-10 induce the differentiation of human type 1 T regulatory cells," *Journal of Immunology*, vol. 166, no. 9, pp. 5530–5539, 2001.

[88] J. S. Stumhofer, J. S. Silver, A. Laurence et al., "Interleukins 27 and 6 induce STAT3-mediated T cell production of interleukin 10," *Nature Immunology*, vol. 8, no. 12, pp. 1363–1371, 2007.

[89] C. L. Maynard, L. E. Harrington, K. M. Janowski et al., "Regulatory T cells expressing interleukin 10 develop from Foxp3$^+$ and Foxp3$^-$ precursor cells in the absence of interleukin 10," *Nature Immunology*, vol. 8, no. 9, pp. 931–941, 2007.

[90] D. G. Brooks, L. Teyton, M. B. A. Oldstone, and D. B. McGavern, "Intrinsic functional dysregulation of CD4 T cells occurs rapidly following persistent viral infection," *Journal of Virology*, vol. 79, no. 16, pp. 10514–10527, 2005.

[91] A. Gallimore, A. Glithero, A. Godkin et al., "Induction and exhaustion of lymphocytic choriomeningitis virus–specific cytotoxic T lymphocytes visualized using soluble tetrameric major histocompatibility complex class I–peptide complexes," *Journal of Experimental Medicine*, vol. 187, no. 9, pp. 1383–1393, 1998.

[92] J. Sun, H. Dodd, E. K. Moser, R. Sharma, and T. J. Braciale, "CD4$^+$ T cell help and innate-derived IL-27 induce Blimp-1-dependent IL-10 production by antiviral CTLs," *Nature Immunology*, vol. 12, no. 4, pp. 327–334, 2011.

[93] T. De Smedt, M. Van Mechelen, G. De Becker, J. Urbain, O. Leo, and M. Moser, "Effect of interleukin-10 on dendritic cell maturation and function," *European Journal of Immunology*, vol. 27, no. 5, pp. 1229–1235, 1997.

[94] F. Capsoni, F. Minonzio, A. M. Ongari, V. Carbonelli, A. Galli, and C. Zanussi, "IL-10 up-regulates human monocyte phagocytosis in the presence of IL-4 and IFN-γ," *Journal of Leukocyte Biology*, vol. 58, no. 3, pp. 351–358, 1995.

[95] D. F. Fiorentino, A. Zlotnik, T. R. Mosmann, M. Howard, and A. O'Garra, "IL-10 inhibits cytokine production by activated macrophages," *Journal of Immunology*, vol. 147, no. 11, pp. 3815–3822, 1991.

[96] N. Makita, Y. Hizukuri, K. Yamashiro, M. Murakawa, and Y. Hayashi, "IL-10 enhances the phenotype of M2 macrophages induced by IL-4 and confers the ability to increase eosinophil migration," *International Immunology*, vol. 27, no. 3, pp. 131–141, 2015.

[97] S. Corinti, C. Albanesi, A. La Sala, S. Pastore, and G. Girolomoni, "Regulatory activity of autocrine IL-10 on dendritic cell functions," *Journal of Immunology*, vol. 166, no. 7, pp. 4312–4318, 2001.

[98] S. Bhattacharyya, P. Sen, M. Wallet, B. Long, A. S. Baldwin Jr., and R. Tisch, "Immunoregulation of dendritic cells by IL-10 is mediated through suppression of the PI3K/Akt pathway and of IκB kinase activity," *Blood*, vol. 104, no. 4, pp. 1100–1109, 2004.

[99] F. O. Martinez and S. Gordon, "The M1 and M2 paradigm of macrophage activation: time for reassessment," *F1000Prime Reports*, vol. 6, article 13, 2014.

[100] A. D'Andrea, M. Aste-Amezaga, N. M. Valiante, X. Ma, M. Kubin, and G. Trinchieri, "Interleukin 10 (IL-10) inhibits human lymphocyte interferon gamma-production by suppressing natural killer cell stimulatory factor/IL-12 synthesis in accessory cells," *Journal of Experimental Medicine*, vol. 178, no. 3, pp. 1041–1048, 1993.

[101] X. Ma, W. Yan, H. Zheng et al., "Regulation of IL-10 and IL-12 production and function in macrophages and dendritic cells," *F1000Research*, vol. 4, 2015.

[102] L. Gabryšová, K. S. Nicolson, H. B. Streeter et al., "Negative feedback control of the autoimmune response through antigen-induced differentiation of IL-10-secreting Th1 cells," *Journal of Experimental Medicine*, vol. 206, no. 8, pp. 1755–1767, 2009.

[103] C. Demangel, P. Bertolino, and W. J. Britton, "Autocrine IL-10 impairs dendritic cell (DC)-derived immune responses to mycobacterial infection by suppressing DC trafficking to draining lymph nodes and local IL-12 production," *European Journal of Immunology*, vol. 32, no. 4, pp. 994–1002, 2002.

[104] Y. Tian, S. B. Mollo, L. E. Harrington, and A. J. Zajac, "IL-10 regulates memory T cell development and the balance between Th1 and follicular Th cell responses during an acute viral infection," *The Journal of Immunology*, vol. 197, no. 4, pp. 1308–1321, 2016.

[105] X. S. Liu, Y. Xu, L. Hardy et al., "IL-10 mediates suppression of the CD8 T cell IFN-γ response to a novel viral epitope in a primed host," *The Journal of Immunology*, vol. 171, no. 9, pp. 4765–4772, 2003.

[106] L. Snell, I. Osokine, D. Yamada, J. De la Fuente, H. Elsaesser, and D. Brooks, "Overcoming CD4 Th1 cell fate restrictions to sustain antiviral CD8 T cells and control persistent virus infection," *Cell Reports*, vol. 16, no. 12, pp. 3286–3296, 2016.

[107] D. G. Brooks, K. B. Walsh, H. Elsaesser, and M. B. A. Oldstone, "IL-10 directly suppresses CD4 but not CD8 T cell effector and memory responses following acute viral infection," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 7, pp. 3018–3023, 2010.

[108] K. Richter and A. Oxenius, "Non-neutralizing antibodies protect from chronic LCMV infection independently of activating FcγR or complement," *European Journal of Immunology*, vol. 43, no. 9, pp. 2349–2360, 2013.

[109] K. A. Kulcsar, V. K. Baxter, I. P. Greene, and D. E. Griffin, "Interleukin 10 modulation of pathogenic Th17 cells during fatal alphavirus encephalomyelitis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 111, no. 45, pp. 16053–16058, 2014.

[110] K. E. Foulds, M. J. Rotte, and R. A. Seder, "IL-10 is required for optimal CD8 T cell memory following *Listeria monocytogenes* infection," *The Journal of Immunology*, vol. 177, no. 4, pp. 2565–2574, 2006.

[111] W. Cui, Y. Liu, J. S. Weinstein, J. Craft, and S. M. Kaech, "An Interleukin-21- Interleukin-10-STAT3 Pathway Is Critical for Functional Maturation of Memory CD8+ T Cells," *Immunity*, vol. 35, no. 5, pp. 792–805, 2011.

[112] B. J. Laidlaw, W. Cui, R. A. Amezquita et al., "Production of IL-10 by CD4$^+$ regulatory T cells during the resolution of infection promotes the maturation of memory CD8$^+$ T cells," *Nature Immunology*, vol. 16, no. 8, pp. 871–879, 2015.

[113] T. Dörner and A. Radbruch, "Antibodies and B cell memory in viral immunity," *Immunity*, vol. 27, no. 3, pp. 384–392, 2007.

[114] N. L. Letvin, "Correlates of immune protection and the development of a human immunodeficiency virus vaccine," *Immunity*, vol. 27, no. 3, pp. 366–369, 2007.

[115] R. M. Zinkernagel and H. Hengartner, "Protective 'immunity' by pre-existent neutralizing antibody titers and preactivated T cells but not by so-called 'immunological memory'," *Immunological Reviews*, vol. 211, pp. 310–319, 2006.

[116] E. Melzi, M. Caporale, M. Rocchi et al., "Follicular dendritic cell disruption as a novel mechanism of virus-induced immunosuppression," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 113, no. 41, pp. E6238–E6247, 2016.

[117] D. D. Richman, T. Wrin, S. J. Little, and C. J. Petropoulos, "Rapid evolution of the neutralizing antibody response to HIV type 1 infection," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 7, pp. 4144–4149, 2003.

[118] X. Wei, J. M. Decker, S. Wang et al., "Antibody neutralization and escape by HIV-1," *Nature*, vol. 422, no. 6929, pp. 307–312, 2003.

[119] K. Itoh and S. Hirohata, "The role of IL-10 in human B cell activation, proliferation, and differentiation," *Journal of Immunology*, vol. 154, no. 9, pp. 4341–4350, 1995.

[120] H. Gary-Gouy, J. Harriague, G. Bismuth, C. Platzer, C. Schmitt, and A. H. Dalloul, "Human CD5 promotes B-cell survival through stimulation of autocrine IL-10 production," *Blood*, vol. 100, no. 13, pp. 4537–4543, 2002.

[121] N. Shparago, P. Zelazowski, L. Jin et al., "IL-10 selectively regulates murine Ig isotype switching," *International Immunology*, vol. 8, no. 5, pp. 781–790, 1996.

[122] F. Malisan, F. Brière, J.-M. Bridon et al., "Interleukin-10 induces immunoglobulin G isotype switch recombination in human CD40-activated naive B lymphocytes," *Journal of Experimental Medicine*, vol. 183, no. 3, pp. 937–947, 1996.

[123] S. Agrawal and S. Gupta, "TLR1/2, TLR7, and TLR9 signals directly activate human peripheral blood naive and memory B cell subsets to produce cytokines, chemokines, and hematopoietic growth factors," *Journal of Clinical Immunology*, vol. 31, no. 1, pp. 89–98, 2011.

[124] V. Lampropoulou, K. Hoehlig, T. Roch et al., "TLR-activated B cells suppress T cell-mediated autoimmunity," *Journal of Immunology*, vol. 180, no. 7, pp. 4763–4773, 2008.

[125] A. Sayi, E. Kohler, I. M. Toller et al., "TLR-2-activated B cells suppress Helicobacter-induced preneoplastic gastric immunopathology by inducing T regulatory-1 cells," *Journal of Immunology*, vol. 186, no. 2, pp. 878–890, 2011.

[126] J. Skok, J. Poudrier, and D. Gray, "Dendritic cell-derived IL-12 promotes B cell induction of Th2 differentiation: a feedback regulation of Th1 development," *Journal of Immunology*, vol. 163, no. 8, pp. 4284–4291, 1999.

[127] L. Giordani, M. Sanchez, I. Libri, M. G. Quaranta, B. Mattioli, and M. Viora, "IFN-α amplifies human naïve B cell TLR-9-mediated activation and Ig production," *Journal of Leukocyte Biology*, vol. 86, no. 2, pp. 261–271, 2009.

[128] X. Zhang, E. Deriaud, X. Jiao, D. Braun, C. Leclerc, and R. Lo-Man, "Type I interferons protect neonates from acute inflammation through interleukin 10-producing B cells," *Journal of Experimental Medicine*, vol. 204, no. 5, pp. 1107–1118, 2007.

[129] A. Mizoguchi, E. Mizoguchi, H. Takedatsu, R. S. Blumberg, and A. K. Bhan, "Chronic intestinal inflammatory condition generates IL-10-producing regulatory B cell subset characterized by CD1d upregulation," *Immunity*, vol. 16, no. 2, pp. 219–230, 2002.

[130] K. Yanaba, J.-D. Bouaziz, K. M. Haas, J. C. Poe, M. Fujimoto, and T. F. Tedder, "A regulatory B cell subset with a unique CD1dhiCD5+ phenotype controls T cell-dependent inflammatory responses," *Immunity*, vol. 28, no. 5, pp. 639–650, 2008.

[131] K. M. Candando, J. M. Lykken, and T. F. Tedder, "B10 cell regulation of health and disease," *Immunological Reviews*, vol. 259, no. 1, pp. 259–272, 2014.

[132] J. M. Lykken, K. M. Candando, and T. F. Tedder, "Regulatory B10 cell development and function," *International Immunology*, vol. 27, no. 10, pp. 471–477, 2015.

[133] N. Matsushita, S. A. Pilon-Thomas, L. M. Martin, and A. I. Riker, "Comparative methodologies of regulatory T cell depletion in a murine melanoma model," *Journal of Immunological Methods*, vol. 333, no. 1-2, pp. 167–179, 2008.

[134] A. Yoshizaki, T. Miyagaki, D. J. Dilillo et al., "Regulatory B cells control T-cell autoimmunity through IL-21-dependent cognate interactions," *Nature*, vol. 491, no. 7423, pp. 264–268, 2012.

[135] M. Horikawa, E. T. Weimer, D. J. DiLillo et al., "Regulatory B Cell (B10 Cell) expansion during listeria infection governs innate and cellular immune responses in mice," *Journal of Immunology*, vol. 190, no. 3, pp. 1158–1168, 2013.

[136] P. Neves, V. Lampropoulou, E. Calderon-Gomez et al., "Signaling via the MyD88 adaptor protein in B cells suppresses protective immunity during salmonella typhimurium infection," *Immunity*, vol. 33, no. 5, pp. 777–790, 2010.

[137] S. Amu, S. P. Saunders, M. Kronenberg, N. E. Mangan, A. Atzberger, and P. G. Fallon, "Regulatory B cells prevent and reverse allergic airway inflammation via FoxP3-positive T regulatory cells in a murine model," *Journal of Allergy and Clinical Immunology*, vol. 125, no. 5, pp. 1114–1124.e8, 2010.

[138] Z. Cen, Y. Guo, Q. Kong, Q. Zhou, and W. Wu, "IL-10-producing B cells involved in the pathogenesis of Coxsackie virus B3-induced acute viral myocarditis," *International Journal of Clinical and Experimental Pathology*, vol. 8, no. 1, pp. 830–835, 2015.

[139] M. Jones, K. Ladell, K. K. Wynn et al., "IL-10 restricts memory T cell inflation during cytomegalovirus infection," *Journal of Immunology*, vol. 185, no. 6, pp. 3583–3592, 2010.

[140] R. Madan, F. Demircik, S. Surianarayanan et al., "Nonredundant roles for B cell-derived IL-10 in immune counter-regulation," *Journal of Immunology*, vol. 183, no. 4, pp. 2312–2320, 2009.

[141] M. B. Mutnal, S. Hu, S. J. Schachtele, and J. R. Lokensgard, "Infiltrating regulatory B cells control neuroinflammation following viral brain infection," *Journal of Immunology*, vol. 193, no. 12, pp. 6070–6080, 2014.

[142] J. Liu, W. Zhan, C. J. Kim et al., "IL-10-producing B cells are induced early in HIV-1 infection and suppress HIV-1-specific T cell responses," *PLoS ONE*, vol. 9, no. 2, Article ID e89236, 2014.

[143] A. Das, G. Ellis, C. Pallant et al., "IL-10-producing regulatory B cells in the pathogenesis of chronic hepatitis B virus infection," *The Journal of Immunology*, vol. 189, no. 8, pp. 3925–3935, 2012.

[144] D. D. Naicker, L. Werner, E. Kormuth et al., "Interleukin-10 promoter polymorphisms influence HIV-1 susceptibility and primary HIV-1 pathogenesis," *The Journal of Infectious Diseases*, vol. 200, no. 3, pp. 448–452, 2009.

[145] D. Verhoeven and S. Perry, "Differential mucosal IL-10-induced immunoregulation of innate immune responses occurs in influenza infected infants/toddlers and adults," *Immunology and Cell Biology*, 2016.

[146] M. M. N. Tun, K. Aoki, M. Senba et al., "Protective role of TNF-α, IL-10 and IL-2 in mice infected with the Oshima strain of Tick-borne encephalitis virus," *Scientific Reports*, vol. 4, article no. 5344, 2014.

[147] V. Saxena, A. Mathur, N. Krishnani, and T. N. Dhole, "An insufficient anti-inflammatory cytokine response in mouse brain is associated with increased tissue pathology and viral load during Japanese encephalitis virus infection," *Archives of Virology*, vol. 153, no. 2, pp. 283–292, 2008.

[148] J. H. Kim, A. M. Patil, J. Y. Choi et al., "CCR5 ameliorates Japanese encephalitis via dictating the equilibrium of regulatory $CD4^+Foxp3^+$ T and IL-17^+CD4^+ Th17 cells," *Journal of Neuroinflammation*, vol. 13, no. 1, article 223, 2016.

[149] M. T. Lin, D. R. Hinton, B. Parra, S. A. Stohlman, and R. C. Van Der Veen, "The role of IL-10 in mouse hepatitis virus-induced demyelinating encephalomyelitis," *Virology*, vol. 245, no. 2, pp. 270–280, 1998.

[150] E. J. Wherry, "T cell exhaustion," *Nature Immunology*, vol. 12, no. 6, pp. 492–499, 2011.

[151] E. J. Wherry, J. N. Blattman, K. Murali-Krishna, R. Van Der Most, and R. Ahmed, "Viral persistence alters CD8 T-cell immunodominance and tissue distribution and results in distinct stages of functional impairment," *Journal of Virology*, vol. 77, no. 8, pp. 4911–4927, 2003.

[152] D. L. Barber, E. J. Wherry, D. Masopust et al., "Restoring function in exhausted CD8 T cells during chronic viral infection," *Nature*, vol. 439, no. 7077, pp. 682–687, 2006.

[153] S. D. Blackburn, H. Shin, W. N. Haining et al., "Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection," *Nature Immunology*, vol. 10, no. 1, pp. 29–37, 2009.

[154] R. Tinoco, V. Alcalde, Y. Yang, K. Sauer, and E. I. Zuniga, "Cell-intrinsic transforming growth factor-β signaling mediates virus-specific CD8+ T cell deletion and viral persistence in vivo," *Immunity*, vol. 31, no. 1, pp. 145–157, 2009.

[155] E. B. Wilson and D. G. Brooks, "The role of IL-10 in regulating immunity to persistent viral infections," *Current topics in microbiology and immunology*, vol. 350, pp. 39–65, 2011.

[156] S. D. Blackburn and E. J. Wherry, "IL-10, T cell exhaustion and viral persistence," *Trends in Microbiology*, vol. 15, no. 4, pp. 143–146, 2007.

[157] J. K. Flynn, G. J. Dore, M. Hellard et al., "Early IL-10 predominant responses are associated with progression to chronic hepatitis C virus infection in injecting drug users," *Journal of Viral Hepatitis*, vol. 18, no. 8, pp. 549–561, 2011.

[158] A. De Maria, M. Fogli, S. Mazza et al., "Increased natural cytotoxicity receptor expression and relevant IL-10 production in NK cells from chronically infected viremic HCV patients," *European Journal of Immunology*, vol. 37, no. 2, pp. 445–455, 2007.

[159] E. A. Said, F. P. Dupuy, L. Trautmann et al., "Programmed death-1-induced interleukin-10 production by monocytes impairs $CD4^+$ T cell activation during HIV infection," *Nature Medicine*, vol. 16, no. 4, pp. 452–459, 2010.

[160] M. A. Brockman, D. S. Kwon, D. P. Tighe et al., "IL-10 is up-regulated in multiple cell types during viremic HIV infection and reversibly inhibits virus-specific T cells," *Blood*, vol. 114, no. 2, pp. 346–356, 2009.

[161] N. Sevilla, S. Kunz, A. Holz et al., "Immunosuppression and resultant viral persistence by specific viral targeting of dendritic cells," *Journal of Experimental Medicine*, vol. 192, no. 9, pp. 1249–1260, 2000.

[162] N. Sevilla, D. B. McGavern, C. Teng, S. Kunz, and M. B. A. Oldstone, "Viral targeting of hematopoietic progenitors and inhibition of DC maturation as a dual strategy for immune subversion," *Journal of Clinical Investigation*, vol. 113, no. 5, pp. 737–745, 2004.

[163] M. B. A. Oldstone, "Biology and pathogenesis of lymphocytic choriomeningitis virus infection," *Current Topics in Microbiology and Immunology*, vol. 263, pp. 83–117, 2002.

[164] C. T. Ng and M. B. A. Oldstone, "Infected $CD8\alpha^-$ dendritic cells are the predominant source of IL-10 during establishment of persistent viral infection," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 109, no. 35, pp. 14116–14121, 2012.

[165] K. Saito, M. Ait-Goughoulte, S. M. Truscott et al., "Hepatitis C virus inhibits cell surface expression of HLA-DR, prevents dendritic cell maturation, and induces interleukin-10 production," *Journal of Virology*, vol. 82, no. 7, pp. 3320–3328, 2008.

[166] C.-C. Liang, C.-H. Liu, Y.-L. Lin, C.-J. Liu, B.-L. Chiang, and J.-H. Kao, "Functional impairment of dendritic cells in patients infected with hepatitis C virus genotype 1 who failed peginterferon plus ribavirin therapy," *Journal of Medical Virology*, vol. 83, no. 7, pp. 1212–1220, 2011.

[167] G. Alter, D. Kavanagh, S. Rihn et al., "IL-10 induces aberrant deletion of dendritic cells by natural killer cells in the context of HIV infection," *Journal of Clinical Investigation*, vol. 120, no. 6, pp. 1905–1913, 2010.

[168] S. Buisson, A. Benlahrech, B. Gazzard, F. Gotch, P. Kelleher, and S. Patterson, "Monocyte-derived dendritic cells from HIV type 1-Infected individuals show reduced ability to stimulate T cells and have altered production of interleukin (IL)-12 and IL-10," *Journal of Infectious Diseases*, vol. 199, no. 12, pp. 1862–1871, 2009.

[169] F. Díaz-San Segundo, T. Rodríguez-Calvo, A. de Avila, and N. Sevilla, "Immunosuppression during acute infection with foot-and-mouth disease virus in swine is mediated by IL-10," *PLoS ONE*, vol. 4, no. 5, Article ID e5659, 2009.

[170] M. Ostrowski, M. Vermeulen, O. Zabal, J. R. Geffner, A. M. Sadir, and O. J. Lopez, "Impairment of thymus-dependent responses by murine dendritic cells infected with foot-and-mouth disease virus," *Journal of Immunology*, vol. 175, no. 6, pp. 3971–3979, 2005.

[171] N. Sánchez-Sánchez, L. Riol-Blanco, and J. L. Rodríguez-Fernández, "The multiple personalities of the chemokine receptor CCR7 in dendritic cells," *Journal of Immunology*, vol. 176, no. 9, pp. 5153–5159, 2006.

[172] S. Nylén, R. Maurya, L. Eidsmo, K. Das Manandhar, S. Sundar, and D. Sacks, "Splenic accumulation of IL-10 mRNA in T cells distinct from $CD4^+CD25^+$ (Foxp3) regulatory T cells in human visceral leishmaniasis," *Journal of Experimental Medicine*, vol. 204, no. 4, pp. 805–817, 2007.

[173] T. H. Ng, G. J. Britton, E. V. Hill, J. Verhagen, B. R. Burton, and D. C. Wraith, "Regulation of adaptive immunity; the role of interleukin-10," *Frontiers in Immunology*, vol. 4, article 129, 2013.

[174] C. H. Maris, C. P. Chappell, and J. Jacob, "Interleukin-10 plays an early role in generating virus-specific T cell anergy," *BMC Immunology*, vol. 8, article 8, 2007.

[175] M. F. Chevalier, C. Didier, G. Petitjean et al., "Phenotype alterations in regulatory T-cell subsets in primary HIV infection and identification of Tr1-like cells as the main interleukin 10-producing CD4+ T cells," *Journal of Infectious Diseases*, vol. 211, no. 5, pp. 769–779, 2015.

[176] H. Groux, A. O'Garra, M. Bigler et al., "A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis," *Nature*, vol. 389, no. 6652, pp. 737–742, 1997.

[177] S. Gregori, D. Tomasoni, V. Pacciani et al., "Differentiation of type 1 T regulatory cells (Tr1) by tolerogenic DC-10 requires the IL-10-dependent ILT4/HLA-G pathway," *Blood*, vol. 116, no. 6, pp. 935–944, 2011.

[178] S. H. Speck and D. Ganem, "Viral latency and its regulation: lessons from the γ-herpesviruses," *Cell Host and Microbe*, vol. 8, no. 1, pp. 100–115, 2010.

[179] A. Alcami, "Viral mimicry of cytokines, chemokines and their receptors," *Nature Reviews Immunology*, vol. 3, no. 1, pp. 36–50, 2003.

[180] A. Alcami and U. H. Koszinowski, "Viral mechanisms of immune evasion," *Trends in Microbiology*, vol. 8, no. 9, pp. 410–418, 2000.

[181] B. P. McSharry, S. Avdic, and B. Slobedman, "Human cytomegalovirus encoded homologs of cytokines, chemokines and their receptors: roles in immunomodulation," *Viruses*, vol. 4, no. 11, pp. 2448–2470, 2012.

[182] K. W. Moore, P. Vieira, D. F. Fiorentino, M. L. Trounstine, T. A. Khan, and T. R. Mosmann, "Homology of cytokine synthesis inhibitory factor (IL-10) to the epstein-barr virus gene BCRFI," *Science*, vol. 248, no. 4960, pp. 1230–1234, 1990.

[183] G. Jayawardane, G. C. Russell, J. Thomson et al., "A captured viral interleukin 10 gene with cellular exon structure," *Journal of General Virology*, vol. 89, no. 10, pp. 2447–2455, 2008.

[184] E. A. R. Telford, M. S. Watson, H. C. Aird, J. Perry, and A. J. Davison, "The DNA sequence of equine herpesvirus 2," *Journal of Molecular Biology*, vol. 249, no. 3, pp. 520–528, 1995.

[185] B. Slobedman, P. A. Barry, J. V. Spencer, S. Avdic, and A. Abendroth, "Virus-encoded homologs of cellular interleukin-10 and their control of host immune function," *Journal of Virology*, vol. 83, no. 19, pp. 9618–9629, 2009.

[186] M. B. Reeves, P. A. MacAry, P. J. Lehner, J. G. P. Sissons, and J. H. Sinclair, "Latency, chromatin remodeling, and reactivation of human cytomegalovirus in the dendritic cells of healthy carriers," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 11, pp. 4140–4145, 2005.

[187] S. V. Kotenko, S. Saccani, L. S. Izotova, O. V. Mirochnitchenko, and S. Pestka, "Human cytomegalovirus harbors its own unique IL-10 homolog (cmvIL-10)," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 4, pp. 1695–1700, 2000.

[188] C. Jenkins, A. Abendroth, and B. Slobedman, "A novel viral transcript with homology to human interleukin-10 is expressed during latent human cytomegalovirus infection," *Journal of Virology*, vol. 78, no. 3, pp. 1440–1447, 2004.

[189] J. V. Spencer, K. M. Lockridge, P. A. Barry et al., "Potent immunosuppressive activities of cytomegalovirus-encoded interleukin-10," *Journal of Virology*, vol. 76, no. 3, pp. 1285–1292, 2002.

[190] S. Avdic, B. P. McSharry, and B. Slobedman, "Modulation of dendritic cell functions by viral IL-10 encoded by human cytomegalovirus," *Frontiers in Microbiology*, vol. 5, 2014.

[191] S. Gordon, "Alternative activation of macrophages," *Nature Reviews Immunology*, vol. 3, no. 1, pp. 23–35, 2003.

[192] S. Avdic, J. Z. Cao, B. P. McSharry et al., "Human cytomegalovirus interleukin-10 polarizes monocytes toward a deactivated m2c phenotype to repress host immune responses," *Journal of Virology*, vol. 87, no. 18, pp. 10273–10282, 2013.

[193] S. Avdic, B. P. McSharry, M. Steain et al., "Human cytomegalovirus-encoded human interleukin-10 (IL-10) homolog amplifies its immunomodulatory potential by upregulating human IL-10 in monocytes," *Journal of Virology*, vol. 90, no. 8, pp. 3819–3827, 2016.

[194] M. K. Eberhardt, A. Deshpande, J. Fike et al., "Exploitation of interleukin-10 (IL-10) signaling pathways: alternate roles of viral and cellular IL-10 in rhesus cytomegalovirus infection," *Journal of Virology*, vol. 90, no. 21, pp. 9920–9930, 2016.

[195] G. M. Mason, S. Jackson, G. Okecha et al., "Human cytomegalovirus latency-associated proteins elicit immune-suppressive IL-10 producing CD4+ T cells," *PLoS Pathogens*, vol. 9, no. 10, Article ID e1003635, 2013.

[196] C. Jenkins, W. Garcia, M. J. Godwin et al., "Immunomodulatory properties of a viral homolog of human interleukin-10 expressed by human cytomegalovirus during the latent phase of infection," *Journal of Virology*, vol. 82, no. 7, pp. 3736–3750, 2008.

[197] J. V. Spencer, J. Cadaoas, P. R. Castillo, V. Saini, and B. Slobedman, "Stimulation of B lymphocytes by cmvIL-10 but not LAcmvIL-10," *Virology*, vol. 374, no. 1, pp. 164–169, 2008.

[198] L. S. Young and A. B. Rickinson, "Epstein-Barr virus: 40 years on," *Nature Reviews Cancer*, vol. 4, no. 10, pp. 757–768, 2004.

[199] S. Jochum, A. Moosmann, S. Lang, W. Hammerschmidt, and R. Zeidler, "The EBV immunoevasins vIL-10 and BNLF2a protect newly infected B cells from immune recognition and elimination," *PLOS Pathogens*, vol. 8, no. 5, Article ID e1002704, 2012.

[200] S. I. Yoon, B. C. Jones, N. J. Logsdon, and M. R. Walter, "Same structure, different function: crystal structure of the Epstein-Barr virus IL-10 bound to the soluble IL-10r1 chain," *Structure*, vol. 13, no. 4, pp. 551–564, 2005.

[201] S. I. Yoon, B. C. Jones, N. J. Logsdon, B. D. Harris, S. Kuruganti, and M. R. Walter, "Epstein-barr virus IL-10 engages IL-10R1 by a two-step mechanism leading to altered signaling properties," *Journal of Biological Chemistry*, vol. 287, no. 32, pp. 26586–26595, 2012.

[202] P. Vieira, R. De Waal-Malefyt, M.-N. Dang et al., "Isolation and expression of human cytokine synthesis inhibitory factor cDNA clones: homology to Epstein-Barr virus open reading frame BCRFI," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 88, no. 4, pp. 1172–1176, 1991.

[203] Y. Ding, L. Qin, S. V. Kotenko, S. Pestka, and J. S. Bromberg, "A single amino acid determines the immunostimulatory activity of interleukin 10," *Journal of Experimental Medicine*, vol. 191, no. 2, pp. 213–224, 2000.

[204] G. J. Lindquester, K. A. Greer, J. P. Stewart, and J. T. Sample, "Epstein-Barr virus IL-10 gene expression by a recombinant murine gammaherpesvirus *in vivo* enhances acute pathogenicity but does not affect latency or reactivation," *Herpesviridae*, vol. 5, article 1, 2014.