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Viruses Strive to Suppress Host Immune Responses and Prolong Persistence

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1. Introduction

Viruses regulate host immune responses to propagate their progeny. Indeed, certain viruses successfully establish viral persistence for long periods of time even in the immunocompetent host. Many viruses seem to have developed clever tactics to elude, utilize, or suppress host innate and adaptive immune systems. Unlike the parental strain, the clone 13 (Cl 13) strain of lymphocytic choriomeningitis virus (LCMV) has been shown to persist in mice for 60 – 100 days by nullifying the function of the host immune system. Multiple findings obtained from this mouse model have held true in humans chronically infected with viruses including human immunodeficiency virus (HIV) and hepatitis viruses. These viruses have evolved a repertoire of mechanisms to suppress and evade the host immune system. By utilizing the model for the LCMV infection of mice, this review will focus on the viral mechanisms for inhibition or escape of host immunity, in particular the host dendritic cell (DC) and T cell responses. Investigating the viral strategies will help us better understand the virus-host interplay and design new immunotherapeutic approaches.

1.1 The lymphocytic choriomeningitis virus model of chronic viral infection

The Cl 13 strain of LCMV is a variant isolated from the spleens of mice infected neonatally with the prototypic LCMV strain, Armstrong 53b (Arm) (Ahmed, Salmi et al. 1984). Mice infected with LCMV Arm develop a robust acute immune response of cytotoxic T lymphocytes (CTLs) that rapidly clears the virus from its host (within 10 days). In contrast, the infection of adult mice with LCMV Cl 13 induces a profound suppression of the host immune system leading to viral persistence (60-100 days following the start of infection) (Figure 1) (Borrow, Evans et al. 1995; Sevilla, Kunz et al. 2003). The clinical importance of virus-induced altered or suppressed immune responses is reflected by several human virus infections that inhibit the immune response such as HIV and hepatitis C virus (HCV) (Steinman, Granelli-Piperno et al. 2003; Liu, Woltman et al. 2009). Thus, the system of LCMV Cl 13 infection of its natural host, the mouse, serves as an excellent model for the mechanistic study of virus-induced immunosuppression and for the development of novel targets controlling viral persistence.

Immunosuppression caused by LCMV Cl 13 is associated with the inhibition of DC function and the reduced frequency and impaired activation (exhaustion) of virus-specific T cells

(Borrow et al. 1995; Sevilla et al. 2003; Barber, Wherry et al. 2006; Trifilo, Hahm et al. 2006). Exhausted T cell responses are characterized by the cells' inability to produce antiviral and immune stimulatory cytokines, destroy virus-infected cells, or proliferate, and have been documented following multiple infections including HIV, HCV, and hepatitis B virus (Yi, Cox et al. 2010).

LCMV Cl 13 differs from Arm by only two amino acids (aa); a Leu in the viral glycoprotein at aa 260 in Cl 13 as compared to Phe in ARM is responsible for DC infection and immunosuppression (Salvato, Borrow et al. 1991). LCMV Cl 13 preferentially replicates in the white pulp of the spleen and infects DCs in spleen and bone marrow (BM) of the mice via the receptor α -dystroglycan (Cao, Henry et al. 1998; Smelt, Borrow et al. 2001; Sevilla et al. 2003). The modulation of immuno-regulatory proteins expressed on DCs was reported to explain the failure of DC function to stimulate or maintain T cell responses upon LCMV Cl 13 infection. Such modulation included the downregulation of MHC molecules and co-stimulatory proteins (Sevilla, McGavern et al. 2004), preferential production of the immunosuppressive cytokine, IL-10 (Brooks, Trifilo et al. 2006; Ejrnaes, Filippi et al. 2006; Brooks, Ha et al. 2008), and increased expression of the negative regulator, programmed death-ligand 1 (PD-L1) on DCs for enhanced PD-L1-PD1 interaction leading to T cell exhaustion (2, 11).

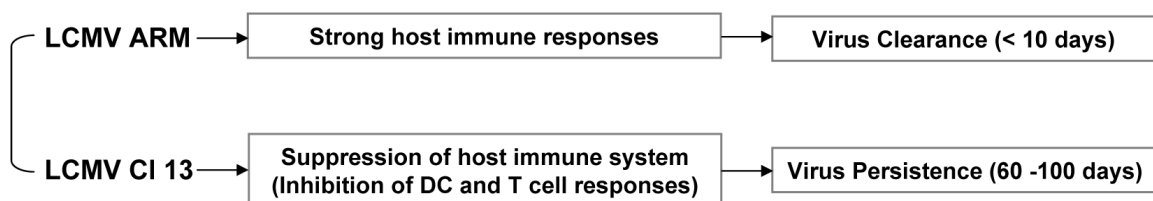


Fig. 1. Characteristics of the different LCMV infection models. LCMV ARM infection of adult mice rapidly generates a strong CD8 T cell response in the host which can clear the virus within 10 days, while an LCMV Cl 13 infection suppresses the host immune responses which leads to a prolonged viral persistence lasting 60 - 100 days.

Furthermore, following LCMV Cl 13 infection, virus-specific CD4⁺ T cells were functionally dysregulated, which contributes to the inability to sustain CTL function and facilitates viral persistence (Matloubian, Concepcion et al. 1994; Brooks, Teyton et al. 2005). Virus-specific CD4⁺ T cells were functionally inactivated early during the transition into viral persistence and failed to produce effector cytokines such as IL-2 and TNF- α . Recently, IL-21 was identified as an essential component of CD4⁺ T cell help to sustain CD8⁺ T cell effector activity and resolve persistent infection (Elsaesser, Sauer et al. 2009; Frohlich, Kisielow et al. 2009; Yi, Du et al. 2009). The detailed underlying molecular mechanism and intracellular signaling path for the virus-induced immunosuppression and viral persistence, however, are unclear.

2. Chronic viral infections inhibit innate and dendritic cell responses

It is generally thought that a robust CD8⁺ T cell response is responsible for clearing an acute LCMV infection (Byrne and Oldstone 1984; Fung-Leung, Kundig et al. 1991). However, a strong innate immune response is important for the generation of an effective adaptive response against viral infections (Jung, Kato et al. 2008; Rahman, Cui et al. 2008; Zucchini,

Bessou et al. 2008). Moreover, DCs are indispensable for the generation of the CD8⁺ effector T cells. The innate immune response provides stimulatory signals, such as type I interferons and IL-12 that promote the priming of CD8⁺ T cells and favor the T-helper 1 phenotype of CD4⁺ T cells. DCs are the key intermediate between the innate immune response and the adaptive immune response. DCs are the major professional antigen presenting cell subset that provides the necessary primary and secondary signals to induce the activation and proliferation of virus-specific CTL. A virus that can actively suppress these two responses has a significant advantage over the host immune system and the opportunity to establish a persistent infection.

2.1 Chronic LCMV infections suppress type I interferon expression

Type I interferons (IFN) and inflammatory cytokines are key to the initiation of anti-viral immune responses (Seo and Hahm 2010). Type I IFN is a family of cytokines comprised of IFN- α , IFN- β , IFN- ϵ , IFN- κ , and IFN- ω . These molecules have been shown to be potent antiviral cytokines by the deletion of the common receptor subunit (IFNAR1). Transgenic mice lacking IFNAR1 have been demonstrated to lose the ability to interfere with the replication of many different viruses (Muller, Steinhoff et al. 1994; Goodman, Zeng et al. 2010; Kolokoltsova, Yun et al. 2010). High levels of type I IFN have been detected at early time points during an acute, LCMV Arm infection (Montoya, Edwards et al. 2005). Zhou et al. have demonstrated that this induction of type I IFN is due at least in part to the recognition of the LCMV RNA genome by retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5) pathway along with toll-like receptor (TLR) 2 and 6 (Zhou, Kurt-Jones et al. 2005; Zhou, Cerny et al. 2010). Similarly, DCs from LCMV CI 13-infected mice have also been shown to produce type I IFN at early time points of virus infection (Dalod, Salazar-Mather et al. 2002; Diebold, Montoya et al. 2003; Zuniga, Hahm et al. 2007). However, several days later, these cytokines are no longer detectable in the sera of LCMV CI 13-infected mice (Martinez-Sobrido, Emonet et al. 2009), which suggests that the virus is actively suppressing the host type I IFN response. This observation was confirmed by Zuniga et al. who specifically examined the production of type I IFN by plasmacytoid DCs during an LCMV CL 13 infection (Zuniga, Liou et al. 2008). Plasmacytoid DCs (pDC) are a specialized subset of DCs that rapidly produce large amounts of type I IFN in response to viral infection (Asselin-Paturel and Trinchieri 2005; Delale, Paquin et al. 2005). In response to certain stimulation conditions, these cells have been observed to dedicate 50% of their cellular transcription to the production of type I IFN (Liu 2005; Lee, Lund et al. 2007). Because of this high level of type I IFN, it is suggested that these cells play a key role in the orchestration of antiviral immune responses. In the case of an LCMV CI 13 infection, the number of pDCs in LCMV CI 13-infected mice was reduced by 50% compared to mice infected with LCMV Arm at 30 days post-infection (Zuniga et al. 2008). Moreover, the production of type I IFN in response to TLR9 activation was severely impaired in pDCs isolated from LCMV CL 13-infected mice, which suggests that the virus is severely limiting the potential of these cells to respond not only to LCMV, but also additional, unrelated pathogenic stimulation (Zuniga et al. 2008).

Indeed, it has been shown that LCMV CI 13 utilizes specific molecular mechanisms to inhibit type I IFN production by the host cells. Martinez-Sobrido et al. have shown that the nucleoprotein of LCMV is responsible for the blockade of the host type I IFN response

(Martinez-Sobrido, Zuniga et al. 2006). This inhibition of cytokine production is due to the interaction of the viral protein with the interferon regulatory factor-3 (IRF-3) activation pathway. The data demonstrated that LCMV nucleoprotein (NP) impaired the nuclear translocation of IRF-3, which is involved in the upregulation of type I IFN synthesis. More specifically, amino acid residue 382 of LCMV NP was sufficient to inhibit the host type I IFN response (Martinez-Sobrido et al. 2009).

Additional studies have been carried out to investigate the mechanisms behind the LCMV-mediated blockade of the host type I IFN response. LCMV NP blockade of the IRF-3 pathway also affects the response to RIG-I and MDA5 (Zhou et al. 2010). Moreover, this same study demonstrated that LCMV NP physically interacts with both RIG-I and MDA5. Mutations in LCMV NP that prevented the inhibition of type I IFN however did not affect this interaction, which suggests that there are additional inhibitory mechanisms (Zhou et al. 2010).

This suppression of type I IFN not only affects the host response against LCMV, but it may also reduce the effectiveness of responses against other opportunistic pathogens whose clearance requires type I IFN (Zuniga et al. 2008). The effects of chronic LCMV CI 13 infections also lead to disruptions in the ability of the host's pDCs to produce type I IFN in response to other unrelated infections such as vesicular stomatitis virus (VSV) or murine cytomegalovirus (MCMV). In addition, LCMV CI 13 infection had deleterious consequences on the host's natural killer cell population which may be important in the immune response to other viral, bacterial, or parasitic infections such as HIV, influenza virus, *Mycobacterium tuberculosis* (Vankayalapati, Garg et al. 2005), and *Plasmodium falciparum* (Alter, Malenfant et al. 2004; Byrne, McGuirk et al. 2004; Siren, Sareneva et al. 2004; Korbel, Newman et al. 2005; Zuniga et al. 2008). Pre-infection with LCMV CI 13 was also demonstrated to prevent the host from counteracting the early spread of MCMV and therefore preventing viral clearance (Zuniga et al. 2008).

2.2 Suppression of dendritic cell functions

DCs are key mediators of adaptive immune responses. This group of cells can efficiently present endogenously and exogenously synthesized viral antigens to CD8⁺ T cells. In addition, these cells provide the necessary co-stimulatory signals to CTL for activation. The effect of chronic LCMV CI 13 infections on the production of type I IFN by pDCs is only one aspect of the virus-induced restrictions of the host's DC responses. Not only do chronically infecting viruses suppress cytokine production by host DCs, but it has also been shown that they can suppress the development of dendritic cells from hematopoietic precursor cells, inhibit the maturation of DCs following exposure to activation signals, and also lead to the destruction of these cells that are critical for effective anti-viral immune responses.

One major mechanism that LCMV CI 13 uses to suppress DC responses is to suppress their development from hematopoietic precursor cells (Hahm, Trifilo et al. 2005; Trifilo et al. 2006). The cytokines fms-like tyrosine kinase receptor-3 ligand (Flt3-L) and granulocyte macrophage-colony stimulating factor (GM-CSF) are major signals in the development of DCs from hematopoietic stem cells and can be used to induce the differentiation of DCs both *in vitro* and *in vivo* (Sevilla et al. 2004; Hahm et al. 2005). When Flt3-L is administered to mice, it dramatically increases the number of splenic DCs (Drakes, Lu et al. 1997). When bone marrow is cultured *in vitro* with GM-CSF, the stem cells differentiate into CD11c+

dendritic cells. It has been demonstrated that LCMV Cl 13-infected mice do not respond to Flt3-L treatment, suggesting that the virus induces an Flt3-L-refractory state in the hematopoietic precursor cells (Sevilla et al. 2004; Hahm et al. 2005). Moreover, *in vitro* culture of bone marrow cells infected by LCMV Cl 13 with GM-CSF induced the development of significantly fewer CD11c⁺ DCs compared to uninfected bone marrow cells (Sevilla et al. 2004; Hahm et al. 2005). Collectively these data indicate that one mechanism that chronic LCMV infection utilizes to evade the immune system is to prevent the development of DCs which are critical to a successful adaptive immune response.

Although LCMV Cl 13 does inhibit the differentiation of DCs from their hematopoietic progenitors, functional DCs do develop. However, the virus employs additional strategies to suppress the responses induced by these cells. Our laboratory and others have demonstrated that LCMV Cl 13 infection of DCs inhibits their ability to upregulate major histocompatibility complex class I (MHC-I) molecules and co-stimulatory molecules such as B7-2 (Figure 2A) (Sevilla et al. 2004). Moreover, the LCMV Cl 13 infection in our studies not only prevented the upregulation of MHC-I and B7-2 but reduced the levels of their expression to below baseline levels. This suppression of MHC-I and co-stimulatory molecule expression renders the DCs unable to efficiently prime CD8⁺ T cells, which are necessary to clear the infecting virus. Although the inhibition of type I IFN expression may be the cause of this downregulation, there may be additional unknown mechanisms for this phenomenon. Further, the infected DCs were impaired in the ability to synthesize IL-12, a critical cytokine for T cell stimulation, in response to TLR9 ligation (Figure 2B). The results also support the functional abrogation of host immunity in LCMV Cl 13-infected mice upon the invasion of a secondary microbe that contains TLR9 ligand components such as DNA viruses or bacteria.

The final postulated mechanism for LCMV evasion of dendritic cell responses is the targeted killing of these cells. It has been shown that persistently infecting strains of the virus have a mutation in the glycoprotein that affects their tropism and increases the infectivity of DCs (Borrow et al. 1995; Sevilla, Kunz et al. 2000). This dendritic cell-specific infection leads to increased antigen load and therefore makes these cells ideal targets for activated CD8⁺ T cells. Indeed, a loss of splenic DCs has been observed in the spleens of LCMV Cl 13-infected mice although, the ability of these infected DCs to act as targets has not yet been confirmed. However, DCs are efficient antigen presenting cells and because they are preferentially infected during an LCMV Cl 13 infection, it has been speculated that they are targeted for destruction by activated CD8⁺ T cells (Odermatt, Eppler et al. 1991; Borrow et al. 1995).

These multiple findings have been recapitulated when DCs were infected with human-tropic viruses. For instance, measles virus (MV) suppressed DC generation from bone marrow progenitor cells under the GM-CSF or Flt3-L-supplemented culture system (Hahm et al. 2005). Further, MV could kill DCs or strongly inhibit the ability of DCs to stimulate anti-viral T cells (Hahm 2009). The decrease in the DC population was also observed in the bloodstream of HCV or HIV-infected patients (Donaghy, Pozniak et al. 2001; Pacanowski, Kahi et al. 2001; Kanto and Hayashi 2004; Kanto, Inoue et al. 2004; Siavoshian, Abraham et al. 2005). Functional abrogation of professional antigen presenting DCs has been reported in multiple cases of patients who were chronically infected with pathogenic viruses.

Like the inhibition of type I IFN, DCs have been shown to play a key role in the host response and elimination of viral infections. Because of this, LCMV and other chronically

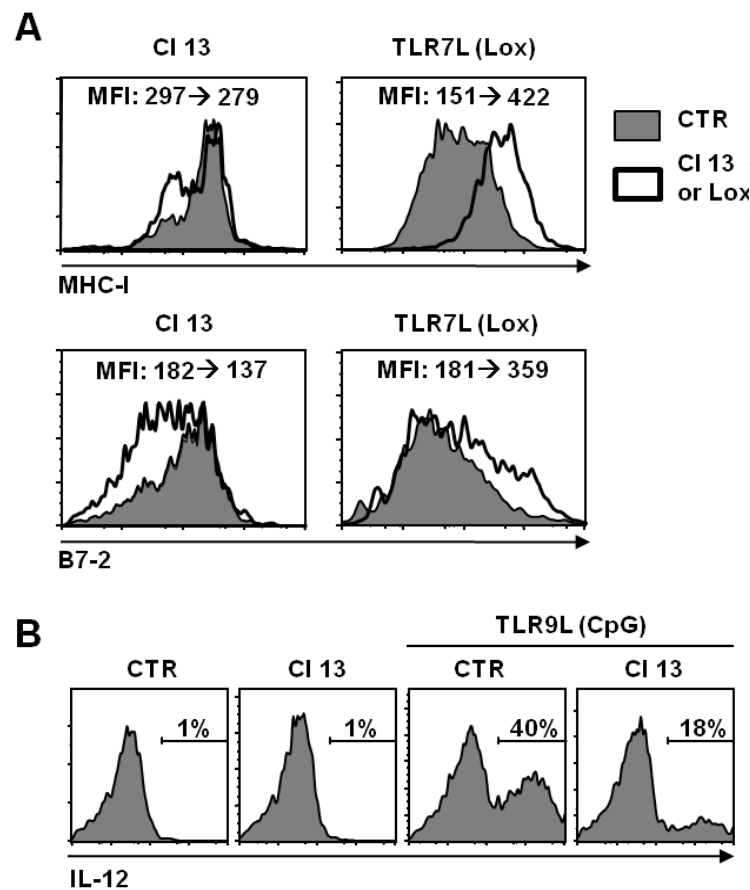


Fig. 2. LCMV CI 13 suppresses DC responses. (A) Bone marrow-derived DCs were untreated (control, CTR), infected with LCMV CI 13 (CI 13), or treated with loxoribine (TLR7 ligand, 0.5mM). DCs were analyzed for the expression levels of MHC-I and B7-2 by flow cytometry on the following day. Mean fluorescent intensities (MFIs) for each molecule are shown. (B) DCs were uninfected (CTR) or infected with LCMV CI 13. At one day post-infection (dpi), these cells were untreated or treated with CpG (TLR9 ligand, 200 ng/ml) and the synthesis of IL-12 was assessed by flow cytometry.

infecting viruses have developed multiple strategies to counteract and evade the dendritic cell responses. Although a great deal of effort has been focused on these evasion tactics, the underlying mechanisms that the viruses use to suppress these responses are still not yet fully elucidated.

3. Virus-mediated T cell exhaustion

CD8⁺ Cytotoxic T lymphocytes (CTLs) are a critical line of defense against viral infections. These cells are responsible for the recognition and subsequent killing of virus-

infected cells. During an acute virus infection, CTLs recognize antigenic peptides displayed on the surface of professional antigen presenting cells (Carbone, Moore et al. 1988). This recognition, along with co-stimulatory signals activate the CTLs to proliferate and gives them license to kill virus infected cells through their effector functions including the release of the cytotoxic molecules perforin and granzyme B (Lancki, Hsieh et al. 1991). In addition, activated CTLs also upregulate inflammatory cytokines including IFN- γ and TNF- α (Murray, Lee et al. 1990; Martin, Vallbracht et al. 1991; Brehm, Daniels et al. 2005). Following the resolution of the infection this large population of effector CTLs contracts into a small pool of memory cells which are able to quickly respond to subsequent infections by the same pathogen.

Because CTLs are able to eliminate replicative reservoirs, persisting viruses have evolved methods for the evasion of these immune responses. Although the suppression of CTL responses begins with the disruption of dendritic cell responses as described previously, persistently infecting viruses such as LCMV and HIV have developed several mechanisms to specifically perturb CTL responses. The first method involves the exhaustion of CTLs in which the cells lose their ability to kill infected cells, while the other involves the modulation of dominant CTL epitopes, allowing the virus to escape immune recognition. These escape mechanisms give the viruses an additional advantage over the host immune system and allow for chronic viral infections.

3.1 Exhaustion of CD8+ T cells by LCMV CI 13

3.1.1 Exhaustion of cytotoxic CD8+ T lymphocytes during chronic viral infection

Exhaustion of CTL has been described in multiple viral infections including both LCMV and HIV as the loss of effector functions by antigen-specific CD8+ T cells. The presence of both acutely-infecting and chronically-infecting strains of LCMV have made this virus an outstanding model for determining both the effects of the virus on CTLs as well as the mechanism by which the virus induces T cell exhaustion. During a chronic LCMV infection, the virus-specific CD8+ T cell response is activated and peaks similar to an acute viral infection (Figure 3). However, instead of clearing the virus, the CTLs lose effector functions (Figure 3). The loss of CTL functionality occurs in a stepwise manner. Individual effector functions are lost at distinct time points over the course of the infection (Wherry, Blattman et al. 2003). Initially, the CTLs lose the ability to proliferate and produce IL-2 in the case of most chronic viral infections (Wherry et al. 2003). As the infection continues, the CTLs become dysfunctional in their ability to produce and secrete the inflammatory cytokine TNF- α (Sakuishi, Apetoh et al. 2010). At later time points of the persistent infection, the cells also fail to produce IFN- γ and lose their cytotoxic potential (Wherry et al. 2003; Jin, Anderson et al. 2010). In certain cases, the end result of T cell exhaustion is the death of T cells which leads to the reduction of the total virus-specific T cell population. The culmination of these dysfunctions is the inability of antigen-specific CTLs to kill virus infected cells, thereby allowing the virus to persist. The mechanisms LCMV CI 13 uses to exhaust CTLs are not yet fully understood. It is known however that the virus activates inhibitory molecules that are involved in the regulation of normal immune responses to exhaust CTLs.

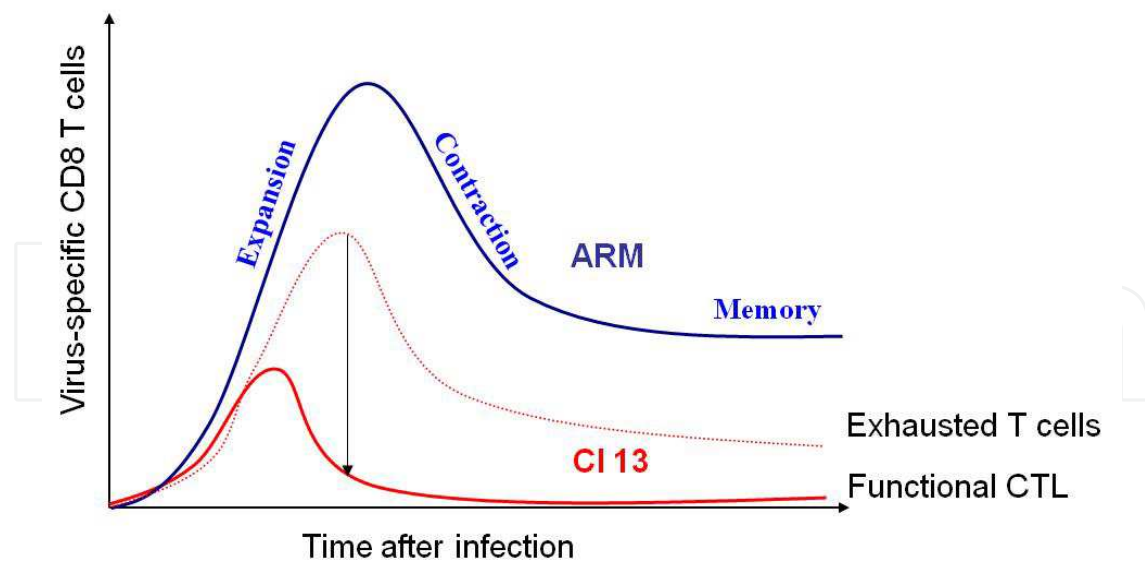


Fig. 3. CD8 T cell response to acute and persistent LCMV infections over time. In response to an acute LCMV infection (ARM, blue line), CD8 T cells rapidly expand until approximately day 7. Following this expansion, the cells contract leaving a small population of memory cells. During a chronic infection (CI 13, red line), CD8 T cells expand in a similar fashion however quickly lose effector functions (dotted red line) and leave only a small population of functional CTL that are unable to resolve the infection (solid red line).

3.1.2 Inhibitory receptors involved in T cell exhaustion

The inhibitory receptor programmed death - 1 (PD-1) is the most extensively characterized molecule associated with LCMV CI 13-mediated T cell exhaustion (Wherry, Ha et al. 2007; Blackburn, Shin et al. 2009; Jin et al. 2010; Vezys, Penaloza-MacMaster et al. 2011). PD-1 is a negative immuno-regulatory molecule in the CD28/CTLA-4 family that is expressed on the surface of activated CD8⁺ T cells. PD-1 has two ligands, PD-L1 and PD-L2 which could be upregulated on the surface of activated DCs and macrophages, although PD-L1 is expressed on multiple cell types (Yamazaki, Akiba et al. 2002; Brown, Dorfman et al. 2003). The expression of this inhibitory receptor has been directly linked to type I IFN production (Terawaki, Chikuma et al. 2011). The role of the PD-1 activation in non-persistent viral infections is the attenuation of T cell responses to prevent unnecessary immunopathology (Freeman, Long et al. 2000). PD-1 is thought to play a critical role in the LCMV-mediated exhaustion of CTLs as virus-specific CD8⁺ T cells express significantly higher levels of this molecule during chronic LCMV infections. The mechanisms behind the LCMV-mediated upregulation of PD-1 have yet to be fully elucidated. However, the blockade of the PD-1 pathway restores functionality of these cells and leads to clearance of the persistent virus infection (Barber et al. 2006).

Another molecule that has been implicated in the exhaustion of CD8⁺ T cells during chronic LCMV infections is lymphocyte activated gene - 3 (LAG-3) (Wherry et al. 2007; Grosso, Goldberg et al. 2009). This molecule belongs to the immunoglobulin superfamily and has been shown to be immunomodulatory in the prevention of autoimmune disorders (Workman, Dugger et al. 2002). The expression of LAG-3 does not change on CD8⁺ T cells during acute infections with LCMV, but is upregulated on CD8⁺ T cells in LCMV CI 13-

infected mice (Richter, Agnellini et al. 2010). It has been suggested that LAG-3 functions in a similar fashion to PD-1 during chronic LCMV Cl 13 infections (Blackburn et al. 2009). Although mice deficient in LAG-3 do not demonstrate improved CD8⁺ T cell responses during persistent LCMV infections (Richter et al. 2010), the simultaneous blockade of both the PD-1 and LAG-3 pathways leads to significant improvements in the CTL responses of LCMV Cl 13-infected mice compared to PD-1 blockade alone (Blackburn et al. 2009).

Multiple other immunomodulatory molecules have been suggested to be involved in the attenuation of virus-specific CD8⁺ T cell responses. An extensive study by Wherry et al. has shown that the expression of many different genes from multiple cellular processes is affected during CD8⁺ T cell exhaustion. These markers include natural killer cell marker 2B4 (2B4), which has since been shown to be involved in the regulation of memory CD8⁺ T cells during chronic LCMV infections (West, Youngblood et al. 2011), T cell Ig- and mucin-domain-containing molecule-3 (Tim-3), CD160, paired Ig-like receptor-B (PIR-B), and GP49B. All of these molecules have been shown to have inhibitory functions during immune responses (Wherry et al. 2007; Jin et al. 2010; Vezys et al. 2011). Although Tim-3 has been shown to act in cooperation with PD-1 in the exhaustion of CD8⁺ T cells during persistent LCMV infections (Jin et al. 2010), no specific mechanisms in the loss of function of CD8⁺ T cells have been attributed to these additional markers of T cell exhaustion. Until these markers are investigated individually or in conjunction with the known inhibitory molecules, they are only guilty by association.

The markers and mechanisms that have been described by comparing the persistent and acute LCMV infections are by no means the only ones involved in the suppression of CD8⁺ T cell responses. Other immunosuppressive molecules have been shown to either be involved in the exhaustion of CD8⁺ T cell responses or upregulated on exhausted T cells in other persistent viral infections. CTLA-4, among the others discussed above, has been shown to be important in serious human infections such as HIV and HCV (Hryniewicz, Boasso et al. 2006; Kaufmann, Kavanagh et al. 2007; Nakamoto, Cho et al. 2009).

3.1.3 Transcription factors involved in T cell exhaustion

Several transcription factors have also been identified as modulators of the CD8⁺ T cell response during a persistent LCMV Cl 13 infection (Shaffer, Lin et al. 2002; Agnellini, Wolint et al. 2007). Nuclear factor of activated T cells (NFAT) is a transcription factor that regulates multiple genes involved in the cytotoxicity and inflammatory cytokine production by CD8⁺ T cells, including IL-2, the loss of which is a hallmark of T cell exhaustion (Wherry et al. 2003). NFAT expression and phosphorylation are unperturbed in the CD8⁺ T cells from mice persistently infected with LCMV. However, the translocation of NFAT molecules from the cytoplasm to the nucleus is disrupted during chronic LCMV infections which prevents the transcription factor from upregulating genes necessary for complete CTL function (Agnellini et al. 2007). The transcription factor B-lymphocyte-induced maturation protein-1 (Blimp-1) which is known to govern the fate decision of B-cells has also been associated with the exhaustion of CD8⁺ T cells (Shaffer et al. 2002; Calame 2006). Blimp-1 expression was shown to be dramatically increased in T cells during chronic viral infections (Shin, Blackburn et al. 2009). In this same series of experiments, a conditional knockout of Blimp-1 resulted in significant decreases of the inhibitory receptors PD-1 and LAG-3 in CD8⁺ T cells during a chronic LCMV Cl 13 infection. Moreover, this conditional knockout resulted in increased cytotoxicity of

LCMV-specific CTL and improved viral control (Shin et al. 2009). Although the research into these transcriptional regulators has revealed another level of immune evasion by LCMV CI 13, they have not completely elucidated the pathway by which the virus induces T cell exhaustion. Therefore more research is still required to fully understand these mechanisms.

3.1.4 Role of chronic antigen stimulation on T cell exhaustion

One possible mechanism that has been postulated to be involved in the upregulation of these markers and the subsequent exhaustion of virus-specific CD8⁺ T cells is the prolonged presence of viral antigens. In a study by Bucks et al., repeated exposure to influenza antigen was shown to induce the exhaustion of antigen-specific CTLs. In these experiments, repeated exposure to antigen reduced both the frequency and number of virus specific CD8⁺ T cells, and significantly impeded the ability of the remaining cells to produce IFN- γ (Bucks, Norton et al. 2009). In support of these findings, a more recent study has investigated the epigenetic regulation CD8⁺ T cells during a chronic LCMV infection (Youngblood, Oestreich et al. 2011). The results of this study indicate that long-term antigen exposure results in prolonged demethylation of the PD-1 gene locus, leading to extended PD-1 expression which has been observed during chronic LCMV infections. In addition, this demethylation does not resolve rapidly in exhausted T cells due to a downregulation of methyltransferases. Consequently, these exhausted CD8⁺ T cells have the potential for rapid upregulation of PD-1 upon subsequent antigen encounters (Youngblood et al. 2011).

3.1.5 Cytokines implicated in T cell exhaustion

Another potential inducer of CD8⁺ T cell exhaustion is the anti-inflammatory cytokine IL-10. IL-10 has been shown to be a potent inhibitor of inflammatory and adaptive immune responses. Two different studies have implicated IL-10 in chronic viral infections (Brooks et al. 2006; Ejrnaes et al. 2006). In these studies it was shown that IL-10-deficient mice chronically infected with LCMV have higher frequencies of virus-specific CTLs and antibody-mediated blockade of the IL-10 receptor can restore the function of exhausted, virus specific CD8⁺ T cells (Brooks et al. 2006; Ejrnaes et al. 2006). Furthermore, the IL-10 receptor blockade also led to accelerated viral clearance in both studies (Brooks et al. 2006; Ejrnaes et al. 2006). The source of the IL-10 involved in the immune suppression as well as the mechanisms by which IL-10 is induced is still under investigation.

Although the inflammatory cytokine IL-21 has not been shown to be directly involved in the induction of T cell exhaustion, its requirement in the clearance of the virus has been clearly demonstrated. IL-21 is produced primarily by CD4⁺ T cells and has been shown to induce the proliferation of CD8⁺ cytotoxic T-lymphocytes in a fashion similar to that of IL-2 (Kasaian, Whitters et al. 2002). Because IL-2 production is lost quickly during a chronic LCMV infection, it is thought that IL-21 may act in a compensatory fashion. The requirement of IL-21 in the clearance of LCMV CL 13 was demonstrated in IL-21 receptor-deficient mice. These mice failed to clear the virus while the wild-type control mice had cleared the infection by day 60 post-infection. (Elsaesser et al. 2009). In the same study by Elsaesser et al., it was shown that IL-21 is produced by CD4⁺ T cells throughout an LCMV CI 13 infection (Elsaesser et al. 2009). However, in parallel experiments by Yi et al., it was shown that the number of IL-21-producing CD4⁺ T cells is 7.8 times lower than in an acute LCMV infection. Therefore, this loss of IL-21-producing, CD4⁺ T cells may be another critical factor in the rapid exhaustion of CD8⁺ T cells during a persistent LCMV infection.

The topic of T cell exhaustion is a major focus in the field of viral immunity. It is still not clear if the expression of these markers is due to the presence of a persisting viral infection, or if viruses have evolved specific mechanisms to activate these immunosuppressive pathways. However, multiple studies have demonstrated that the targeting of certain molecules relieves the suppression and allows the host CTL response to reassert control over the infection and accelerate viral clearance. If the mechanisms behind the virus-mediated upregulation of these molecules and CD8+ T cell exhaustion can be determined, the many new targets for immune-based therapies can be designed, giving medicine a much needed advantage in the treatment of chronic viral infections.

3.2 Dysfunction of CD4+ T cells during chronic LCMV infection

CD4+ T cells have been shown to not play a major role in the clearance of an acute, LCMV Arm infection. Experiments conducted with mice deficient in CD4+ T cells demonstrate that they are able to clear the infection as efficiently as their wild-type counterparts (Matloubian et al. 1994). However in the case of a chronic LCMV Cl 13 infection, CD4+ T cells appear to play a more significant role, as depletion of CD4+ T cells prevents mice from clearing the virus (Matloubian et al. 1994). One of the major contributions these cells make is the production of IL-21, which as described above appears to be critical for viral clearance (Elsaesser et al. 2009; West et al. 2011). In addition, there is evidence that CD4+ T cells also become exhausted during an LCMV Cl 13 infection. Brooks et al. have demonstrated that CD4+ T cells begin to lose the ability to make inflammatory cytokines such as IFN- γ and TNF- α as well as IL-2 as early as day 9 post-infection (Brooks et al. 2005). Moreover, an increase in the production of the anti-inflammatory cytokine IL-10 by virus-specific CD4+ T cells was also observed during the chronic LCMV infection (Brooks et al. 2005). There was however no increase in the number of T regulatory CD4+ T cells observed during the course of the viral infection (Brooks et al. 2005). Similar to exhausted CD8+ T cells, exhausted CD4+ T cells have also been shown to upregulate the expression of PD-1 (Day, Kaufmann et al. 2006; Kasprowitz, Schulze Zur Wiesch et al. 2008). In addition, recent evidence suggests that viral persistence actually reprograms the differentiation of CD4+ T cells from the T-helper 1 phenotype to a T-follicular helper cells (Fahey, Wilson et al. 2011).

System Targeted	Disruption of Cellular Function	Phenotype/Mechanism
Type I Interferon	Inhibition of type I IFN production	LCMV NP - Inhibition of IRF3 - Inhibition of MDA5 and RIG-I Inhibition of plasmacytoid DCs
Dendritic Cells	Inhibition of DC development	Decrease in the frequency of CD11c+ cells
	Inhibition of DC maturation	MHC-I and B7-1/B7-2 upregulation impaired following PAMP ligation Loss of IL-12 production Increased IL-10 synthesis
T cells	Suppression of T cell function (exhaustion)	PD-1 \uparrow , LAG-3 \uparrow , Tim-3 \uparrow , Blimp-1 \uparrow , NFAT \uparrow IFN- γ \downarrow , TNF- α \downarrow , IL-2 \downarrow , Proliferation \downarrow , Cytotoxic activity \downarrow

Table 1. Immunological Effects of Persistent LCMV Cl 13 Infections.

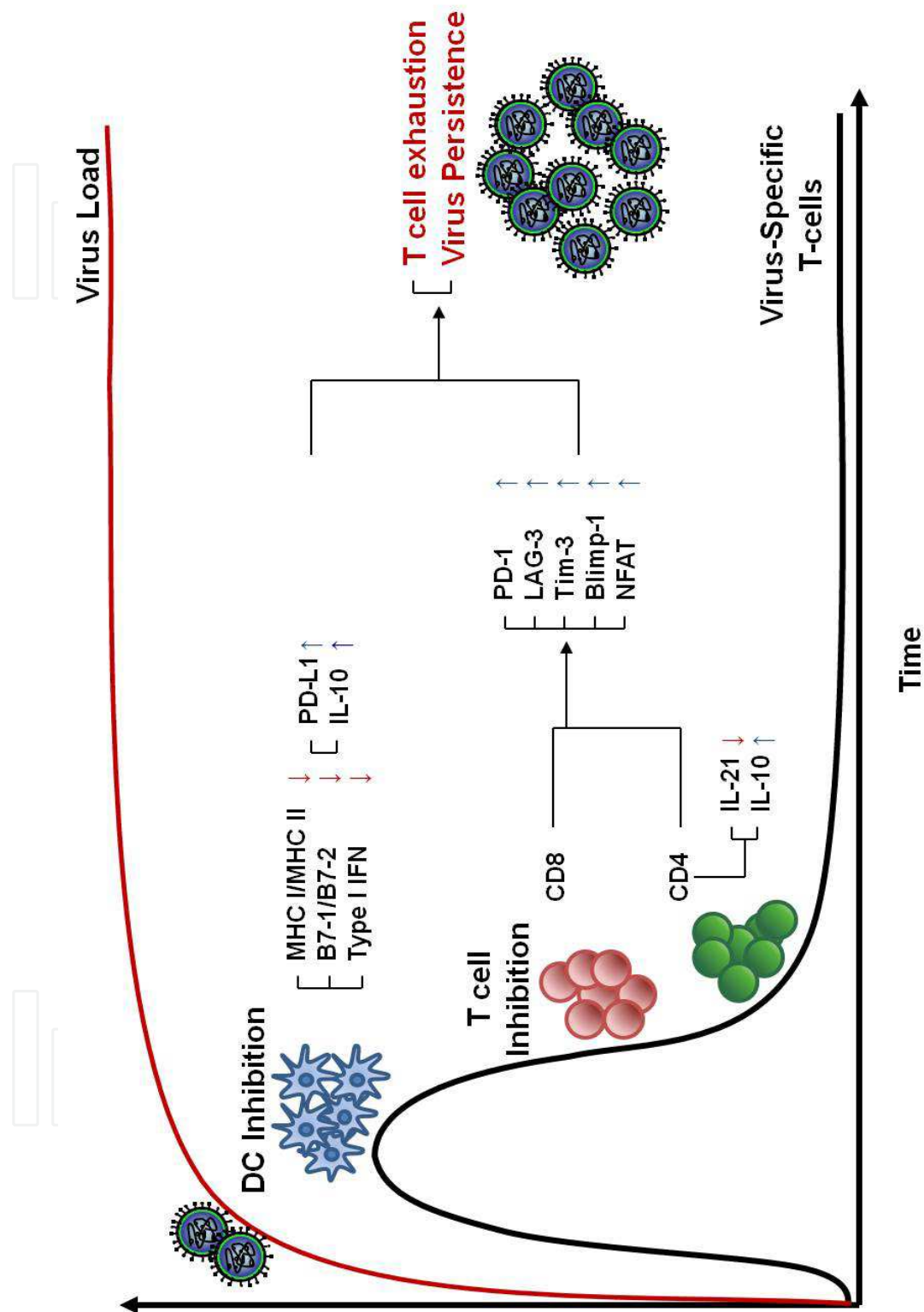


Fig. 4. Schematic representation of the immune cell phenotypes during a chronic LCMV infection. Viral load over time is represented by the red line. The functional T cell response is illustrated using the black line. Alterations in cell surface molecule and cytokine expression is noted with each cell type.

4. Perspectives

Chronic viral infections continue to be a tremendous burden on human health. Many years of research, especially with LCMV Cl 13, has led to a large body of knowledge as to how these viruses subvert and evade both innate and adaptive immune responses (Figure 4 and Table 1). Although there is still a great deal of research needed, several potential molecular immunotherapeutic treatment options have been developed through these studies. First, findings by Brooks *et al.* and Ejarnes *et al.* have clearly demonstrated that the blockade of IL-10 signaling could be used as a potential treatment to restore functionality to exhausted CD8⁺ T cells. This has been examined recently and it was found that CD8⁺ T cells from HIV positive patients could be restored using an IL-10-specific antibody (Brockman, Kwon *et al.* 2009). Similarly, clinical trials are being conducted to evaluate a treatment consisting of inhibition of the PD-1/PD-L1 interaction to recover exhausted CD8⁺ T cells during HIV infection and certain types of cancer (Sakthivel, Gereke *et al.* 2011). Other treatment options have been explored including multiple therapeutic vaccination strategies such as DNA vaccines (Martins, Lau *et al.* 1995), recombinant virus vectors (Wherry, Blattman *et al.* 2005), and lipo-peptide vaccines (von Herrath, Berger *et al.* 2000). Finally, the use of IFN- α for the treatment of chronic virus infections was introduced in 1986 for the treatment of hepatitis C virus infections (Hoofnagle, Mullen *et al.* 1986). However, some evidence suggests that therapeutic vaccination post-infection may not be as effective as hoped because of the immunosuppressed state of the host caused by the infection (Wherry *et al.* 2005).

In addition to the molecular therapies, immune cell-based therapeutic approaches have been developed. Since CD8⁺ CTLs are principal players for the eradication of viruses, the CD8⁺ T cell-based therapy has been implemented (Gottschalk, Bollard *et al.* 2006; Kapp, Tan *et al.* 2007). However, the requirement of CD4⁺ T cells for the maintenance of CTL activity has prompted the use of combined T cell therapies. Further, owing to the extraordinary ability of DCs to serve as natural adjuvants, the potential of antigen-mounted, activated DCs for the treatment of infectious diseases has been confirmed in multiple experimental models (Inaba, Metlay *et al.* 1990; Fajardo-Moser, Berzel *et al.* 2008). If DCs are suppressed by chronic viral infections for T cell exhaustion or deletion, provision of active, modulatory DCs presenting viral epitopes could overcome virus-induced suppressive environments and initiate vigorous anti-viral T cell immunity. The proper use of DC subtypes, DC modulation methodology and the way to activate intracellular class I MHC antigen presenting pathways as well as MHC class II pathways need to be considered to maximize the efficacy of DC-based immunocytotherapy.

Collectively, there is a great deal of understanding the mechanisms behind LCMV-induced immunosuppression (Figure 4 and Table 1) that has had practical applications for serious chronic human viral infections and have led to clinical trials for therapeutic interventions. However, many of the underlying causes have yet to be determined and further investigations are needed. In conjunction with molecular mechanistic studies, the approach to subvert the immunosuppressive environment caused by chronic viral infections could aid the development of immune-therapeutic drugs and treatments to combat many viral diseases.

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Immunology is the branch of biomedical sciences to study of the immune system physiology both in healthy and diseased states. Some aspects of autoimmunity draws our attention to the fact that it is not always associated with pathology. For instance, autoimmune reactions are highly useful in clearing off the excess, unwanted or aged tissues from the body. Also, generation of autoimmunity occurs after the exposure to the non-self antigen that is structurally similar to the self, aided by the stimulatory molecules like the cytokines. Thus, a narrow margin differentiates immunity from auto-immunity as already discussed. Hence, finding answers for how the physiologic immunity turns to pathologic autoimmunity always remains a question of intense interest. However, this margin could be cut down only if the physiology of the immune system is better understood. The individual chapters included in this book will cover all the possible aspects of immunology and pathologies associated with it. The authors have taken strenuous effort in elaborating the concepts that are lucid and will be of reader's interest.

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