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Viral infections and autoimmune disease: roles of LCMV in delineating mechanisms of immune tolerance

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Abstract

Viral infections make a natural part of our existence. They can affect us in hundreds of different ways that are the result of the interaction between the viral pathogen and our immune system. Most times the resulting immune response is beneficial for the host. The pathogen gets cleared protecting our vital organs with no other consequences. Sometimes, things go wrong and the reaction of our immune system against the pathogen causes organ damage (immunopathology) or leads to autoimmune disease. To date, there are several mechanisms for virus-induced autoimmune disease, including molecular mimicry and bystander activation, in support of the "fertile field" hypothesis. On the flip side, viral infections have been associated with protection from autoimmunity through mechanisms that include Treg invigoration and immune deviation, in support of the "hygiene hypothesis". Infection with lymphocytic choriomeningitis virus (LCMV) is one of the prototype viral systems showing that the interaction of our immune system with the viruses can either accelerate or prevent autoimmunity. Studies using LCMV have helped conceive and establish several concepts that we today know and explain how viruses can lead to autoimmune activation or induce tolerance. Some of the most important mechanisms established in LCMV are described in this short review.

Keywords: lymphocytic choriomeningitis virus (LCMV); viral infection; autoimmunity; molecular mimicry; bystander activation; immune tolerance

Introduction

Lymphocytic choriomeningitis virus (LCMV) is the prototype viral system that has been used to address several mechanisms of tissue-specific tolerance. In general, LCMV has been used to address two main objectives: to understand the mechanisms that induce or break tolerance at a tissue/organ level causing autoimmune-mediated tissue damage that resembles the clinical features of human autoimmune disease [1]. It has also been used to address the efficacy of therapeutic strategies to prevent or reverse autoimmune disease progression, as well as the safety of those treatments in the context of a viral infection.

To achieve the first objective, transgenic mouse models that express viral proteins (model antigens) in specific tissues have been generated [2]. These models have allowed the precise tracking of the antiviral/autoimmune responses and crossing to other gene-deficient or transgenic mice has unraveled the molecules that mediate tissue-specific tolerance. The generation of T-cell-receptor transgenic mouse models that specifically recognize the model antigens have been used to trace and characterize the autoreactive T cells after adoptive transfer *in vivo*. These "reductionist approaches" have allowed investigators to decipher basic mechanisms that control immune activation and determine tolerance [3]. Although these models may not recapitulate all the characteristics of the human disease, they are used to study the role of environmental triggers and particularly viral infections to autoimmune disease pathogenesis [1, 4, 5]. They can also be used to address how the combination of genetic and environmental factors converge and define disease susceptibility. In this review we summarize the concepts that were generated by studying autoimmune disease development in mouse models of autoimmunity where LCMV was used to trigger the disease. We also address how LCMV infection has helped unravel the mechanisms by which viral infections promote peripheral tolerance, in support of the hygiene hypothesis.

1. LCMV-induced mouse models of autoimmunity

LCMV is the most common cause of viral encephalitis and can be transmitted to humans by rodents [6]. LCMV is not a lytic virus and is able to generate robust cytotoxic lymphocyte responses. As a consequence, tissue inflammation after LCMV infection is caused by the immune system. Central nervous system (CNS) infection by LCMV leads to an intense antiviral T-cell response and consequent fatal choriomeningitis [7, 8]. The development of LCMV-induced meningitis was the first example of disease caused as a collateral immune damage, a process now known with the term **immunopathology**. These experiments set the stage to address how infection with a non cytolytic virus activates the immune system and turns its action against its own self causing autoimmunity. Below we briefly describe some of these LCMV-induced models of autoimmunity and the concepts that were reached through their study.

Back in 1991 a breakthrough in our understanding on the role of viruses in triggering autoimmunity came by two studies published in the same issue in *Cell* describing for the first time the LCMV-induced model of autoimmune diabetes [9, 10]. Two independent groups led by Zinkernagel and Oldstone showed for the first time that transgenic mice expressing the glycoprotein (GP) or nucleoprotein (NP) of LCMV as a self-antigen in their islets (under the control of the rat insulin promoter [RIP]) can turn diabetic after viral clearance, 10-15 days after infection with LCMV. RIP-LCMV diabetic mice developed a predominantly T-cell (CD8) mediated acute form of autoimmune diabetes and interestingly enough, the autoreactive T cells (and antibodies) were not only specific to LCMV but also to islet antigens. Thus, a single infection with LCMV led to breakdown of tolerance to islet antigens through mechanisms known today as **molecular mimicry**, **bystander activation** and **antigen spreading**.

One mouse model of autoimmune hepatitis has heavily relied on the same concept of virally-induced disease. It uses a similar approach as the RIP-LCMV model of autoimmune diabetes described above. More precisely, the GP or NP protein of LCMV is expressed in transgenic mice under the control of the albumin promoter (Alb) [11-13]. In contrast to RIP-LCMV mice however, Alb-LCMV mice develop transient hepatitis following infection with LCMV, due to the strong

tolerogenic nature of the liver. An additional adoptive transfer of GP-$_{33-41}$-specific CD8 T cells (P14) from T-cell receptor (TCR) transgenic mice is required to definitively break tolerance in Alb-LCMV mice and cause long-lasting autoimmune hepatitis. Of note, P14 T cell transfer in either RIP-LCMV or Alb-LCMV does not cause disease suggesting that LCMV-induced inflammation is necessary to break tolerance in this setting. This became the basis of another immunological concept known as **immune ignorance** we describe below**.**

A mouse model of experimental autoimmune encephalomyelitis similar to the RIP-LCMV and Alb-LCMV models has also been established. Transgenic mice were generated to express the NP or GP of LCMV in oligodendrocytes under the guidance of the myelin base protein (MBP) promoter [14, 15]. Intraperitoneal infection with LCMV in MBP-LCMV mice led to infection of tissues in the periphery but not the CNS, and the virus was cleared within 7–14 days. After clearance, a chronic inflammation of the CNS occurred, characterized by upregulation of major histocompatibility (MHC) class I and II molecules. A second LCMV infection led to enhanced CNS pathology, characterized by loss of myelin and clinical motor dysfunction. Disease enhancement also occurred after a second infection with unrelated viruses that cross-activated LCMV-specific memory T cells [14, 15]. This model, similarly to the previous ones, allowed investigators to establish the concepts of **molecular mimicry, bystander activation** and **antigen spreading** as potential mechanisms of autoimmunity triggered by infection.

Through the use of these models of virally-induced autoimmune disease, researchers have been able to investigate several basic mechanisms of immune activation and tolerance and were helpful at assessing the efficacy and safety of novel therapies. These mouse models also served to address the immunosuppressive action of LCMV and its role in inhibiting autoimmune disease progression through several mechanisms. Below we describe the lessons learned and concepts formed from the study of these models and also address how LCMV infection can promote immunological tolerance in different settings.

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2. Mechanisms that can lead to autoimmunity following viral infection

2.1 The concepts of clonal deletion, T-cell anergy and immune ignorance

Before the discovery of viral persistence, it was thought that a virally-infected host would either succumb to the infection or clear the infection [16, 17]. That is, either the immune system wins and clears the infection, or the infection overcomes the immune system and kills the host. However, early studies showed that this is not absolutely true. Mice infected with LCMV in the utero or shortly after birth with a viral dose able to kill and adult mouse were shown to "tolerate" the infection and survive just fine with high viral titers present in their blood [18, 19]. These newborn mice were persistently infected with LCMV because they were **immunologically tolerant** to the virus.

One of the most common experiments done back in the nineties was the crossing of TCR transgenic mice to antigen expressing mice. When TCR (GP_{33-41}-specific, P14) transgenic mice were crossed to transgenic mice ubiquitously expressing LCMV GP antigen, **clonal deletion** of T cells was seen in the thymus at the early $CD4^+8^+$ double positive stage [20]. The remaining cytotoxic T lymphocytes (CTLs) were unresponsive and virus persisted upon infection (**peripheral anergy**). However, when the same TCR transgenic mice were crossed to RIP-LCMV mice where the antigen was expressed on non-lympho-hematopoietic cells in the periphery (pancreatic beta islet cells), then CTL reactivity was normal. These experiments became the basis of another mechanism of peripheral tolerance known as **immune ignorance** [21]**.** This term was originally coined by Ohashi and colleagues to describe LCMV-reactive T lymphocytes present in RIP-LCMV crossed with LCMV-specific TCR transgenic P14 mice. LCMV-specific T cells were neither deleted nor anergic but, instead, were unaffected by the presence of LCMV antigens on pancreatic beta cells [9]. Adoptive transfer of P14 mice in RIP-LCMV or Alb-LCMV mice leads to no activation of the cells through the same mechanism. This state of tolerance (ignorance) could be overcome upon LCMV infection, showing that appropriate presentation of the self-epitope on antigen presenting cells (APC) promptly induces effector T cells and causes disease (diabetes or hepatitis, respectively). Generally,

inflammation caused by infections is thought to be one of the leading mechanisms activating autoreactive T cells [22].

2.2 The concepts of molecular mimicry, epitope spreading and bystander activation

The hypothesis of **molecular mimicry** dates several decades back and has been used as the basis for several of the experimental autoimmune animal models used including the ones we described above. These models are the perfect example supporting the "fertile field" hypothesis of autoimmune disease pathogenesis. Molecular mimicry suggests that environmental factors such as viruses potentiate an autoimmune process by activating autoreactive T cells that recognize viral epitopes due to cross-reactivity [15, 23, 24]. The mechanism of molecular mimicry has been proposed to account for the connection between coxsackievirus B3 (CVB) infection and autoimmune diabetes and myocarditis [25-27]. Same mechanism was found responsible for experimental allergic encephalomyelitis in rabbits [28].

Another possible mechanism that could account for the activation of autoreactive T cells by virus infection is **bystander activation**. This model suggests that autoreactive T cells become "bystander" activated due to virus-induced inflammatory events causing tissue damage and release of sequestered tissue antigens, leading to enhanced self-antigen presenting activity by APC [29-31]. This concept seems to be the case for autoreactive memory T cells, as these cells become more effectively activated than naïve T cells from repeated infections with viruses of unrelated specificity [32, 33]. Possibly, both molecular mimicry and bystander activation act in precipitating autoimmunity as it was shown in an experimental model of multiple sclerosis [34].

Another mechanism that contributes to autoimmune disease predisposition is e**pitope spreading** [35]. Today we know that B and T-cell immune responses are not static but continue to evolve throughout the course of antigenic exposure and that this phenomenon contributes to the activation of T cells of additional specificities [36]. The concept of epitope spreading was once again demonstrated using the LCMV viral system. Immune responses to LCMV are different when acute

versus chronic T-cell epitopes are compared. In the acute response to LCMV, T cells are restricted to a couple immunodominant peptides, in part, based on the high affinity of T cells for these peptides. In contrast, chronic T-cell responses that arise and persist long after the clearance of virus are directed at subdominant determinants with lesser affinity to MHC [37]. This form of epitope spreading especially during chronic infections could lead to the activation of cross-reactive low-affinity autoreactive T cells that in the case of autoimmunity, could fuel the autoreactive process.

Recent evidence has shown that viral exposure can also lead to unrelated responses [38-41] that in the case of transplantation represent a potent barrier of tolerance induction [42]. This phenomenon termed **heterologous immunity**, occurs by at least two mechanisms, TCR cross-reactivity or non-specific bystander activation, we described above [43-46]. Infection with LCMV at the time of transplantation was shown inhibit the beneficial effects provided by costimulation blockade preventing the establishment of tolerance [44]. We showed that LCMV infection cannot break tolerance once it has been established after the adoptive transfer of donor-specific T regulatory type 1 (Tr1) cells or treatment with G-CSF/rapamycin ([47] and unpublished data). Interestingly, analysis of the alloreactive repertoire in LCMV mice showed that LCMV increased the number of donor-specific T cells, with a mechanism that remains still unclear ([44] and our unpublished data).

2.3 The concept of T cell exhaustion and immunopathology

Another important mechanism of T cell unresponsiveness and state of tolerance is known as **T cell exhaustion** [48, 49]. T cells show strong expression of co-inhibitory molecules including PD-1, LAG-3, CTLA-4 during infection with LCMV [50, 51]. While the expression of these molecules becomes downregulated in activated virus-specific T cells after the clearance of an acute infection, it remains high after infection with viral strains that cause persistent infection [52]. This strong PD-1 expression by the T cells results in increased interaction with the PD-L1 expressing parenchymal cells of the infected tissues and is associated with the strongly anergic phenotype of T cells [53]. The exhausted T cells show strong expression of additional inhibitory receptors (TIM3, LAG-3, etc.) and poor effector functions. The T-cell response is augmented via administration of blocking antibodies

for PD-1 (TIM3, LAG-3, etc.) in both acute and chronic infection, suggesting that PD-1–PD-1 ligand interaction attenuates T-cell activation. Currently, checkpoint inhibitors targeting PD-1 and others are used in the clinic to counteract the exhausted state of T cells in patients with advanced cancer [54, 55].

One obvious question is why would there be a need of a control system to attenuate T cell activation, thus perturbing viral clearance? It seems that co-inhibitory molecules like PD-1 protect the host by preventing a strong T-cell attack against infected cells. This idea is again supported by an animal model of chronic infection with LCMV. When PD-L1 knockout mice were infected by LCMV Clone 13, all the mice died of severe immune inflammation due to exaggerated T cell response [56]. This exaggerated response causing tissue damage is now known as **immunopathology.** Thus, PD-1 that was discovered in experiments using LCMV acts by slowing the course of immune response during infection, limiting a rapid and possibly more aggressive response that could lead to tissue destruction, immunopathology with severe consequences for the health of the host.

While PD-1 restricts T-cell activation to limit immunopathology following an infection, this molecule is essential to promote self-tolerance to autoantigens. Mice deficient for PD-1 develop a late-onset lupus-like autoimmune syndrome on the C57BL/6 and lethal dilated cardiomyopathy on the BALB/c background [57, 58]. NOD mice with a null mutation of PD-1 or its ligands show heightened disease penetrance, earlier onset, and more severe diabetes progression than control mice [59, 60]. Similarly to NOD, MRL mice that are prone to autoimmunity develop severe myocarditis and pneumonia when they lack either PD-1 or PD-L1, and more than 70 % of the mice die within the first 10 weeks of age [61]. Thus, a molecule that was discovered to control T cell activation and exhaustion in LCMV infection was found to be essential for T cell tolerance to autoantigens in several disease settings.

3. The concept of hygiene hypothesis and how viral infections protect from autoimmunity

Epidemiologic data indicate that infections can play a role in preventing rather than enhancing autoimmunity. The fact that the incidence of most infectious diseases is declining, while that of autoimmune diseases is increasing, suggests that there must be a link between the two phenomena. These observations have led to the **hygiene hypothesis**, which postulates that the increase in the frequency of autoimmune diseases is due to a reduction in the frequency of infections [62]. Although this hypothesis in humans is supported by epidemiological data, experiments with LCMV proved to be true in experimental models where autoimmune disease was prevented by infection [63, 64]. Prediabetic NOD mice infected with LCMV (or with CVB3) were fully protected from developing T1D [64-67]. The way viral infections promote tolerance seems to include several mechanisms, including **antigen-specific tolerance**, **Treg induction/invigoration**, **immune deviation**, many of them discovered/established with the use of the LCMV viral system.

3.1 The concept of antigen-specific tolerance

As we explained above, molecular mimicry and antigen cross-reactivity is one of the mechanisms by which viruses promote autoimmunity. Paradoxically, the same mechanism can promote tolerance and prevent autoimmunity. The idea is that the cross-reactive epitope is a tolerazing antigen instead of promoting autoimmunity and here are some examples of how a virus can do that. When mice were infected with a vaccinia virus (VV) encoding for some of the immunodominant amino acids of myelin base protein (MBP), these mice did not develop experimental autoimmune encephalomyelitis (EAE) and were protected from subsequent induction of EAE via MBP peptide immunization [68]. Interestingly, when the infected mice were immunized with whole MBP, still tolerance prevailed. However, mice were not protected against EAE when whole spinal cord lysate was used to induce EAE, suggesting that **antigen-specific tolerance** had occurred. Peptide-specific tolerance was also established in RIP-LCMV mouse model of T1D after synthetic (GP) peptide treatment [69].

Interestingly, in the EAE experiments, the part of MBP that was cloned in VV was not acetylated as in the native molecule suggesting that antigen-specific tolerance occurred via the presentation of an altered peptide ligand (APL) [70, 71]. One of the possible mechanisms that induce

tolerance after viral infection today still postulates the involvement of APLs as tolerazing antigens. This knowledge has had significant impact on the way antigen-specific therapies are designed. For some diseases, APLs were shown to be more effective than native epitopes at inducting tolerance [72]. These experiments therefore pointed to applications for APL in antigen-specific therapy to prevent autoimmune disorders [73, 74].

3.2 The concepts of immune suppression, Treg invigoration and immune deviation

Infection with CVB or LCMV can abrogate the development of T1D in NOD and RIP-LCMV prediabetic mice when infected at early during disease pathogenesis [65-67]. Mechanistic explanations comprise an upregulation of PD-L1 and TNF-α production, as well as a bystander activation of protective Treg cells. More precisely, virus infection induced the expression of PDL-1 on lymphoid cells, which prevented the expansion of a set of diabetogenic $CD8^+$ T cells expressing PD-1, and increased the frequency of TGFβ-producing $CD4^+CD25^+FOXP3^+$ Treg cells [66, 67]. Furthermore, adoptive cell transfer of Treg from the protected to mice but not from uninfected mice to another NOD mice protected the latter from developing T1D, suggesting that the viral infection **invigorated the Treg** function/fitness [67]. The enhancing effects of CVB on the NOD Tregs were mainly elicited through TLR2 [66].

Another interesting observation made with the use of the LCMV viral infection in NOD and RIP-LCMV mice was the following: infection of prediabetic mice resulted in a substantial viral grown in the pancreatic lymph nodes bus not the pancreas (or islets). This strong inflammation caused and elevation of CXCL10 levels specifically in the pancreatic lymph nodes, which led to the deviation of the inflammatory (autoreactive) lymphocytes from the pancreas/islets to the pancreatic lymph nodes. As a result, the number of autoreactive lymphocytes in the islets of prediabetic mice was drastically reduced [65, 75]. This mechanism is now known as **immune deviation**. Interestingly, a significant increase in the apoptosis of antigen-specific autoreactive T cells was seen, as a result of their hyperactivation or the action of Tregs. Thus, in addition to immune deviation, **immune suppression**

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and (hyper)activation induced cell death contributed in the protection of mice form autoimmune diabetes [76, 77].

4. Conclusions

Much of our knowledge in several clinically-relevant immune processes derives from studies in the mouse model of LCMV infection. Studies using this model have formed the foundation for our understanding of human T cell activation, contraction and memory development, but also tolerance. LCMV and transgenic mouse models have been used as examples to address the efficacy of immunotherapies in treating T cell exhaustion, preventing/reversing autoimmunity, and measuring the safety of these treatments in the context of viral infections. There is no doubt that our understanding of T cell immunity to pathogens and self-tolerance to autoantigens has seen a revolution in the last three decades with the use of LCMV. Fundamental aspects of basic immunology were conceived and demonstrated using this viral system. We believe that LCMV will continue to serve at illuminating our path in understanding basic immunology and human research approaches will once more benefit from the value of LCMV studies.

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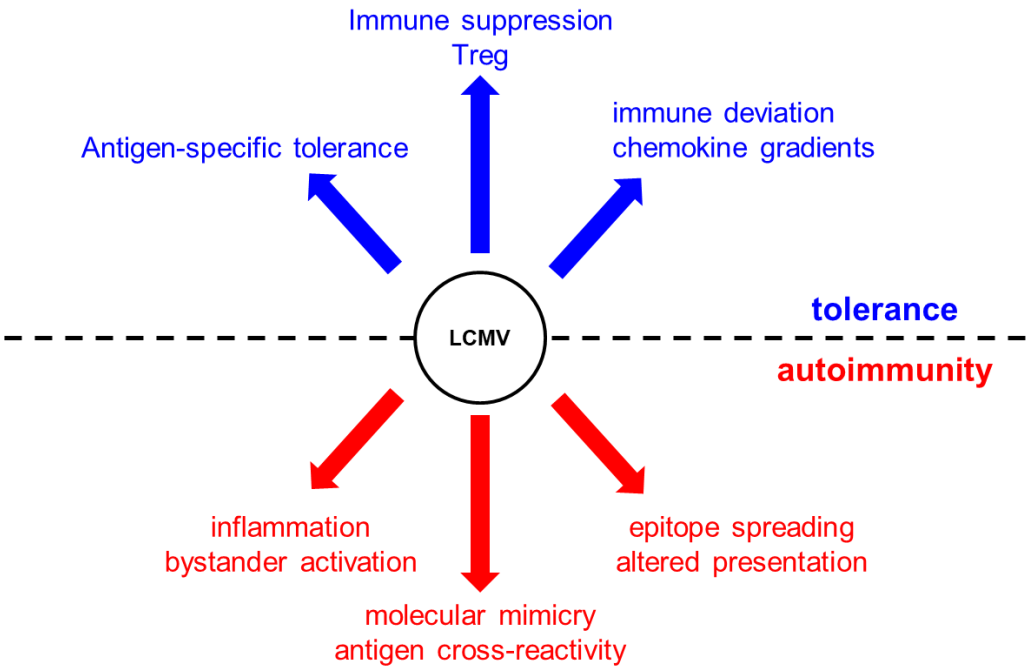
Figure



Virus (LCMV) infection can induce tolerance and promote autoimmunity via mechanisms that include antigen-specific tolerance, immune suppression (death of autoreactive T cells) Treg invigoration, and immune deviation via chemokine gradients (e.g. CXCL10). On the flip-side, virus infection can initiate or propagate an autoimmune disease via epitope spreading and molecular mimicry, inflammation and activation of APCs that present self-antigens.