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Review

TNFRs and Control of Chronic LCMV Infection: Implications for Therapy

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The control of persistent viral infections requires the immune system to limit the spread of the virus while avoiding immunopathology. Recent studies have revealed that members of the tumor necrosis factor receptor (TNFR) superfamily play unique and pivotal roles in control of chronic lymphocytic choriomeningitis virus (LCMV) infection and in some settings can tip the balance between immune control and immune pathology. We review these findings and discuss how our understanding of the role of TNFRs in the immune response to chronic LCMV infection may shed light on what happens during HIV infection in humans. We discuss preclinical models of TNF/TNFR family-targeted immunotherapy of chronic LCMV infection and evaluate which TNFRs present the most promising targets for immune intervention.

Introduction

Control of persistent infection requires a balance between antiviral immunity and immune regulation to allow a détente to be reached between virus and host, thereby allowing control of the infection while limiting collateral damage. LCMV, a natural rodent pathogen, has provided valuable insights into these processes with implications for human disease [1,2]. Early control of LCMV is mediated primarily by CD8 T cells [3,4]. Late control of LCMV, as exemplified by LCMV clone (cl 13) or LCMV Docile, is achieved by a functionally exhausted – but still effective – CD8 T cell response as well as by neutralizing antibodies (nAb). Importantly, early CD4 T cell induced inflammatory cytokine production, polyclonal B cell activation, and hypergammaglobulinemia contribute to a delay in the nAb response to chronic LCMV [5–8]. Hypergammaglobulinemia resolves when CD4 and CD8 T cell responses become functionally exhausted [9–11], corresponding with the induction of nAb and ultimately the clearance of the virus from most organs [7,8].

The complete lack of CD4 T cells results in lifelong LCMV infection accompanied by exacerbated CD8 T cell exhaustion and impaired antibody responses [11–15]. However, CD4 T cells also contribute to LCMV-associated pathology [4,16–20]. Supraphysiological CD4 T cell responses, such as induced by vaccination or transfer of LCMV-specific CD4 T cells, can result in delayed nAb production, the establishment of extralymphoid viral reservoirs, delayed viral clearance, and lethal immune pathology [8,21]. Conversely, mild attenuation of the CD4 T cell response through a tolerizing vaccine strategy can improve the nAb response and viral control [6]. Thus, the nature and magnitude of the CD4 T cell response is crucial in determining the quality of the ensuing CD8 T cell response, nAbs and, ultimately, viral clearance and/or immune pathology. A key question is how the immune system achieves the appropriate level of T cell response and what immunotherapeutic manipulations can be brought to bear to improve control of chronic viral infection in humans.

The induction of inhibitory receptors and their ligands as well as the production of anti-inflammatory cytokines play key roles in restraining T cell responses during chronic infection

Trends

Expression of several TNFR family members can be induced or sustained on T cells during an immune response, providing NF-κB- and MAPK-mediated pro-survival signals.

Recent studies using mice lacking specific TNFRs, or using agonists and blocking antibodies, have revealed non-redundant roles for individual TNFRs in the control of chronic LCMV infections.

Transient expression of GITR and OX40 ligands limits signaling via these receptors in chronic infection. GITR and OX40 enhance T cell responses and the control of chronic LCMV infection.

Persistent CD27–CD70 signaling results in CD4 T cell and cytokine-mediated destruction of secondary lymphoid organ architecture; blockade of this co-signaling pathway improves control of chronic LCMV.

4-1BB has a limited role in control of chronic viral infection owing to degradation of the signaling adaptor TRAF1. IL-7 can restore TRAF1 and enhance the effects of 4-1BB agonists.

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[22]. However, persistent infections also result in sustained antigen-driven upregulation of several costimulatory members of the TNFR superfamily on T cells, including 4-1BB (TNF receptor superfamily member 9/TNFRSF9), OX40 (TNFRSF4) and GITR (glucocorticoid-induced TNF receptor family-related protein/TNFRSF18), as well as sustained expression of the CD27 ligand, CD70 (TNFSF7), on B and T cells [23]. This raises the question of how these TNFR family members contribute to control of chronic viral infection and whether one can manipulate these pathways to improve viral control. Several recent studies of chronic LCMV infection have addressed these questions [24–29]. We review these findings and their implications for immunotherapy of human chronic infections, such as HIV.

Role of TNFRs During Acute Versus Chronic LCMV Infection

The TNFR family members CD27, GITR, OX40, and 4-1BB each have distinct patterns of expression and this likely contributes to their unique roles during LCMV infection (Table 1). As reviewed in detail elsewhere [30], TNFRs use TRAF (TNF receptor-associated factor) signaling adaptors to turn on cell survival and activation pathways through NF-κB (nuclear factor κB), MAPK (mitogen activated protein kinase), and, in some cases, PI3K (phosphoinositide 3-kinase) and AKT (protein kinase B) activation. Whether signaling through these TNFRs improves or impairs viral control depends on the context.

CD27 is expressed on naïve T cells and is maintained throughout the course of acute LCMV infection. Signaling through CD27 is largely regulated through expression of its ligand, CD70 (reviewed in [31]). During acute infection with LCMV Armstrong, CD70 is barely detected on dendritic cells (DC), peaking at day 2 post-infection (p.i.) and returning to baseline by day 6 [32,33]. CD70 is more highly expressed on T cells and even more so on B cells, peaking at day 8 on T cells and day 15 p.i. on B cells, with expression persisting to at least day 35 of acute infection with LCMV WE [33]. Addition of CD70 blocking antibody or the absence of CD70 ($CD70^{-/-}$ mice) during acute LCMV infection results in a decreased effector CD8 T cell response and a modest delay in viral clearance, but ultimately the virus is cleared and an unimpaired memory response ensues [34,35]. By contrast, during chronic infection with LCMV Docile [33] or cl 13 [35], the persistent expression of CD70 contributes to pathological cytokine production that limits viral control. Normally, splenic microarchitecture is disrupted during persistent LCMV

Table 1. Effects of Disruption of 'Co-Stimulatory' TNFRs During Acute and Chronic LCMV Infection in Mice.

Target Disrupted	Acute Infection (LCMV Armstrong or WE)			Chronic Infection (LCMV clone 13 or Docile)		
	LCMV-Specific T cell response	LCMV-Specific IgG	Viral Burden	LCMV-Specific T cell Response	LCMV-Specific IgG	Viral Burden
CD27/CD70	↓ CD8, modest ↓ CD4 [34,35]	↑ [35]	Delayed clearance [34,35]	No change day 7 ↑ CD4, CD8 >day 21 p.i. [33,35]	↑ [33,35]	cleared [33] or transient ↓ [35] (shorter treatment)
GITR/GITRL	↓ CD4 and CD8 [28]	?	Still cleared by day 8 [28]	↓ CD4 and CD8 [28]	↓ [28]	↑ [28]
OX40/OX40L	↓ CD4, no change CD8 [24]	No effect [24]	No effect [24]	↓ CD4 >↓ CD8 [24]	↓ [24]	No change early, ↑ >day 50 [24]
4-1BB/4-1BBL	Modest ↓ CD8 [45]	?	No effect [44,45]	↓ CD8; NP396 epitope GP33, no change [25]	?	↑ D8, no effect day 60 [25]