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Mini review

The Lymphotoxin Network: Orchestrating a Type I interferon response to optimize adaptive immunity

Jennifer L. Gommerman [a], Jeffrey L. Browning [b], Carl F. Ware [c,*]

[a] Department of Immunology, University of Toronto, Toronto, Ontario, Canada
[b] Department of Microbiology and Section of Rheumatology, Boston University School of Medicine, Boston, MA 02118, USA
[c] Infectious and Inflammatory Disease Center, Sanford-Burnham Medical Research Institute, La Jolla, CA 92037, USA

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ABSTRACT

The Lymphotoxin (LT) pathway is best known for its role in orchestrating the development and homeostasis of lymph nodes and Peyer's patches through the regulation of homeostatic chemokines. More recently an appreciation of the LTβR pathway in the production of Type I interferons (IFN-I) during homeostasis and infection has emerged. LTβR signaling is essential in differentiating stromal cells and macrophages in lymphoid organs to rapidly produce IFN-I in response to virus infections independently of the conventional TLR signaling systems. In addition, LTβR signaling is required to produce homeostatic levels of IFN-I from dendritic cells in order to effectively cross-prime a CD8+ T cell response to protein antigen. Importantly, pharmacological inhibition of LTβR signaling in mice has a profound positive impact on a number of autoimmune disease models, although it remains unclear if this efficacy is linked to IFN-I production during chronic inflammation. In this review, we will provide a brief overview of how the "Lymphotoxin Network" is linked to the IFN-I response and its impact on the immune system.

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1. Ligands and receptors of the Lymphotoxin Network

The Lymphotoxin-alpha (LTα) soluble homotrimeric cytokine, which binds to TNFRI and TNFRII receptors was first discovered in 1968 and shown to exert cytotoxic activity in delayed type hypersensitivity [1,2]. Due to its homology to TNFα, it was assumed that LTα would have redundant functions with this pathway. However, LTα has distinguishing features from TNFα, namely forming a complex with LTβ anchoring $LT\alpha_1\beta_2$ heterotrimers to the cell membrane of activated lymphocytes [3].

The $LT\alpha_1\beta_2$ heterotrimer bound a distinct receptor, known now as the LTβ receptor, and a new pathway emerged with unique biological functions [4]. Mice with genetically targeted deletion of LTα and LTβR were shown to have a dramatically different phenotype than TNFα and TNFR knock-out mice. In particular $Lt\alpha^{-/-}$ or $Lt\beta r^{-/-}$ [5,6] mice lack all lymph nodes and Peyer's patches, and $Lt\beta^{-/-}$ mice lack most lymph nodes and Peyer's patches, [7] whereas *Tnfα* deficient mice do not exhibit significant defects in lymphoid tissue development (although some TNFα deficient mice lack Peyer's patches) [8]. As such, it was quickly appreciated that the LTαβ–LTβR pathway played an important and distinct role in lymphoid tissue development and homeostasis. Thus, a new TNF superfamily receptor/ligand pathway was defined that plays an important role in immune system homeostasis.

Subsequently, a second ligand for the LTβR was discovered called LIGHT (TNFSF14), which also engaged another member of the TNFR superfamily, the herpesvirus entry mediator (HVEM, TNFRSF14) [9]. HVEM also binds LTα3, and two members of the Ig superfamily: B and T lymphocyte attenuator (BTLA) and CD160. The HVEM-BTLA connection functions to counter-regulate some cellular functions controlled by the LTβR [10], whereas HVEM-CD160 activates NK cells [11]. Thus, this subset of TNF superfamily receptor and ligands serves as a network of signaling pathways playing important roles in immune system homeostasis, cellular activation and host defense. From the broad expression patterns of these LT related cytokines and receptors one anticipates that more biology will emerge from understanding the TNFRSF-IgSF pathways.

2. A role for the LT pathway in lymphoid tissue homeostasis

Subsequent studies showed that LTβR signaling in radio-resistant lymphoid tissue "organizer" cells was required to

* Corresponding author. Tel.: +1 858 795 5335.
E-mail address: cware@sanfordburnham.org (C.F. Ware).

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orchestrate lymph node development [12]. Furthermore, significant evidence has revealed a critical role for LTβR signaling in stromal cells in the adult animal for maintaining homeostatic chemokines in lymphoid tissue [13], and for inducing chemokine production at sites of inflammation leading to the formation of ectopic follicle-like structures [14]. In addition to chemokine production, LTβR signaling is required to maintain both specialized reticular stromal cell networks, high endothelial venules [15] and homeostatic VEGF expression [16] as well as specialized niches within lymphoid tissues such as the marginal zone of the spleen and the germinal center environment within the splenic B cell follicle [17]. Subsequent studies using viral infections implicated the LT pathway in orchestrating immune responses, and in many cases, this was attributed to the role of LTβR in lymphoid tissue development and homeostasis [18,19].

However, in addition to its important role in stromal cell biology, the LTβR is also expressed in cells of the myeloid lineage such as dendritic cells and macrophages [20,21]. Accumulating evidence indicates that signaling through the LTβR in the myeloid compartment is also of biological importance. Intrinsic LTβR signaling in dendritic cells is required to maintain certain dendritic cell subsets ($CD4^+$ and $CD4/8^-$ subsets) through homeostatic proliferation [20]. Limiting the homeostatic proliferation of LT-sensitive dendritic cell subsets is mediated by the HVEM-BTLA pathway [10]. In addition, signals through the LTβR in dendritic cell and macrophages have been shown to shape the immune response to protein antigen [22,23] independent of the role of LTβR signaling in lymph node development or in LTβR-dependent maintenance of lymphoid tissue architecture. While the precise role for this pathway is very much dependent on the type of immune response (i.e., viral infections, bacterial infections, autoimmune responses, graft-*versus*-host disease) one theme that has emerged is that the LT pathway controls the production of cytokines, in particular Type I interferon (IFN-I) [22,24–26].

3. The Lymphotoxin pathway and autoimmune disease models

The discovery that LTαβ binds the LTβR and exerts biological functions distinct from TNFα signaling prompted an examination of whether the LTβR network plays a role in autoimmune disease. Multiple studies have demonstrated that the LTβR pathway plays a key role in the pathogenesis of experimental autoimmune diseases [17]. For example, pharmacological inhibition of the LT pathway is effective in reducing the clinical severity of several murine models of autoimmune disease including experimental autoimmune encephalomyelitis [27,28], Type I diabetes [29–31], collagen-induced arthritis [32], uveitis [33], Sjogren's syndrome [34], colitis [35] and graft *vs* host disease [36]. While this non-exhaustive list of autoimmune diseases signifies an important role for this pathway in the regulation of lymphocyte responses to self-antigen, one of the big challenges is to understand the mechanism of action of how inhibitors of this pathway attenuate a complex chronic disease. Is efficacy due to disruption of homeostatic chemokines, inhibition of ectopic chemokine expression in the target organ, or effects on homeostasis of lymphoid cells themselves such as dendritic cells? Systems that inhibit LTβR-signaling in specific cell types such as gut epithelial cells [37] or dendritic cells [38] are beginning to illuminate unique functions for this pathway in specific cell types. Importantly, subsets of patients with autoimmune diseases, such as systemic lupus erythematosus or Sjögren's syndrome consistently express IFN-induced genes in blood cells [39–41]. The origin of the "interferon signature" and what specific pathologies are being reflected remains very perplexing. To date, the initial clinical studies attempting to inhibit the IFN signature have not been obviously successful suggesting that the signature is not tightly coupled to organ-specific manifestations.

4. IFN-I shapes the immune response

4.1. IFN-I and the anti-viral state

Interferon, originally defined by the induction of cellular resistance to virus infection, is recognized as a family of cytokines that also shape the innate and adaptive immune responses [42]. The family of innate interferons (collectively referred to as IFN-I) includes IFNβ, and multiple IFNα genes, yet all engage the same cell surface receptor, IFNαβ receptor (IFNAR) comprised of two subunits, IFNAR-1 and 2 [43]. Different Type I IFN can trigger quantitative differences in signaling due to varying kinetics of receptor occupancy [44]. The interferon-γ and IFN-λ families can also induce cellular resistance to infection, but are encoded by distinct genes and utilize distinct receptor systems. Transcriptional control of IFN-I genes involves coordinate activation of IFN response factors, IRF3 and IRF7 that are regulated by the protein kinases, IKKε and TBK1, which receive signals from distinct pathogen recognition receptors including TLR, NLR and RNA helicase sensor families [45,46]. The IFNAR initiates the antiviral response *via* the Janus-associated kinases (JAK) and the STAT family of transcription factors. Interferon receptor signaling induces the expression of hundreds of genes in cells, many of which are not expressed under homeostatic conditions [47]. Interferon initiates gene expression programs that are crucial for antiviral responses, reshape the proteasome, alter protein stability and affect immune function in many ways. Characteristic IFN-I stimulated genes (ISG) include OAS1 and ISG15. OAS1, a 2′-5′-oligo synthetase, promotes viral RNA degradation [48] and ISG15, a ubiquitin-like protein, stabilizes newly induced IFN-dependent proteins [49]. Many of the interferon stimulated genes remain functionally undefined.

4.2. IFN-I and lymphocyte trafficking

In addition to its effect on constraining viral replication, in the context of viral infections IFN-I can also modulate the circulation of leukocytes, constraining them to lymphoid tissues [50]. This is presumably so that lymphocytes have a maximal opportunity to be primed within the antigen-draining lymph nodes. Indeed, it has been long appreciated that following viral infection, local draining lymph nodes rapidly swell in size, and injection of IFN-I recapitulates this phenomenon in mouse and man in the absence of virus [51]. The increase in size in lymph nodes is in part due to prevention of lymphocyte egress through the lymphatic sinuses, thus trapping lymphocytes for a longer transit time within the lymph node. Theoretically, this increases the odds that rare antigen-specific T cells can encounter antigen-presenting dendritic cells that have migrated from the site of infection into the local draining lymph node. Normally lymphocytes spend a brief amount of time in a lymph node before sensing gradients of sphingosine-1 phosphate (S1P) in the efferent lymph [52]. However, IFN-I disrupts this process by activating lymphocytes to express CD69, which in turn results in the down-regulation of S1P-receptors, thus preventing egress [50]. Once the initial wave of IFN-I subsides, lymphocytes down-regulate CD69 and can re-express S1P receptors, thus facilitating their exit out of the lymph node. It is the balance between expression of S1P receptors (and responsiveness to sphingosine-1 phosphate) *versus* the attraction toward lymphoid tissue chemokines that likely dictates the residence time of lymphocytes, and during chronic infection/inflammation, this residence time may be dysregulated. Thus, IFN-I production early during the immune response to virus can have a dramatic effect on the migration properties of leukocytes.

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