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The Lymphotoxin Network: Orchestrating a Type I Interferon Response to Optimize Adaptive Immunity

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Abstract

The Lymphotoxin (LT) pathway is best known for its role in orchestrating the development and homeostasis lymph nodes and Peyer's patch through the regulation of homeostatic chemokines. More recently an appreciation of the LT α R pathway in the production of Type I interferons (IFN-I) during homeostasis and infection has emerged. LT α R 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, LT α R 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 LT α R 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.

Keywords

Autoimmunity; cytokines; dendritic cells; Interferon (IFN); Lymphotoxin- α (LT α); stromal cells

Ligands and Receptors of the Lymphotoxin Network

The Lymphotoxin- α (LT α) soluble homotrimeric cytokine, which binds to TNFR1 and TNFR2 receptors was first discovered in 1968 and shown to exert cytotoxic activity in delayed type hypersensitivity[1, 2]. Due to its homology to TNF α , it was assumed that LT α

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would have redundant functions with this pathway. However, LT β has distinguishing features from TNF β , namely forming a complex with LT β anchoring LT β $\alpha_1\alpha_2$ heterotrimers to the cell membrane of activated lymphocytes [3].

The LT β $\alpha_1\alpha_2$ heterotrimer bound a distinct receptor, known now as the LT β Receptor, and a new pathway emerged with unique biological functions [4]. Mice with genetically targeted deletion of LT β and LT β R were shown to have a dramatically different phenotype than TNF β and TNFR knock-out mice. In particular *Lt β ^{-/-}* or *Lt β r^{-/-}* [5, 6] mice lack all lymph nodes and Peyer's patches, and *Lt β ^{-/-}* mice lack most lymph nodes and Peyer's patches, [7] whereas *Tnf β* deficient mice do not exhibit significant defects in lymphoid tissue development (although some TNF β deficient mice lack Peyer's patches)[8]. As such, it was quickly appreciated that the LT β ! -LT β R 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 LT β R was discovered called LIGHT (TNFSF14), which also engaged another member of the TNFR superfamily, the herpesvirus entry mediator (HVEM, TNFRSF14)[9]. HVEM also binds LT β 3, 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 LT β R[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.

A role for the LT pathway in lymphoid tissue homeostasis

Subsequent studies showed that LT β R signaling in radio-resistant lymphoid tissue “organizer” cells was required to orchestrate lymph node development[12]. Furthermore, significant evidence has revealed a critical role for LT β R 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, LT β R 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 LT β R in lymphoid tissue development and homeostasis [18, 19].

However, in addition to its important role in stromal cell biology, the LT β R is also expressed in cells of the myeloid lineage such as dendritic cells and macrophages[20, 21]. Accumulating evidence indicates that signaling through the LT β R in the myeloid compartment is also of biological importance. Intrinsic LT β R 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 HVEM-BTLA pathway [10]. In addition, signals through the LT α R in dendritic cell and macrophages have been shown to shape the immune response to protein antigen [22, 23] independent of the role of LT α R signaling in lymph node development or in LT α R-dependent maintenance of lymphoid tissue architecture. While the precise role for this pathway is very much dependent on the type of immune response (ie, 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].

The Lymphotoxin pathway and autoimmune disease models

The discovery that LT α binds the LT α R and exerts biological functions distinct from TNF α signaling prompted an examination of whether the LT α R network plays a role in autoimmune disease. Multiple studies have demonstrated that the LT α R pathway plays a key role in the pathogenesis of experimental autoimmune diseases [27]. For example, pharmacological inhibition of the LT pathway is effective in reducing the clinical severity of multiple murine models of autoimmune disease including Experimental Autoimmune Encephalomyelitis [28, 29], Type I Diabetes [30-32], collagen-induced arthritis [33], Uveitis [34], Sjogren's Syndrome [35], Colitis [36] and graft vs host disease [37]. 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 LT α R-signaling in specific cell types such as gut epithelial cells [38] or dendritic cells [39] 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 [40-42]. 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.

IFN-I shapes the immune response

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[43]. The family of innate interferons (collectively referred to as IFN-I) includes IFN α , and multiple IFN β genes, yet all engage the same cell surface receptor, IFN α receptor (IFNAR) comprised of two subunits, IFNAR-1 and 2 [44]. Different type I IFN can trigger quantitative differences in signaling due to varying kinetics of receptor occupancy [45]. The interferon- α and IFN- β 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, IKK α and TBK1, which receive signals from distinct pathogen recognition receptors including TLR, NLR and RNA helicase sensor families [46, 47]. The IFNR initiates the antiviral response via 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 [48]. 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 [49] and ISG15, a ubiquitin-like protein, stabilizes newly induced IFN-dependent proteins [50]. Many of the interferon stimulated genes remain functionally undefined.

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 [51]. 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 [52]. 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 [53]. 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 [51]. 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 towards 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.

IFN-I and regulation of lymphocyte responses

The effects of IFN-I in regulation of lymphocyte priming are variable. In some cases, IFN-I has been shown to promote the differentiation of T-regulatory cells [54]. In other scenarios, expression of IFNAR, has been shown to be important for CD8 cross-priming and clonal expansion during viral infection [55]. It has been hypothesized that the production of both IFN-I and IL-12 by dendritic cells play a complementary role in priming CD8⁺ T cell responses [56]. This may be due to the unique effects of both cytokines in chromatin remodeling within CD8⁺ T cells, and given the complexity of pathways that are involved in

CD8⁺ T cell priming and effector functions, it is reasonable to assume that various cytokines secreted by dendritic cells can have non-redundant effects in this process.

It is unclear why IFN-I would have differential effects on leukocytes: cytopathic in some cases whereas pro-stimulatory in others [57]. One possibility is that the amount of IFN-I and the tempo of its production by antigen-presenting dendritic cells is a critical rheostat that dictates the outcome on CD8⁺ T cell priming. Another possibility is that differential STAT phosphorylation in the IFN-I-receiving cell (ie, the CD8⁺ T cell) will dictate the functional outcome of IFNAR signaling [58].

LT ! R-dependent stromal cells and macrophages as IFN-producing viral sensors

Herpesviruses revealed the first link between the LT! R signaling pathway and the induction of IFN-I. The human !-herpesvirus, cytomegalovirus (HCMV) replicates in dermal fibroblasts by suppressing induction of IFN! . Signaling via the LT! R or TNFR1 overrides this viral suppressive mechanism allowing induction of IFN! , which protects surrounding cells from virus spread [59]. The virus however is not eliminated from the infected cell but rather held in a state of stasis or “détente” by the LT! R-IFN! pathway [60].

Investigations in mice reinforced the physiological importance of the LT! R system in the induction of the initial wave of IFN-I in response to infection with mouse CMV, and a key role for IFN-I in protecting the integrity of lymphoid organs during infection [61]. Mouse CMV is captured in the splenic marginal sinus where it infects LT! R-differentiated stromal cells that become the source of virus production [62]. Within hours IFN! is rapidly induced in stromal cells in the spleen following infection, paralleling expression of viral genes, with peak IFN-I expression in the spleen and serum at 8-12hrs post-infection, ahead of IFN-I production in other visceral organs such as the liver. B lymphocytes expressing LT! ! and LT! R⁺ stromal cells form this IFN-I defense system against MCV[25].

CMV is not unique in utilizing a defense mechanism that relies on LT! ! expression in B cells. Several other viruses are restricted by the LT-IFN host defense axis. Studies by Moseman et al. [63] and Honke, et.al., [64] using cell specific gene knockouts and the LT! R-Fc antagonist clearly established that B cells expressing LT! ! are essential for the first wave of IFN-I to control these RNA viruses. LT! R signaling induces the differentiation of sinus-lining macrophages in lymphoid organs into IFN-I producers. The subcapsular sinus-lining macrophages in lymph nodes and the apparently similar metallophilic macrophages in the splenic marginal zone function as the sentinel cells that capture blood and lymph born pathogens [65]. IFN-I production following VSV infection is initiated in the subcapsular lining macrophages, identified by Siglec1 expression (CD169). Siglec1 expression is dependent upon LT! ! expression in B cells, yet independent of B cell antigen recognition [63]. These LT! R-differentiated macrophages capture VSV allowing a permissive site for replication due to expression of Usp18, an attenuator of IFN-I antiviral state [64, 66]. Conceptually, these observations indicate that Siglec1 macrophages under the control of the LT! R system allow high viral replication, providing a source of antigen for the adaptive immune system (**Figure 1**). Simultaneously, it is likely that lack of IFN responsiveness in these cells prevents selection of IFN-I resistant viral mutants during the initial replication cycle of infection. Blocking LT! R signaling results in the inappropriate infection of

neuronal cells by VSV with significant pathologic consequences resulting from an otherwise benign pathogen [67]. Inhibiting the initial IFN-I response by blocking the LT! R pathway also results in inappropriate apoptotic death of T and B cells in response to MCMV infection [61], reflecting the essential role of IFN-I in the survival of antigen-activated T cells [68]. Collectively, these results suggest that the LT! R pathway maintains sentinel pathogen permissive cells in lymphoid organs that in turn provide an important source of the initial interferons required for both innate and adaptive arms of host defense. This defense system is a preset component of homeostasis of the spleen, lymph nodes and intestinal lymphoid organs maintained through the LT! ! -LT! R pathway [69].

LT! R-dependent production of IFN-I in Dendritic Cells

Several studies have highlighted a role for the LT pathway in DC. In particular, CD8⁻CD11b⁺ DC in the spleen require LT! R signaling for their homeostatic maintenance by inducing proliferation locally in lymphoid tissue [20]. The LT-sensitive DC subset was further refined and shown to express the Endothelial cell-selective adhesion molecule (ESAM) in the spleen [70]. Interestingly, CD4⁺ DC are enriched in the bridging channels of the spleen due to their expression of EB12 and migration towards the oxysterol ligand 7! , 25-OHC. In the absence of EB12, these DC are absent but can be rescued by enforced LT! R signaling [71]. Outside of the spleen, a similar subset of DC in the gut (CD11b⁺CD103⁺) also rely on LT! R signaling for their homeostatic maintenance [72]. Thus, even though LT! R is a cardinal signal for stromal cell maturation, it appears to play a role in antigen-presenting DC as well.

To dissect what this DC role may be, a protein antigen-based system (Ovalbumin - OVA) was employed, with mice immunized with OVA in adjuvant. As expected, when DC were removed from the draining lymph nodes 36 hours post-immunization, they were found to have the capacity to prime naive OVA-specific CD4⁺ and CD8⁺ T cells *ex vivo* in the absence of any further added antigen. However, in the same experiment, if DC were removed from mice in which the LT pathway was inhibited, DC were dysfunctional *ex vivo* and could not effectively prime naive OVA-specific T cell responses. Nevertheless, in the context of global pharmacological inhibition of the LT pathway by LT! R-Fc decoy, it was unclear whether DC were rendered dysfunctional due to a dysregulation of the chemokine environment, or because of impaired DC:T cell crosstalk. Indeed, LT! ! is expressed in T cells activated with Ag[23]. Moreover, LIGHT is also expressed in T cells and can mediate considerable pathology when over-expressed [73, 74]. To resolve this, either LIGHT or LT! ! ligands were removed only from the OVA-specific CD4⁺ T cells *in vivo*. Interestingly, DC from mice that received *Lt!*^{-/-} OVA-specific CD4⁺ T cells exhibited a similar phenotype to DC derived from mice that received LT! R-Fc pharmacological treatment, whereas *Light*^{-/-} OVA specific T cells did not appear to have a significant effect on dendritic cell function. The effect of removing LT! ! ligand from Ag-specific CD4⁺ T cells was quantitatively similar to the removal of CD40L from Ag-specific CD4⁺ T cells. These experiments implied that, independent of its role in maintaining lymphoid tissue micro-architecture, the LT pathway is critical for optimal DC function *ex vivo*, and in the context of protein Ag, DC require both LT! R and CD40 signaling [23]. Subsequent experiments showed that these DC defects were relevant to the *in vivo* priming and expansion of Ag-

specific CD8⁺ T cells in response to cell-associated protein Ag. However, cytokine secretion by Ag-specific CD8⁺ T cells appeared to not be impaired when DC lacked LT! R [22]. Collectively, these experiments revealed a new and non-redundant role for the LT pathway in T cell: DC cross-talk *in vivo*.

To understand the mechanism of this defect, several possible hypotheses were tested. *Lt! r^{-/-}* DC were found to migrate normally to the draining LN and were able to process and present antigen. DC homeostasis was unaffected by the absence of LT! R in Ag-specific T cells, thus this was not a likely explanation for the observed phenotype. Moreover, expression of most co-stimulatory molecules (CD80, CD86 for example) was either unaffected in *Lt! r^{-/-}* dendritic cells, or not coupled to the observed phenotype.

Since IFN-I is important for shaping T cell responses, the hypothesis was tested that this may also be true for DC. To test this, an *in vitro* LT! R stimulation assay was used that examined the effect of stimulation with lipopolysaccharide (LPS) with or without additional LT! R signaling in bone marrow derived dendritic cells. As expected, IFN-I was produced in response to LPS. However, if LT! R signaling was also triggered in concert with TLR4, IFN-I production was significantly augmented and sustained. This augmentation was strictly dependent on the expression of LT! R in dendritic cells. Furthermore, stimulation of LT! R alone, in the absence of LPS, could induce a modest amount of IFN-I in WT but not *Lt! r^{-/-}* dendritic cells. While this response was not as rapid or robust as what is observed with LPS, it is comparable to what has been observed with TNF! stimulation in macrophages [75] and RANKL stimulation in thymic medullary epithelial cells [76, 77]. Thus, LT! R stimulation promotes IFN-I production by DC, although the mechanism by which this occurs remains unclear [22].

The production of IFN-I in DC was subsequently linked to the quality of the CD8⁺ T cell response, with impaired proliferation and activation of Ag-specific CD8⁺ T cells observed in the context of priming with *Lt! r^{-/-}* DC. Importantly, these impairments were corrected if IFN-I was added back to cultures. Thus, signals from the LT! R integrate with the IFN-I “rheostat” that controls CD8⁺ T cell responses to protein antigen (d). Importantly, while DC homeostasis is affected by dendritic cell-intrinsic LT! R expression, DC-intrinsic IFNAR expression was not required for optimal dendritic cell homeostasis *in vivo*. Thus, while the control of CD8⁺ T cell responses to protein antigen relies on LT-dependent IFN-I production, this does not appear to be true for DC homeostasis [72].

In general, these studies point towards a model wherein LT! R signaling leads to cell differentiation albeit stromal cell or DC, to a state of competence for an IFN response to virus and presumably innate stimuli. In hindsight, the ability of LT! R or TNFR activation to efficiently drive tumor cell death in the presence of IFN may reflect components of this model [78]. TNF can directly elicit a weak IFN response in macrophages [75], yet other than DC where IFN-I responses are also modest, LT! R does not obviously have this competency. This could reflect the importance of an optimal level of IFN-I that is required specifically in cell types such as DC and macrophages that directly interact with TNFSF-expressing activated lymphocytes, especially during “sterile” inflammation where pathogen associated molecular patterns are more limiting. This may also be the case for optimal thymocyte

selection: medullary thymic epithelial cells, which interact closely with TNFSF-expressing thymocytes, produce modest levels of IFN γ in response to RANK-ligand stimulation [76, 77]. Recently, like IFNAR, LT α R activation alone was shown to induce Apobec3B expression and drive the clearance of closed circular HBV DNA in hepatocytes [79]. This observation provides evidence of convergent signaling in these two pathways and a more detailed understanding the interplay between these pathways will be important.

Future perspectives

Integration of multiple TNFSF signals: Consideration of Co-therapies

Better comprehension of activation and expansion of the CD8 compartment may lead to more rational strategies for therapeutic control. In the context of CD8 $^{+}$ T cell responses, we noted that while LT α R-inhibition impacted clonal expansion, it did not affect CD8 $^{+}$ T cell mediated cytokine secretion or killing of Ag-loaded target cells. In contrast, inhibition of the CD40 pathway had a preferential effect on CD8 $^{+}$ T cell mediated cytokine production, in particular IFN γ , but had little effect on CD8 $^{+}$ T cell clonal expansion[22]. Thus, in the context of protein Ag, it is possible that the CD40 and LT α R pathways are acting cooperatively (**Figure 2**). This observation was consistent with our finding that stimulation of the CD40 pathway in bone marrow derived dendritic cells could not induce IFN-I, but effectively induced the production of IL-12, while the reverse was true when the LT α R pathway was stimulated in bone marrow derived dendritic cells[22]. This raises an interesting question: given that their respective ligands (LT α and CD40L) are coincidentally up-regulated on activated T cells, how does the dendritic cell integrate CD40 and LT α R-derived signals to mediate different outcomes? While there is significant overlap in the signaling pathways utilized by these two TNF superfamily receptors (for example activation of the alternative NF κ B pathway), there are some subtle differences [80]. Such differences may drive differential cytokine production, although this remains to be formally demonstrated. Nevertheless, given their different activities in dendritic cells, dual inhibition of the LT α R and CD40 pathway may be desirable for optimal therapeutic efficacy in a variety of disease states. Indeed, potent inhibition of graft-versus-host disease was achieved by dual inhibition of both pathways[81].

Clinical perspectives on the LT pathway

Clinical exploration of LT α R pathway inhibition in autoimmune disease has been slow to develop [82]. Biogen Idec developed an LT α R-Fc fusion protein called baminercept that blocks both LT α and LIGHT triggered events. In 2008, they reported that the drug did not meet the primary endpoint in two Phase II studies in RA patients with either an inadequate response to standard of care (DMARDs or TNF inhibitors)(clinical trial #NCT00664716 and NCT00458861 at clinicaltrials.gov). Baminercept currently remains in testing in a NIH sponsored randomized placebo-controlled phase II study in Sjögren's syndrome (NCT01552681). An antibody to LT α made by Genentech can deplete surface LT-positive lymphocytes, notably some innate lymphoid cells (ILC) and Th17 cells, and is being tested in Rheumatoid Arthritis (RA). This antibody also blocks LT α binding to LT α R and hence is partially similar to baminercept. Recently, blocking antibody to LIGHT is also in has entered into clinical testing. Based on the rodent data, a potential concern with LT α R

inhibition could be viral recrudescence. As the baminercept trials were run to completion accruing roughly 500 patients, it appears that serious adverse events were not frequent. Presumably previously established humoral and cellular anti-viral responses continue to maintain viral latency in the face of LT! R inhibition.

One could question whether the choice of RA for baminercept as an indication was optimal given the dominant role of TNF! in driving joint inflammation. In this regard, an interesting dichotomy was put forth by Banchereau and colleagues based on multiple observations including, notably, that TNF! inhibition in systemic early-onset idiopathic arthritis patients led to the emergence of an IFN-I signature in the blood [83]. They proposed that there are diseases dominated by TNF! and attendant inflammation and others characterized by an IFN-I driven pathology. Indeed Sjögren's syndrome, like SLE, has a high percentage of patients with an IFN signature and these Sjögren's patients have clearly not responded to TNF! inhibitor therapy [84]. TNF inhibition can also result in patients becoming positive for anti-nuclear antigens as in SLE, although the condition reverses itself upon cessation of therapy. In this light, the current NIH Sjögren's study with Baminercept may not only explore a different pathological process, but also provide information on the interplay between LT! R signaling and the IFN axis.

One possible scenario in autoimmune disease is that the IFN-I signature is a sign of smoldering systemic immunological processes that are occurring similar to the response to infectious disease. Debris from organ damage, whether apoptotic, necrotic or neutrophil nets, etc, could be eliciting an anti-viral like response in the draining lymph nodes. As such the IFN-I signature could be reporting on some undercurrent of disease that is poorly coupled to the specific organ manifestations that drive the clinical symptoms. Longer trials than the 3 month baminercept RA studies may be required to uncouple the systemic component from local organ manifestations. Alternatively, the systemic component may be a second pathology that is a consequence but not a driver of the organ specific disease.

Conclusions

Work from different avenues has highlighted previously unforeseen coupling between the LT! R and IFN pathways and mouse models point to the pathogenic roles of the LT and IFN-I pathways in human autoimmune diseases. Given that a number of disease states are characterized by chronic IFN-I production, it will be important to consider inhibitors of the LT pathway as potential therapies for quieting the immuno-stimulatory aspects of IFN-I. A better understanding of how the "Lymphotoxin/IFN" axis operates in the human system will shed light on the therapeutic potential of the Lymphotoxin network.

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Biography

Dr. Jen L. Gommerman is an Associate Professor in the Department of Immunology at the University of Toronto St. George Campus. She received her Ph.D. (Immunology) at the University of Toronto (Toronto, Canada) in 1998 with Dr. Stuart Berger where she studied growth factor receptor signaling. She did a post-doctoral fellowship at Harvard Medical School (Boston) studying the complement pathway with Dr. Michael Carroll and then joined Biogen-Idec Inc. as a staff scientist in 2000 working with Dr. Jeff Browning. During her tenure at Biogen, she became interested in B cells, Multiple Sclerosis and the TNF superfamily of molecules. After 3 years in industry, she returned to academia as an Assistant Professor and CIHR New Investigator in the Department of Immunology at the University of Toronto in 2003. Dr. Gommerman's work continues to focus on how members of the TNF superfamily of molecules regulate immunity and autoimmunity, and how B cells regulate MS pathogenesis. She holds funds from the MS Society of Canada, the Canadian Institutes for Health Research, and the Kidney Foundation. Along with Dr. Linda Burkly, she was the co-organizer of the 14th International TNF Meeting in Quebec City, Canada. As of July, 2013 she has taken on the role of Associate Chair of Graduate Studies in the Department of Immunology.

Dr. Jeffrey L. Browning is a Professor of Microbiology at Boston University School of Medicine engaged in translational medicine and the analysis of immunological involvement in scleroderma and fibrosis. He obtained his doctorate degree from the biochemistry department at the University of Wisconsin studying ion channels with Dr. David Nelson followed by postdoctoral research on biophysics of lipid membrane structure at the Biozentrum in Basel Switzerland with Dr. Joachim Seelig and on neuromuscular junctions at UCSF with Dr. Louis Reichardt. From 1984 to 2012, Jeffrey Browning was a research scientist with the biotech firm Biogen Idec in Cambridge MA where he led discovery efforts on various TNF family members including the lymphotoxin ! ! , TWEAK, BAFF and TROY systems and the subsequent exploration of their biology. He was instrumental in moving inhibiting and activating agents for the lymphotoxin and BAFF pathways into clinical trials in autoimmune disease and oncology.

Dr. Carl F. Ware is a leading immunologist and virologist recognized for his scientific discoveries and advances in the study of the immune system that are leading to new therapeutics for autoimmune and viral diseases and cancer. Dr. Ware is currently Director of the Infectious and Inflammatory Diseases Center Director at the Sanford|Burnham Medical Research Institute in La Jolla, and Professor at University of California, San Diego. Dr. Ware received his Ph.D. in Molecular Biology and Biochemistry from the University of California, Irvine in 1979 with GA Granger, and postdoctoral training at the University of Texas Health Science Center, and at the Dana-Farber Cancer Institute, Harvard Medical

School in Boston with Tim Springer and Jack Strominger. Dr. Ware established his research laboratory in 1982 at the University of California, Riverside. From 1996-2010 he served as Head of the Division of Molecular Immunology at the La Jolla Institute for Allergy and Immunology. Dr. Ware is noted for discovering several cytokines in the TNF Superfamily, including Lymphotoxin β , with Jeffrey Browning, and LIGHT. Dr. Ware is a recipient of National Merit Award from the US National Institutes of Health, and past President of the International Cytokine Society and Scientific Advisor for the International Conferences on TNF Related Cytokines. His current research program is focused on the structure-function relationships and clinical utility of Lymphotoxins, and cytokine-directed immune evasion mechanisms in persistent viruses.

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Figure 1. Innate B cells and Sentinel Pathogen Permissive Cells

In lymphoid organs, stromal cells produce IL-7 that induces LT $\alpha\beta$ expression on the surface of B cells. B cells engage LT $\alpha\beta$ expressing stromal cells and macrophages in marginal sinuses of lymphoid organs promoting their differentiation into sentinel cells that upon virus infection rapidly produce IFN-I. For example, cytomegalovirus (CMV) productively infects splenic stromal cells, which also produce type 1 interferons (IFN-I). In response to vesicular stomatitis virus (VSV), sinus-lining macrophages are productively infected and also produce IFN-I. These sinus-lining macrophages are themselves resistant to the effect of IFN-I via Usp18, an ISG-15 deconjugating enzyme that also blocks IFN Receptor signaling. Consequently these cells are permissive for VSV infection. It is thought that the permissive state of these macrophages provides high antigen production for capture and presentation to the adaptive immune system.

Figure 2. Proposed model of LT! R-dependent dendritic cell licensing during a help-dependent immune response

In settings where CD8⁺ T cell responses are help-dependent (such as immune responses to non-replicating antigen or cell-associated antigen), dendritic cell-intrinsic LT! R signals are important for optimizing local production of IFN-I. This modest amount of IFN-I is required for optimal CD8⁺ T cell clonal expansion. The dendritic cell-intrinsic LT! R signal is not required for CD8⁺ T cell effector function, such as IFN_γ secretion. Conversely, CD40 signaling in dendritic cells is necessary for CD8⁺ T cell effector function but dispensable for CD8⁺ T cell clonal expansion.