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NETWORK COMMUNICATIONS: Lymphotoxins, LIGHT, and TNF

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■ **Abstract** Lymphotoxins (LT) provide essential communication links between lymphocytes and the surrounding stromal and parenchymal cells and together with the two related cytokines, tumor necrosis factor (TNF) and LIGHT (LT-related inducible ligand that competes for glycoprotein D binding to herpesvirus entry mediator on T cells), form an integrated signaling network necessary for efficient innate and adaptive immune responses. Recent studies have identified signaling pathways that regulate several genes, including chemokines and interferons, which participate in the development and function of microenvironments in lymphoid tissue and host defense. Disruption of the LT/TNF/LIGHT network alleviates inflammation in certain autoimmune disease models, but decreases resistance to selected pathogens. Pharmacological disruption of this network in human autoimmune diseases such as rheumatoid arthritis alleviates inflammation in a significant number of patients, but not in other diseases, a finding that challenges our molecular paradigms of autoimmunity and perhaps will reveal novel roles for this network in pathogenesis.

INTRODUCTION

Cytokines provide essential communication signals for the highly motile cells of the immune system. Positional location within the different organs and subsequent differentiation to acquire effector function require that lymphocytes communicate with the surrounding tissue, with the role of communicator often played by tumor necrosis factor (TNF) and lymphotoxin (LT)-related cytokines.[1] Lymphotoxins are part of a complex communication system linking lymphocytes and surrounding parenchymal and stromal cells that can act locally or at distant sites. Two distinct structural forms of LT are recognized, LTα and LTβ, each localizing to distinct physical compartments (secreted or membrane restricted). Alone or in combination, LTα and LTβ form trimeric molecules that engage different cellular receptors and account, in part, for the specificity in eliciting distinct cellular responses. The

[1]See Appendix for a full list of abbreviations used.

extent to which the biological processes are regulated by LT$\alpha\beta$ is now being elucidated, although the clinical importance of LT has yet to be fully realized, especially when compared with its close structural homologue, TNF.

Lymphotoxin-α (formerly known as TNFβ) and TNF were once considered redundant forms. However, as a complex with LTβ, LTα has emerged with roles in the immune system quite distinct from that of TNF, a theme repeatedly corroborated at the molecular and cellular levels. Recent evidence indicates that for some physiological processes TNF and LT$\alpha\beta$ work together as components of an integrated signaling network. This signaling network is defined in part by communal sharing of receptors and ligands: LTα, LTβ, TNF, and LIGHT are linked into a common signaling network involving five distinct receptors (Figure 1). Moreover, the LT/TNF network is connected to specific chemokines, interferons, and other TNF family ligands in larger arrays of signaling networks. The concept of integrated signaling networks has important implications for the use of therapies targeted at these cytokines.

In the clinic, TNF/LTα have proven to be important targets for suppressing inflammation in certain autoimmune diseases, including rheumatoid arthritis (RA) and inflammatory bowel syndrome, but not others, such as multiple sclerosis (MS).

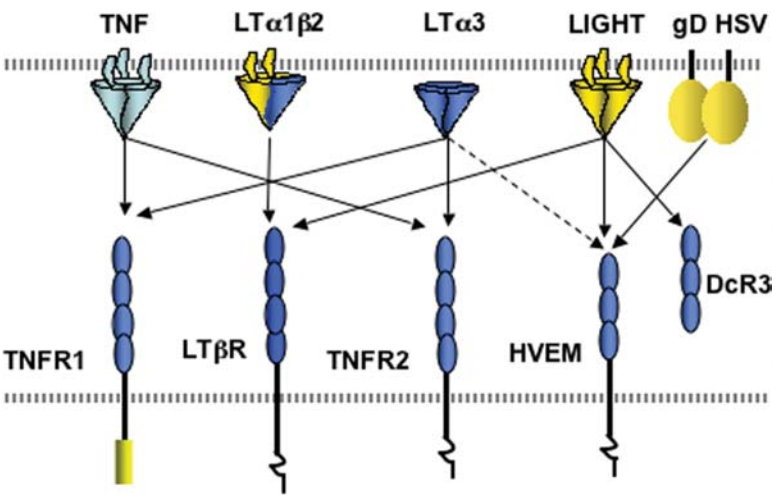

Figure 1 Molecular switches of the LT/TNF/LIGHT network. The ligands (*upper portion*) are depicted as membrane-anchored or secreted trimers, with the solid lines indicating their respective high-affinity receptors (*lower portion*); dashed line indicates relatively low-affinity binding. Cysteine-rich domains in the various receptors are depicted in blue; the yellow box in the cytosolic region indicates presence of a death domain and black squiggle line a TRAF binding motif. Decoy receptor 3 (DcR3) lacks a transmembrane domain. Glycoprotein D (gD) is an envelope protein of the HSV virion and is expressed on the surface of infected cells.

Moreover, side effects of TNF inhibitors include increased susceptibility to certain infectious diseases. Recent advances in identifying the molecular mechanisms in LT/TNF signaling may help clarify seemingly contradictory results in human patients treated with TNF/LT inhibitors. Here we review the structural and functional features of the LT/TNF/LIGHT signaling systems, in the context of the larger signaling networks. Although LT are well defined as key elements required for lymphoid organogenesis and organization, the effector genes activated by LT signaling pathways are just now beginning to emerge. Clinical results using LT/TNF inhibitors in various human autoimmune diseases suggest that the mechanisms controlling inflammation are much more complex than current models predict.

COMPONENTS OF THE NETWORK

Lymphotoxins and TNF are members of the TNF superfamily, a diversified family of ligands and corresponding family of receptors defined by a cysteine-rich ectodomain that control signaling pathways that initiate cell death, survival, and cellular differentiation. More than 20 distinct ligand-receptor systems now recognized in the TNF superfamily are involved in regulating the development and function of bone, neuronal, ectodermal, and lymphoid organs (reviewed in 1–3). The genes encoding LTβ, TNF, and LTα reside in a tightly linked loci within the major histocompatibility complex on Chromosome (Chr) 6 in humans (Chr 17 in the mouse). The receptors TNFR1, CD27, and LTβR are linked on Chr 12 (mouse Chr 6). Three other MHC paralogus genomic regions contain the related family members (Chr 19 LIGHT, CD27L, 41BBL; Chr 1 FasL, GITRL, Ox40L; Chr 9 CD30, TL1A) revealed by their conserved gene structure, transcriptional orientation, and function (4, 5). The receptors for these ligands (except FasL) are linked on Chr 1p36.

Molecular Switches: Ligands and Receptors

The signaling network in which lymphotoxins act is complex, comprising unique and shared ligand-receptor systems (Figure 1). LTα and LTβ form three distinct ligands. LTα can exist as a homotrimer (LTα3) that is exclusively secreted owing to cleavage of its traditional signal peptide, a unique feature in the TNF superfamily. LTα3, like TNF, binds two receptors, TNFR1 and TNFR2. Two membrane-anchored heterotrimers can be formed by LTβ and LTα during biosynthesis: LTα1β2 (the predominant form) and LTα2β1. LTβ, like other TNF superfamily ligands, is a type II transmembrane protein but lacks a traditional signal peptide cleavage site anchoring the bound LTα subunit to the cell surface. The LTβ subunit in the LTα1β2 heterotrimer changes the receptor binding specificity to engage with high affinity the LTβ receptor (LTβR). Although the LTα2β1 binds TNFR1, 2, and LTβR (with low avidity, mid-nM range), it is a minor form expressed by T cells ($<2\%$) and thus has no defined role. The LTβ-related ligand LIGHT, the most recently defined member of the network, binds to the herpesvirus entry mediator

(HVEM), which was discovered as an entry route for herpes simplex virus (HSV) (6). Glycoprotein D of HSV is a virokine encoded by HSV that blocks LIGHT binding to HVEM (7). LTβR is a second receptor for LIGHT (7–9). HVEM may also serve as a third receptor for LTα, although binding is relatively weak (7). DcR3 is a secreted receptor for LIGHT, Fas ligand, and TL1A (10), demonstrating a broader functionally conserved relationship among these ligands.

Targeted deletion of the LT/TNF ligands and receptors in mice has aided significantly in defining unique and complementary physiological roles associated with each cytokine system (reviewed in 11, 12). The phenotypes of mice deficient in the LT system are complex and affect multiple aspects of the immune system, including lymphoid organ development and organization and host defense systems (see Table 1). As expected for a simple signaling system, genetic deletion of the ligand or receptor is expected to give identical phenotypes, which was partially true for the LT/TNF systems. For instance, with the lymph node–deficient phenotype, LT$\alpha^{-/-}$ and LTβR$^{-/-}$ are replicas, whereas the TNF$^{-/-}$ and TNFR$^{-/-}$ mice have a full complement of LN, which clearly separated the biological processes signaled by these two systems. However, LT$\beta^{-/-}$ mice lacked most LN but retained some mesenteric LN, implying there must be another ligand for LTβR. However, LIGHT$^{-/-}$ mice had a full complement of LN, although LIGHT can

TABLE 1 Genetic deficiencies in LT$\alpha\beta$/TNF/LIGHT

	Phenotypes					
Gene deletion	**LN[a]**	**PP[b]**	**Architecture[c]**	**NK[d]**	**NKT[e]**	**DC[f]**
LTα	−	−	Disrupted	Impaired	Impaired	Migration
LTβ	−	−	Disrupted	Impaired	Impaired	Migration
LIGHT	+	+	+	+	+	+
LTβ-B[g]	+	+	Disrupted	Nr	Nr	Nr
LTβ-T[g]	+	+	+	Nr	Nr	Nr
TNF	+	−	Disrupted MZ	+	+	Maturation
LTβR	−	−	Disrupted	−	−	Migration
TNFR1	+	−	Disrupted MZ	+	+	Maturation
TNFR2	+	+	+	+	+	+

[a]Lymph nodes; LT$\beta^{-/-}$ mice have ~75% of mesenteric LN.

[b]Peyer's patches.

[c]Architecture of the splenic white pulp includes T- and B-zone segregation; marginal zone (MZ); germinal center; follicular dendritic cell network.

[d]Natural killer (NK) cell deficiency includes reduced cell numbers and enhanced tumor susceptibility.

[e]NKT cells Vα14 subset.

[f]Dendritic cells phenotype includes impairment of migration to spleen or maturation in bone marrow.

[g]LTβ conditionally deleted in B cells or T cells. LTβ-B showed partial disruption in architecture; normal for LTβ-T, but combined knockout in both B and T cells was worse than LTβ-B.

Absent, −; normal, +; not reported, Nr.

contribute to LN development, as revealed by LIGHT$^{-/-}$ LT$\beta^{-/-}$ double knockout mice. A common phenotype linking LT and TNF pathways is seen in the formation of Peyer's patches (PP), which are poorly developed or missing in some TNF/TNFR1-deficient mice as well as in LT$\alpha^{-/-}$, LT$\beta^{-/-}$, and LTβR$^{-/-}$ mice. Some collateral damage to neighboring genes may indeed have occurred by the targeting vector imposed by the tight genetic linkage of the LTα/LTβ/TNF loci. However, a comparison of mice deficient in all three ligands (TNF, LTα, and LTβ) with individually gene-deficient mice indicated that LT and TNF systems functioned largely independently but overlapped in organizing the microarchitecture of the spleen, particularly in the compartmentalization of T and B cells (13). More recent results using mice conditionally deleted for LT or TNF in T or B lymphocytes are challenging some previous assumptions, particularly in distinguishing between the roles played by LT during lymphoid organ development, homeostasis and maturation (14, 15).

The TNF-TNFR1 system provides a key element as a sentinel cytokine produced by innate recognition pathways that are involved in promoting inflammatory processes, whereas LT$\alpha\beta$ signaling is centered more in the realm of development and homeostasis of lymphoid tissue, although LTα signaling can promote the formation of tertiary lymphoid tissues at sites of chronic inflammation (16). The biology of LIGHT at present seems more prominent in regulating T cell–based inflammatory reactions, particularly in the mucosal tissue. At the same time, the evidence points to significant overlap in biological responses among these cytokines. Attempts to understand the mechanisms underlying this network at the level of signaling cascades have focused on the NF-κB family of transcription factors, which in gene-deficient mice share common phenotypes with the LT/TNF system.

SIGNAL TRANSMISSION

Receptor signaling is initiated by ligand-induced clustering of cell surface receptors. Trivalent ligands or bivalent receptor-specific antibodies function as agonists for TNFR or LTβR. The receptor aggregation model seems to apply for all members of the TNF superfamily, although for apoptosis induction by Fas ligand and TRAIL higher ordered aggregation of receptors may be required (17).

A basic framework has been assembled for TNFR1 and LTβR pathways that lead to cell death and activation of the NF-κB transcription factor family, although the mechanisms governing signaling specificity, signal relay, and kinetics of activation remain active research areas (Figure 2). The coupling of activated TNF receptors to various adaptor proteins that link to intracellular signaling pathways is a complex process. TNFR1 as a death domain (DD)–containing receptor can couple to the apoptotic cascade via TNFR-associated DD (TRADD). LTβR, TNFR2, and HVEM utilize TNFR receptor-associated factors (TRAFs), a family of zinc RING finger proteins, to connect to intracellular signaling pathways. However, TNFR1 also engages TRAF2 via TRADD, coupling it to NF-κB activation, a crucial regulatory point in cellular resistance to apoptosis. Recent experiments by Micheau

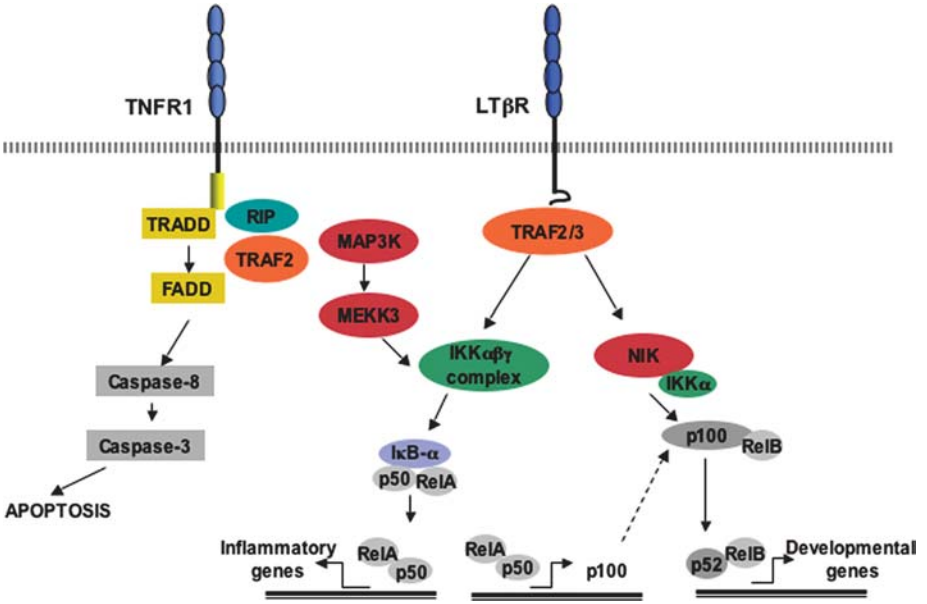

Figure 2 TNFR1 and LTβR signal transmission pathways for cell death and NF-κB activation. The death domain recruits TRADD/FADD leading to Caspase 8 activation linking TNF to the apoptotic pathway. TNFR1 can also engage TRAF2 to activate the canonical NF-κB pathway (p50/p65) via IκB degradation. This pathway controls many inflammatory genes and p100 synthesis. The LTβR induces both the canonical and the NF-κB2 pathway via the processing of p100 and formation of p52/RelB target genes.

et al. (18) have determined the importance of the FLICE inhibitory protein (FLIP) in resistance to apoptosis signaling. FLIP functions as an attenuating switch for apoptosis by displacing the FADD-Caspase 8 complex. However, FLIP expression is dependent on activation of NF-κB1/relA and transcription/translation, which are often compromised in pathogen-infected cells. Thus, the apoptotic pathway becomes the dominant default pathway in cells that are biosynthetically compromised.

The TRAF family includes six members that are related to a larger number of proteins (19), defined by a common C-terminal domain folded as a beta sandwich that form trimers. TRAFs can also contain RING finger and multiple zinc fingers typically at the N terminus, which can contribute to ubiquitinylation of substrates (20), and a coiled coil domain that acts to stabilize the trimeric structure (21). The TRAF interacting region in LTβR and other TNFR are short peptide motifs (22). The crystal structure of the TRAF domain of TRAF3 and TRAF2 provided key insight into the mechanism of receptor binding. The mushroom-shaped TRAF domain contains a peptide-binding crevice in each subunit that allows accommodation of a surprisingly large variety of sequences and conformations contained within

the myriad of receptors and regulators that bind TRAF (22). The TRAF-binding crevice may have evolved this plasticity to accommodate the large expansion of the TNFR superfamily, thereby providing a greater capacity to link to various signaling pathways. The zinc RING finger moiety appears to function as part of a ubiquitin ligase complex leading to proteosome degradation, a feature common to the activation or turnover of many components in these signaling pathways. Currently, biochemical evidence indicates that TRAF2 and 3 are important in enabling lymphotoxins to activate NF-κB. However, an unresolved conundrum remains in that genetic deletions of TRAF2 or 3 in mice do not phenocopy LT deficiency. The other TRAF members, such as TRAF5, are important for signaling by Ox40 (23), whereas TRAF6 is necessary for signaling by IL-1 receptor and Toll-like receptors (24, 25), as well as some other TNFR superfamily members including RANK and CD40 (26). In each case, NF-κB is an important target of the signaling pathway.

NF-κB is a major control point for the expression of inducible genes regulating inflammation that underlie innate and adaptive defenses. Recent results showing that distinct forms of the NF-κB family of transcription factors are activated by TNF-TNFR1 and LT$\alpha\beta$-LTβR systems have provided new insight into the differential actions of these cytokines. Moreover, these results provide evidence of a plausible mechanism for overlapping phenotypes in mice deficient in LT and NF-κB. The NF-κB family comprises five members: RelA (p65), RelB, c-Rel, NF-κB1 (p50 and its precursor p105), and NF-κB2 (p52 and its precursor p100). These proteins form a collection of homodimers and heterodimers that can function as transcriptional activators or inhibitors. The NF-κB family of transcription factors regulates hundreds of genes crucial to the development of cells and organs of the innate and adaptive immune responses (27–30). NF-κB1/RelA is most closely associated with activation by inflammatory stimuli. NF-κB1 complex is held in a latent form in the cytosol by the Inhibitors of κB (IκB), requiring the IκB kinase complex (IKK) to phosphorylate IκB, inducing ubiquitination and degradation by the proteosome and releasing the NF-κB1/relA dimer for transport into the nucleus. The IKK complex is composed of two catalytic subunits (IKKα and IKKβ) and a regulatory subunit (IKKγ, also called NEMO) and is the point of convergence of varied stimuli.

LTβR, unlike TNFR1, activates NF-κB2 by a mechanism distinct from that of NF-κB1 (31–35). The NF-κB2 pathway, which mediates the processing of p100 to p52, is dependent on the NF-κB-inducing kinase (NIK) and IKKα, but is independent of IKKβ and γ (33, 35–37). Activation of the p52/RelB pathway by LTβR signaling results in the translocation of the NF-κB2/relB dimers to the nucleus, leading to gene transcription involved in the development of lymphoid organs and maintenance of architecture in secondary lymphoid organs. Like LTβR$^{-/-}$ mice, alymphoplasia (*aly*) mice, which contain a point mutation in the TRAF-binding region of NIK required to activate the IKKα complex, and NIK$^{-/-}$ mice lack secondary lymphoid organs and have disrupted splenic microarchitecture (37, 38).

The capacity of TNFR1 to activate proinflammatory genes is relative strong when compared with LTβR (39). In part, this may be due to the ability of LTβR

to activate the IKKα-dependent NF-κB2 pathway, which can attenuate gene expression turned on by NF-κB1/relA (33, 34). The NF-κB2 pathway is slow to initiate but then is sustained (hours) compared with the rapid induction and short duration of activating NF-κB1/relA. The slow kinetics is attributed in part to a transcriptional and cotranslational processing needed by p100. That p100 synthesis is dependent on NF-κB1/relA inextricably links these two pathways together, suggesting an additional mechanism of cooperation between LTβR and TNFR1 signaling.

The phenotypes of mice deleted for various NF-κB members are complex, affecting development and immune functions. Some are lethal, no doubt due to the roles this family plays in controlling genes that determine cell survival or death. Additionally, NF-κB deficiency prominently affects responses of stromal cells coincident with the expression of LTβR. For instance, deletion of relA in mice is embryonic lethal unless crossed onto a mouse deficient in TNF-TNFR1, which results in an animal with a phenotype similar to that of a LTβR-deficient mouse: no secondary lymphoid organs and disrupted architecture (40). The complexity of protein interactions within the TNF pathway was revealed in a proteomics approach that used tandem affinity purification to isolate protein complexes associated with TNFR or known signaling molecules and identification by tandem mass spectrometry (41). As many as 241 molecular contacts were identified within the TNF pathway, confirming many basic aspects of TNF/LT signaling outlined above and adding several new components. For instance, a TRAF homologue (TRAF7) was identified as a modulator of MEKK3, a protein necessary for NF-κB1/relA activation. In the near future, the convergence of proteomic and genetic analyses should yield a comprehensive outline of the TNF/LT signaling network.

NETWORK DYNAMICS

Changes in the expression of the LT/TNF ligands and receptors among various cell types will determine the dynamics of this intercellular communication network. LT$\alpha\beta$, TNF, and LIGHT are all induced following activation of lymphocytes and monocytes via their respective recognition systems, which gave rise to the concept that these cytokines are inducibly expressed. However, more recent examination of gene expression profiles in naive mice revealed that these cytokines are constitutively expressed on lymphocytes within lymphoid organs, perhaps contributing to the homeostasis of the tissue (42, 43). Antigen-specific and -nonspecific activation of T and B lymphocytes and NK cells from peripheral blood induces LTα and LTβ transcription and protein expression (44, 45). A recent histological study revealed LTβ expressed not only in chronic inflammatory tissue on T cells and plasma cells but also on epitheloid histiocytes and multinucleated giant cells (46). LT$\alpha\beta$ expression is regulated by cytokines, including Interleukin (IL)-2, which induces LT$\alpha\beta$ expression on human T cells from peripheral blood (44); in mice

IL-4 and IL-7 cytokines and the chemokines CCL19 and CCL21 can induce LT$\alpha\beta$ expression on splenic T cells (47) (Figure 3*A*). In the spleen of naive mice, LT$\alpha\beta$ is constitutively expressed on most follicular B lymphocytes, controlled in part by CXCL13 (B lymphocyte chemoattractant); CD40-CD40L can induce expression of LTα in B cells (48) but CD4 T cells also constitutively express LT$\alpha\beta$. By contrast, the LTβR is not expressed on T or B lymphocytes or NK cells but is constitutively expressed on fibroblasts (stroma), epithelial cells, and myeloid cells (monocytes, dendritic, and mast cells) (49–51), suggesting that LT$\alpha\beta$-LTβR allows unidirectional communication between lymphocytes and the surrounding stromal and parenchymal cells. By contrast, TNF is produced by a wide array of cells, especially in response to inflammatory stimuli, but substantially by cells of the myeloid lineage. TNFR1 is broadly distributed, whereas TNFR2 is inducible on T and B lymphocytes but constitutively expressed on monocytes. Both receptors are rapidly shed from the cell surface, accumulating in plasma to significant levels during inflammatory processes. LIGHT is inducibly expressed in T cells yet is constitutively expressed by myeloid cells, primarily immature DC, a pattern intermediate to LT$\alpha\beta$ and TNF (7, 52). HVEM is broadly distributed within the lymphoid and nonlymphoid compartment, although a systematic study has not been performed (53).

The physical location of these ligands may also contribute to the network dynamics. LTβ is not cleaved into a soluble form, and thus the LT$\alpha\beta$ complex remains cell-associated, which dictates that signaling via the LT$\alpha\beta$-LTβR system will require cell-to-cell contact. TNF, LIGHT, and LTα are active in their membrane-anchored and secreted positions, theoretically acting at locations distant from the site of production. However, an additional control mechanism, the presence of soluble decoy receptors including shed forms of TNFR1, TNFR2, and DcR3, may limit the bioavailability of TNF, LTα, and LIGHT. The dynamics of these regulatory controls will depend on the concentrations and relative avidity of the ligand receptor pair. TNF and LTα bind cellular receptors with high affinity (K_d = mid-pM), whereas engineered soluble forms of LT$\alpha\beta$ and LIGHT interact with their cell-bound receptors with moderate avidity (K_d = low nM), suggesting that even moderate avidity for a diffusion-restricted ligand is sufficient to form stable signaling complexes. By contrast, the avidity of LTα for HVEM is low (mid-nM), suggesting that physiological levels of these reactants may not be sufficient to initiate signaling, although high local concentrations may conceivably achieve levels above the threshold required for signaling.

Regulatory mechanisms affecting transcriptional induction and stability, and restricted cellular patterns of expression, among other mechanisms, also contribute to signaling specificity (reviewed in 54). The regulation of TNF transcription requires a multicomponent enhancesome that varies with the specific stimulus (55, 56). The molecular regulation of LTα, LTβ, and LIGHT gene expression is just beginning to be dissected (57, 58), but will become crucial if their polymorphic alleles are linked to disease pathogenesis.

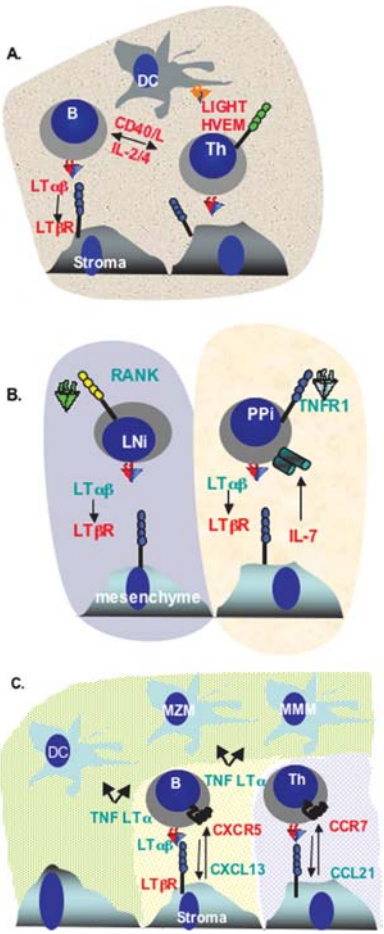

Figure 3 Lymphotoxin and TNF networks form between multiple cell types. (*A*) T and B cell expression of LT$\alpha\beta$ is regulated via interleukins 2 and 4 and the CD40 system. LIGHT is constitutively expressed on DC by an unknown mechanism. T and B cells engage stroma expressing the LTβR, which forms appropriate microenvironments. (*B*) The development of lymph nodes and PP require distinct progenitors: the LN inducer requires RANK ligand to induce LT$\alpha\beta$ expression, whereas the PP inducer expresses LT$\alpha\beta$ in response to IL7 or TNF. The inducer cells interact with LTβR expressing lymphoid-specific mesenchymal cell. (*C*) Chemokine circuits form between lymphocytes and stroma. Depicted are cellular interactions in the architecture of white pulp in the spleen dependent on LT/TNF signaling. The marginal zone (*green*) contains marginal zone macrophages (MZM) and metallophilic macrophages (MMM). Dendritic cells (DC) require LT signaling for emigration to the spleen. B and T lymphocytes are compartmentalized in discrete areas in the white pulp [B cell follicle (*yellow*) and T cell zone (*blue*)] through the reciprocal induction of LT expression on lymphocytes by chemokines and chemokine expression by stromal cells via the LTβR.

THE NETWORK IN ACTION

Lymphatic Organ Formation

The formation of secondary lymphoid organs is instructive of a signaling pathway involved in mammalian organ development that includes the LT signaling network. The development and homeostasis of microenvironments in secondary lymphoid tissue are absent in mice deficient in LTα, LTβ, and LTβR (reviewed in 59, 60). At least two cell types are necessary for secondary lymphoid organ formation, the LT$\alpha\beta$ expressing "inducer" cell (a $CD4^+CD3^-$ IL7Rα^+ mononuclear cell) and an embryonic stroma organizer cell expressing the LTβR (reviewed in 59) (Figure 3*B*). The PP inducer is distinct from the LN inducer cell in respect to the requirement for IL-7 and the RANK system (26, 61). The LN- or PP-deficient phenotype is observed in several other knockout mice, delineating the framework of a signaling pathway involved in lymphoid organ development. Ikaros, ID2, and RORγ are transcriptional regulators essential for lymphocyte progenitors to develop, and recent results indicate that RORγt is specifically expressed in the inducer cells (62). Fox 1 is needed for LTβR expression in PP (63). Mice deficient in certain members of the NF-κB activation pathway, including NIK, IKKα and Rel B, have deficient lymphoid organogenesis (64).

An interesting but perplexing discordance between genetic and biochemical evidence arose with the TRAF adaptors. TRAF2-, 3-, or 5-deficient mice have secondary lymphoid organs, yet, unexpectedly, LN deficiency was found in $TRAF6^{-/-}$ mice even though LTβR does not utilize TRAF6. Moreover, the TRANCE/RANK (TNFSF11A) system, which utilizes TRAF6 as an adaptor, when genetically deleted, also revealed an LN-deficient phenotype (26, 65). In this case, the experimental results obtained by Yoshida and colleagues indicated that the RANK/TRAF6 pathway was required for the induction of LT$\alpha\beta$ on the LN inducer cell, thus accounting in part for the discordance with the biochemical data (LTβR does not bind TRAF6) (61). IL-7 and TNF were also shown to induce LT$\alpha\beta$ on PP inducer cells, which may explain why some TNF/TNFR1 mice have defects in PP development (66). These results provide another example of the concatenation of the LT network with other members of the TNF superfamily.

LT-Chemokine Circuits in Tissue Architecture

The spleen (60), nasal lymphoid tissue (67), and uterine aggregates (68) develop independently of the LT$\alpha\beta$-LTβR network, yet the organization of the microarchitecture in these secondary lymphoid tissues depends on LT signaling. LT-dependent microarchitecture includes the integrity of the marginal zone and the presence of MZ macrophages, the function of stromal cells that allow recruitment and clustering of B cells in the follicle, T cell migration into the T cell zone, creation of follicular dendritic cell (FDC) networks, and the formation of germinal centers during immune responses (reviewed in 60, 69). In the spleen, the tissue-organizing chemokines intersect with the LT/TNF network to form a signaling amplification

circuit between lymphocytes and stroma. The tissue-organizing chemokines include CXCL13 (B lymphocyte chemoattractant), CCL21 (secondary lymphoid chemokine), and CCL19 (EBV-like chemokine), where expression levels are decreased in LT-null mice (42). B cells play a vital role in forming the FDC network as well as the T cell zone, compartmentalizing lymphocytes in the splenic white pulp. A circuit is initiated by $CXCR5^+$ B cells sensing CXCL13 produced by $LT\beta R^+$ stromal cells, which induces $LT\alpha\beta$ expression on B cells. B cell-to-stromal cell contact then promotes stromal secretion of CXCL13 via $LT\alpha\beta$ and $LT\beta R$, thereby completing the circuit (42, 47) (Figure 3*C*). As B cells emigrate to the blood the expression of $LT\alpha\beta$ is lost, but as they reenter the B cell areas in response to CXCL13 they regain surface expression (42).

Similar circuits may be involved in maintaining the T cell zone through the action of the CCR7-binding chemokines, CCL19 and CCL21, produced by gp38 expressing stromal cells (47, 70). Recent results revealed that $LT\beta R$ signaling induces CCL20 expression in mucosal cells (71), suggesting that a parallel circuit could be formed between $LT\alpha\beta$/LIGHT-$LT\beta R$ and CCL20-CCR6 (72, 73). Moreover, these tissue-organizing chemokines are expressed in nonlymphoid tissues, including tumor and pancreatic tissue, upon initiation of $LT\beta R$ signaling (16, 43).

Cyster and colleagues identified the LT-chemokine circuit as a homeostatic mechanism that maintains the microarchitecture of the spleen (42, 47, 74), yet some of the associated phenotypes may be intertwined with neonatal developmental/maturational processes. Cellular reconstitution of LT-deficient mice with LT-sufficient wild-type bone marrow restores FDC differentiation but fails to restore chemokine levels (75). Conditional deletion of $LT\beta$ from B or T cells provided another approach in distinguishing developmental from homeostatic processes (15). Lymph nodes and PP develop in the conditional knockout (14) owing to the separate lineage of the inducer cell from B and T cell lineages (59). $LT\beta$ expression by B lymphocytes is important for proper marginal zone structure and FDC networks, yet when $LT\beta$ was conditionally deleted in both B and T cells, disruption of the splenic microarchitecture became even more exaggerated (14). Enforced expression of LIGHT in T cells in $LT\alpha^{-/-}$ mice restored CCL21 but not CXCL13 expression, yet corrected T and B cell segregation (76). Thus, B and T cell expression of $LT\alpha\beta$, TNF, LIGHT, and perhaps others may contribute to the regulation of the tissue-organizing chemokines that impart selected features of lymphoid tissue microarchitecture.

Work by Ruddle et al. helped to establish the idea that sites of lymphocyte aggregates in chronically inflamed tissue, termed lymphoid organ neogenesis, is controlled in part by TNF/$LT\alpha$ and $LT\alpha\beta$ signaling (16, 74). TNF and $LT\alpha\beta$ are needed for the formation of granulomas that contain persistent bacterial pathogens (46, 77–80). These results suggest that modulation of the TNF/$LT\alpha\beta$/LIGHT network can be used to manipulate chemokine networks affecting inflammation and immune responses.

Deficiency in LT/TNF network in mice affects several other components of the innate and adaptive immune systems, including DC, NK cells, NKT cells, as

well as differentiation of T and B cells. The differentiation of DC from bone marrow precursors requires the TNF/LTα-TNFR1 system, whereas DC recruitment to secondary lymphoid organs requires LTβR signaling (81, 82). In LT$\alpha^{-/-}$ mice, NK cells fail to differentiate into effector cells capable of restricting metastasis of transplanted tumor cells (83–85). The differentiation of NKT cells is dependent on LTβR signaling via the NIK-NF-κB2/relB pathway (86). The functions of T and B cells are altered by deprivation of LTβR signaling; however, LTβR is not expressed on T or B cells, indicating the mechanisms are indirect, presumably via stromal cell functions. This presumption is supported by results showing that FDC networks are dependent upon continuous LT$\alpha\beta$-LTβR signaling (87, 88), which can be disrupted by LTβR-Fc decoy (89). The disruption of FDC networks influences the ability of B cells to form germinal centers, affecting antibody production to specific T cell–dependent antigens. Although T and B cells appear to differentiate to normal numbers and appropriate subclasses, recent evidence is teasing out the influence of LTβR signaling on thymic medullary epithelial cell differentiation (90). In part, the control of thymic autoimmune regulator (AIRE) expression through LTβR signaling provides a critical pathway for the development of central tolerance (91). These findings reiterate the concept that LT$\alpha\beta$-LTβR signaling provides essential lines of communication between lymphocytes and stromal cells in forming crucial tissue microenvironments.

NETWORK SUBVERSION BY PATHOGENS

It has long been recognized that viruses interfere with cytokine communication pathways. Several viral families including herpes-, adeno-, papova-, and poxviradae have evolved strategies specifically targeting the LT/TNF network. Undoubtedly, the cellular survival and apoptotic pathways regulated by the TNF superfamily provide strong selective pressures for pathogens to evolve specific counter strategies that aid pathogen replication and dissemination (reviewed in 92–95).

Molecular Strategies

The most obvious viral regulators of the TNF/LT network include structural homologues from large DNA viruses, including poxviridae and herpesviruses. Historically, the first example of a viral gene product inhibiting TNF was gleaned from the genome of rabbit poxvirus, which contains an orf encoding a type II TNFR ortholog (96). A dramatically attenuated infection occurs following deletion of the MX-T2 gene, establishing the relevance of this mechanism to viral pathogenesis (96). The diversity and conservation of TNF inhibitors found in poxvirus imply an important role in pathogenesis, yet poxviruses target many cytokine signaling pathways, such as IFN and chemokines, as part of their seemingly global attack on signaling pathways of the innate and adaptive defense systems (97).

Herpesviruses cause lifelong infections and establish latent states maintained by competent immunity, although they sporadically reemerge in immune-competent

host and become virulent opportunistic pathogens in the immune suppressed. The genomes of herpesvirus also contain a collection of immune modulators, including several that target the LT/TNF network. HSV (αherpesvirus) enters cells through binding of viral envelope glycoprotein D (gD) to HVEM (6), one of several HSV entry receptors (98). Crystallographic analysis of the gD-HVEM complex reveals that gD binds to a discrete region in the first cysteine-rich domain near the N terminus, albeit on the opposite face of the receptor predicted to engage the cellular ligand LIGHT or LTα (99), yet gD can compete for HVEM binding to membrane-anchored LIGHT (7). The Epstein Barr virus (γ-herpesvirus)–encoded latent membrane protein 1 (LMP1) binds TRAF adaptors (100) and activates both NF-κB1 and NF-κB2 complexes (101), behaving like a constitutively activated receptor (e.g., CD40, BAFFR) that promotes B cell survival and differentiation. Conversely, HHV8 and related γ-herpesvirus contain orthologs of FLIP, which disrupt Caspase 8 activation but also mediate NF-κB activation (102). A β-herpesvirus, human cytomegalovirus (CMV), expresses a TNFR ortholog (UL144 orf), which is closest in sequence to the extracellular domain of human HVEM and TRAIL-R2, although none of the known cellular ligands bind UL144 (103). Antibodies to UL144 ectodomain are detected in the serum from CMV-positive patients, although hypervariability in UL144 sequences does not directly correlate with virulence in humans (104); to date a functional role has not been uncovered.

Collectively, these examples represent viral mechanisms targeted specifically at the LT/TNF network. These specific mechanisms are set within a broader strategy evolved by herpesvirus that targets many other aspects of innate and adaptive immunity, necessary in order for the pathogen to successfully occupy a niche in the vertebrate host without causing overt disease. Multiple strategies targeted at NK and T cell recognition systems, effector molecules, and cytokine signaling pathways are known for cytomegalovirus (for example, see 105). The persistence of CMV and other herpesviruses in immunocompetent hosts suggests that the balance of resistance and countermeasures must be critically maintained. The molecular processes involved in the maintenance of host-virus coexistence are anything but passive, as all herpesviruses readily reactivate in patients with compromised immune systems and result in increased morbidity.

The LT/TNF-Interferon Axis

The mechanisms controlling host-virus coexistence are not well defined, but recent evidence suggests a role for interferons (106) and LT/TNF systems (107), potentially functioning as a cytokine axis. TNFR1 and LTβR signaling efficiently arrests CMV replication in human dermal fibroblasts without inducing cell death, whereas activation of Fas and TRAILR are completely ineffective at inducing death of infected cells or restricting virus replication (107). The mechanism underlying the arrest of CMV replication involves the cooperative induction of IFNβ mRNA, which inhibits virus replication after immediate early viral gene expression but

before virion release. Virus spread to adjacent cells is also blocked. HCMV infection normally suppresses the IFNβ response, eventually inducing cytopathic effects that lead to cell death. However, LTβR or TNFR1 activation of an NF-κB-dependent pathway precedes or overcomes the virus imposed IFNβ blockade. IFNβ blocks virus replication and protects the cell from cytopathic effects, yet the viral genome remains in the cell. Upon cessation of IFN signaling, virion production reinitiates. This observation may represent a molecular mechanism of cooperation between host and pathogen that may help establish persistence. It is not known if this pathway is important in controlling reactivation from latency. Nonetheless, the LTβR/TNFR connection to the IFNβ system may have important implications in interpreting clinical outcomes of TNF inhibitors in human autoimmune diseases.

Experimental Animal Models

The role of the LT network in host defense against viral, bacterial, and parasitic infections in animal models depends in part on the specific pathogen (Table 2). In LT$\alpha^{-/-}$ mice, for instance, the ability to control infection with mouse γ-herpesvirus (MHV68) is not overtly compromised (108), whereas a modest increase in susceptibility to HSV-1 was observed with an underlying reduction in the ability of $CD8^+$ T cells to differentiate into effector cells (109). By contrast, LTα-deficient mice were highly susceptible to mouse CMV owing to the inability to control the initial infection, suggesting compromised innate defenses (107). Host defense may be compromised in LT-deficient mice from a general inadequacy due to structural defects in lymphoid organs or from a lack of signaling required during infection (effector responses), or both.

Bacterial defenses also require the LT signaling network. Host responses to pulmonary infection with *Mycobacterium tuberculosis* were significantly impaired in LTβR$^{-/-}$ mice but not in LIGHT$^{-/-}$ mice, indicating LT$\alpha\beta$-LTβR signaling is crucial in host defenses to this intracellular organism (80). This study by Ehlers et al. pointed to a defect in macrophage-expressed nitric oxide synthetase as a potential mechanism missing in LTβR$^{-/-}$ mice. In slight contrast, LT$\beta^{-/-}$ mice were not significantly impaired to *M. tuberculosis*, although LT$\alpha^{-/-}$ mice were susceptible (79). Chimeric mice constructed with LT$\alpha^{-/-}$ bone marrow revealed that lung granulomas were abnormal and lacked T cells normally required to corral infected macrophages (79). This result implies that LTα is required during the response to the infection and that developmentally determined lymphoid tissues are less important for this organism. Using a pharmacologic approach, Lucas et al. (78) demonstrated that LTβR-Fc increased susceptibility of mice to *Mycobacterium bovis* and that this treatment exacerbated the susceptibility with concurrent with TNFR-Fc decoy treatment, indicating independent but cooperating action of these ligands in host defense to this bacterial pathogen. Effective defenses to some pathogens depend upon LT-dependent architecture [such as lymphocytic choriomeningitis virus (LCMV)] (110), whereas the absence of lymph

TABLE 2 Lymphotoxins in host defense: mouse models

Pathogen[a]	Mouse model[b]	Susceptibility	Mechanism	Reference
Herpesvirus:				
MHV68	LT$\alpha^{-/-}$	Minimal	Nd[c]	(108)
HSV-1	LT$\alpha^{-/-}$	Increased	Decreased effector $CD8^+$ T cells	(109)
MCMV	LT$\alpha^{-/-}$	Increased	Nd	(107)
MCMV	LTβR-Fc Tg	Increased	Poor innate defenses	(107)
LCMV	LT$\beta^{-/-}$; LT$\alpha^{-/-}$	Increased	Defective architecture	(110, 176)
LCMV	LTβR-Fc	Decreased	Decreased $CD8^+$/IFNγ	(177)
Theiler's virus	LT$\alpha^{-/-}$; LTβR-Fc	Increased	Defective architecture	(178)
Influenza	LT$\alpha^{-/-}$	Minimal	Nd	(111)
M. tuberculosis	LTβR$^{-/-}$	Increased	NO_2 synthase decreased	(80)
M. tuberculosis	LT$\alpha^{-/-}$	Increased	No T cells in granuloma	(79)
M. bovis	LTβR-Fc	Increased	Poor granuloma formation	(78)
Listeria m.	LTβR$^{-/-}$	Increased	Nd	(80)
Leishmania m.	LT$\beta^{-/-}$	Increased	Defective architecture	(179)
Toxoplasma g	LT$\alpha^{-/-}$	Increased	NO_2 synthase decreased	(180)
Plasmodium b.	LT$\alpha^{-/-}$	Decreased	Decreased LTα-dependent inflammation	(181)

[a]Virus: mouse γ-herpesvirus-68 (MHV68); herpes simplex virus (HSV1, α-herpesvirus); mouse cytomegalovirus (MCMV); lymphocytic choriomeningitis virus, (LCMV). Bacteria: *Mycobacterium*; *Listeria* monocytogenes. Parasite: *Leishmania* major; *Toxoplasma gondii*; *Plasmodium berghei.*

[b]Studies conducted in gene-deficient mice ($^{-/-}$); LTβR-Fc Tg, mice expressing LTβR-Fc as a transgene; LTβR-Fc, mice injected protein.

[c]Nd, no data.

nodes and splenic architecture seem largely unimportant for others (influenza) (111).

TNF- or TNFR1-deficient mice show a pronounced susceptibility to bacterial pathogens (112) but surprisingly minimal deficiency to several viruses (113). The TNF system in resistance to LCMV is complex. TNFR1 participates in the clearance of virus, but it is also necessary for down-modulation of effector T cells and inflammation in the lung and liver following recovery (114). The ability of TNF-TNFR1 and Fas-Fas ligand systems in controlling the persistence of effector T cells (antiinflammatory) in tissues following herpesvirus infections may be

particularly relevant to anti-TNF therapies in autoimmune diseases with a potential underlying infectious etiology. Although the influence of the LIGHT system on host defenses has not been systematically studied, it is reasonable to predict that unique roles may be revealed by a specific pathogen. LT-deficient mice are not globally impaired in their immune responses to all pathogens; rather, specific pathogens during their coevolution with a vertebrate host have developed specific niches that may be dependent on the LT/TNF/LIGHT signaling network. In clinical situations where TNF/LT inhibitors are administered, specific pathogens might be expected to predominate as side effects to such therapy.

NETWORK CENSORING

Blockade of the TNF/LT/LIGHT network can modulate autoimmune diseases in mice and humans. In mice, collagen-induced arthritis (CIA), inflammatory bowel disease (IBD), and experimental autoimmune encephalomyelitis (EAE) represent three antigen-specific T cell–mediated inflammatory conditions often used as models for human diseases. The immunoregulatory roles of the LT$\alpha\beta$/LIGHT network have been investigated in several experimental animal models, with somewhat differing outcomes (recently reviewed in 115).

Collagen-Induced Arthritis

CIA, a disease with similarities to human RA, is initiated following immunization with chick type II collagen, which results in the forced recognition of self antigen. Arthritis did not develop in mice treated with LTβR-Fc several weeks prior to immunization with collagen (116). Milder disease developed if animals were treated with LTβR-Fc at the time of immunization, and some disease-modifying results were seen in established disease (116). The mechanism for reduced pathogenesis of disease following LTβR treatment may lie in alteration of the lymphoid microenvironment within the draining lymph node because, in both the lymph nodes and spleen, FDC networks were eliminated, resulting in decreased autoantibodies to collagen-II. However, LT$\alpha\beta$ and LIGHT could also be affecting other parameters of pathogenesis, including innate components of early recognition, T cell differentiation, and chemokine production required for the generation of an immune response.

Inflammatory Bowel Disease

The LT$\alpha\beta$/LIGHT-LTβR network is emerging as a critical signaling pathway in the gut and highly relevant to intestinal inflammatory disease in humans, including Crohn's disease (reviewed in 117). The biologic functions of LTβR are critical to mucosal immune responses and emerged as a key element in IgE (118) and IgA production (73, 119). Treatment of mice with LTβR-Fc or TNFR-Fc decoys blocked T cell–driven intestinal inflammation in mouse models of IBD, such as

CD45RBhi $CD4^+$ T cell–reconstituted SCID and the bone marrow–transplanted tg26 models (120), Th2-induced inflammatory response to hapten (121) and DSS-induced colitis models (122). Constitutive expression of LIGHT as transgene in mouse T cells induced chronic inflammation that specifically targets the intestine and presents with patterns of tissue destruction similar to those of human Crohn's disease (123, 124). In addition, although absent in the wild-type mice, transgenic expression of DcR3, a soluble regulator of LIGHT, TL1A, and Fas ligand, protected against diabetes (125). In humans, LIGHT is a candidate for the Crohn's disease susceptibility locus found on chromosome 19p13.3 (126); it was recently reported to be differentially regulated in the intestinal compartment and capable of inducing proinflammatory cytokine production by gut T cells (127). Thus, both human data and animal models suggest that TNFR/LTβR signaling systems may be important regulators of mucosal inflammation and immune function.

Experimental Autoimmune Encephalomyelitis

EAE is a T cell–mediated demyelinating disease that is induced in animals by immunization with myelin-basic protein in adjuvant. A role for the LT/LIGHT system in EAE has been controversial (128). Pertussis toxin, often used to induce blood-brain barrier permeability in some animal models of EAE, also blocks G protein–coupled chemokine receptor signaling, thus potentially disrupting the LT-chemokine circuit and nullifying the effect of the LTβR-Fc decoy. To circumvent such potential masking, Gommerman et al. employed models of EAE independent of the pertussis toxin, which revealed significant efficacy of LTβR-Fc in preventing paralysis (129). At the cellular level, treatment of mice with LTβR-Fc resulted in impaired secondary T cell responses to EAE autoepitopes, but there was no inhibition of T cell priming or clonal expansion, suggesting a role for LT$\alpha\beta$ in peripheral T cell differentiation (129). However, the regulatory effects of LT$\alpha\beta$/LIGHT on T cell function may also include additional indirect mechanisms, given the distribution of receptors and the complexity of dependent functions such as chemokine-directed migration and maintenance of lymphoid architecture.

IN THE CLINIC

The TNF/LTα system is now well established as an effective target to control inflammatory processes in certain human autoimmune diseases, such as rheumatoid arthritis (RA), but not others, such as MS (reviewed in 130–132). Although generally safe, TNF therapy is not without side effects, which include a small but increased risk of infectious diseases. The issue of increased incidence of non-Hodgkin's lymphoma is debated but occurs near the levels expected in patients with RA, who have a higher incidence than the general population (133). Moreover, differences in the efficacy of several TNF inhibitors (e.g., IBD) suggest multiple

mechanisms of action. To a certain degree, the clinical results reaffirm prevailing paradigms in which the TNF/LT network functions in inflammation; however, some clinical experiences with these inhibitors were unexpected and may challenge current paradigms envisioned for some autoimmune diseases. Our current paradigms see RA, IBD, and MS as multifactorial, immunological diseases with significant T cell–driven inflammation. All three human conditions have unknown etiologies, with underlying genetic factors that contribute in poorly defined ways to pathogenesis. However, the use of molecularly defined drugs with well-understood mechanisms of action provides a reasonable real world experimental database of information with which to examine the role of TNF and LTα in the pathology of these human autoimmune diseases.

Two major types of drugs—anti-TNF neutralizing antibody (134), generically known as infliximab, and a chimera decoy receptor comprised of the TNFR2 ectodomain and the Fc of human IgG1, etanercept (135)—show dramatic efficacy and are approved for use in treating patients with RA (Table 3). These drugs competitively inhibit receptor binding by the respective antigen or ligand constituting distinct yet overlapping mechanisms of action. Infliximab recognizes an antigenic epitope on human TNF in either membrane or soluble form, but does not cross-react with LTα. Likewise, etanercept binds both membrane and soluble TNF, but also engages with high affinity to LTα in its secreted homotrimeric form, a feature distinguishing it from infliximab. Neither drug binds to the membrane LT$\alpha 1\beta 2$ or LIGHT, although the LT$\alpha 2\beta 1$ complex, which is a minor form expressed by T cells, can bind to either TNFR1 or TNFR2, and thus can interact with etanercept (7, 136, 137).

At least theoretically, the differences in ligand specificity between infliximab and etanercept could distinguish roles for LTα and TNF in human disease pathogenesis. However, evaluating the clinical results is not so straightforward because these reagents may have additional mechanisms of action in vivo. Infliximab has been shown to activate complement and engage cellular Fc receptor–bearing cells when bound to TNF-expressing cells (138–140). Thus, in vivo the monoclonal

TABLE 3 Features of TNF inhibitors used in the clinic

Name	Trade name	Molecular form	Target	Mechanism
Infliximab	Remicade™	IgG1 mouse-human chimera	Human TNF	Competitive antagonist; cell elimination
Adalimumab	Humira™	Human IgG1	Human TNF	Competitive antagonist; cell elimination
Etanercept	Enbrel™	TNFR2 (p75)-Fc IgG1 chimera	TNF/LTα	Competitive antagonist
Lenercept		TNFR1(p55)-Fc IgG1 chimera	TNF/LTα	Competitive antagonist

antibody to TNF can also eliminate cells expressing membrane TNF, including activated T cells or macrophages; etanercept does not appear to have these secondary interactions. Additional considerations include intrinsic binding affinities and avidity of the drugs for their ligands, competing endogenously produced soluble receptors; and antibodies directed to the drugs themselves, as well as pharmacologic parameters associated with biologicals (half-life, bioavailablity, etc.) and concurrent immunomodulating therapy. Significant clinical experience using these TNF/LTα inhibitors has accumulated over the past few years and has generated an informative literature and database. The clinical data originate from a variety of sources, ranging from controlled clinical trials with statistical significance to those with less statistically robust sources, including open-label extension studies, case reports, and spontaneous adverse event reporting (141).

Most strikingly, the results of controlled clinical trials indicate that antibodies to TNF and the decoy receptor beneficially impact human RA through control of inflammation, tissue destruction, and improvement of function (142, 143). These results are certainly consistent with various animal models demonstrating TNF as a major cytokine in regulating inflammation and that blockade of TNF prevents joint destruction in experimental animals (144). However, in about one third of patients with RA neither of these drugs has efficacy (for review see 130). The basis underlying this nonresponsiveness in some populations is unclear, but the implication that other TNF family members may be involved has not been overlooked. Preclinical investigations of LT$\alpha\beta$ and LIGHT are in fact in progress. Given the foregoing assumptions surrounding the clinical evidence, the overall results implicate TNF as a significant factor in RA, and perhaps a less important role for LTα. However, a recent case report of a patient refractory to treatment with infliximab but responsive to LTα and TNF-blocking etanercept challenges that conclusion (145). Furthermore, LTα expression was present in biopsied joint tissue, suggesting that LTα may have a role in some cases of RA.

Perhaps more telling is the evidence arising from diseases and side effects where these TNF inhibitors differ from each other, as in iIBD (Table 4). Anti-TNF antibody is approved for use in treating Crohn's disease and is beneficial for a subset of

TABLE 4 Response of human autoimmune diseases to cytokine biologicals

	Treatment[a]		
Disease	**Anti-TNF (infliximab)**	**TNFR2-Fc (etanercept)**	**IFNβ (IFNβ-1b)**
Rheumatoid arthritis	+	+	−
Crohn's disease	+	−	−
Multiple sclerosis	CI	CI	+

[a] +, approved for use; −, no efficacy reported; CI, contraindicated.

Crohn's patients, but leaves another substantial nonresponsive subset, reminiscent of the response profile in RA (146). In contrast, the decoy receptor has not shown significant efficacy in IBD (147), although one early report indicated etanercept mediated a decrease in C-reactive protein, a biological marker for inflammation in some patients with Crohn's disease (148). Is the difference between these drugs in Crohn's disease due to differences in TNF and LTα biological activities in the mucosa, or are the mechanisms of drug action distinct? Secondary mechanisms other than TNF-blocking activity are reported for infliximab including activating complement, FcR, and apoptosis (139, 140), which could eliminate specific subsets of effector cells expressing TNF and would undoubtedly have a profound antiinflammatory action. However, similar anti-TNF antibody constructs, which do not induce apoptosis, can still effectively abrogate disease (147).

TNF is also required to suppress inflammation, likely by elimination of activated T cells (see 149, 150 for discussion). Hence, another plausible explanation is that neutralizing TNF disrupts the antiinflammatory action of TNF, which may outweigh its proinflammatory action in the intestine. Thus, etanercept may lose efficacy in this context, whereas infliximab specifically eliminates an "activated" lymphocyte subset and thereby augments the antiinflammatory action of TNF. An alternate hypothesis suggests that LTα may be involved in attenuating TNF function in the intestine. Here, tissue culture models indicate that LTα acts as a partial agonist when compared with TNF (151) and also has the potential to engage another receptor (HVEM), although the molecular mechanism for LTα partial agonist effect is not yet defined. Of interest is the discordance with mouse models of intestinal inflammatory disease, where both TNFR and LTβR decoys were able to suppress T cell–mediated inflammation (152). This discordance with the animal models suggests that the mechanism(s) of action of infliximab, other than TNF blockade, may underlie this difference with etanercept. However, the clinical results do not rule out other contributing factors, such as bioavailability and additional pharmacologic parameters, which might account for the differences in efficacy between the antibody and decoy receptor.

Another clinical situation that distinguishes antibody from decoy receptor is reactivation of *M. tuberculosis*. Although both etanercept and infliximab therapies are associated with increased incidence of some infectious diseases, there is a stronger link between infliximab treatment and reactivation of latent tuberculosis (153). Animal models strongly indicate that the TNF-TNFR1 system plays a role in controlling granuloma formation crucial for preventing *Mycobacterium* reactivation (154). Antibody-dependent elimination of TNF-expressing effectors cells (macrophages and T cells) would incur loss of several other effector mechanisms that may participate in controlling granuloma formation (such as LT$\alpha\beta$ system), and thus higher rates of mycobacterium reactivation might be expected. The finding that both drugs show increased incidence of infectious diseases including *Mycobacterium* and some other organisms associated with chronic/persistent infections is consistent with the roles of TNF and LTα in host

defenses. Fortunately, prescreening patients for latent tuberculosis and antibiotic treatment can alleviate this side effect of TNF therapy.

Anti-TNF therapy does not improve survival in patients with acute bacterial sepsis (155), although animal models showed that endotoxin shock was controlled by TNF inhibitors (156), a distinction attributed to infection with a replicating pathogen versus treatment with sterile toxin. Both infliximab and etanercept are contraindicated for patients with MS, based in part on the unexpected symptoms of demyelinating disease (paresthesia, optic neuritis, and confusion) developing in people with quiescent MS and new-onset cases of demyelinating disease, which reversed upon drug removal (157) (Table 4). Another TNF decoy receptor, lenercept (composed of TNFR1-Fc decoy) exacerbated symptoms in patients with MS. In a controlled phase II study, patients with relapsing-remitting MS who were treated with lenercept showed a significant exacerbation of brain lesions when compared with placebo (158). These clinical results stand in contrast to that predicted from experimental animal models examining the acute phase of EAE, which showed that TNF inhibitors could effectively block antigen-induced inflammation, although the antiinflammatory properties of TNF may be compromised simultaneously (159). That three inhibitors of TNF/LTα are linked to exacerbation of demyelinating disease in humans suggests that their common mechanism of action, blockade of TNF, is influencing pathogenesis.

What plausible mechanisms might account for this discordance in human and experimental animal models? An important finding is the efficacy of the IFN system in the treatment of MS (160). Human IFN-β-1b, (Betaferon^{TM}; Betaseron^{TM}) is effective in treating patients with relapsing-remitting forms of MS (161). The mechanism of action of IFNβ in MS is not understood, although its antiviral actions remain a highly plausible explanation. From tissue culture and experimental animal models, IFNβ is recognized as the sentinel mediator of innate defenses, primarily to viral pathogens, that induces a generalized nonpermissive state for viral replication (106, 162). IFNβ is also essential for amplification of the IFNα cascade, as well as hundreds of other genes with potent antipathogen and immunomodulatory activities (163).

The evidence that TNF/LT network forms a crucial link to the IFN responses system that effects host defense (107) provides an intriguing hypothesis in view of the findings that TNF/LT inhibitors can exacerbate MS. This hypothesis necessarily raises the issue of whether an infectious agent plays a significant role in MS, a hypothesis long considered but unproven because of the lack of definitive results. Accumulating evidence has identified human herpesvirus 6 (HHV6, a β-herpesvirus) as a possible causative agent, although causality remains a controversial issue because of the ubiquitous prevalence of HHV6 (prevalence in the population may as high as $>90\%$) (see reviews 164–167). Evidence for HHV6 in MS includes increased frequency of detection of viral genomes in MS plaques and blood (168–171) and decrease in new lesions in MS patients treated with antiherpesvirus drug (172). Moreover, T cells crossreactive to myelin basic protein peptides and HHV6 antigens have been identified (173), and differential antibody

responses to HHV6 are detected in MS patients (174). HHV6 is sensitive to IFNβ in tissue culture models (175), suggesting that the regulation of IFNβ by LTα/TNF observed with human CMV may be operative with HHV6.

These clinical results are consistent with the notion that TNF/LT and IFN systems are important cytokines modulating the pathogenesis of MS. Plainly, MS could be exacerbated if TNF/LTα inhibitors disrupt the production of IFNβ in response to HHV6, allowing the virus to transiently escape immune control. However, other significant disposing factors must contribute to the control of HHV6 because the prevalence of HHV6 is high, although demyelinating syndrome is rare in patients treated with infliximab or etanercept. Disruption of the TNF/LT pathway may expose such host predisposition, leading to enhanced viral reactivation and antigen expression in the brain, and thus increasing the probability of tissue damage and consequent loss of tolerance. Concurrent IFN treatment would inhibit viral functions and potentially restore a balanced host-pathogen interaction.

Perspective

The clinical trials and experiences directed at altering the TNF/LTα network provide real world data upon which the accuracy of our paradigms of immune function can be tested. The dramatic clinical results with TNF inhibitors are inspiring and continue to drive development of additional disease-modifying drugs by manipulating cytokine pathways, although the results are equally sobering given that a significant fraction of patients are not responsive to TNF inhibitors. Likewise, situations in which TNF/LTα inhibitors are inadequate offer challenges for the immunopathological paradigms currently employed and can rationally offer new directions toward clinical relevance.

APPENDIX

Abbreviations used: CMV, human cytomegalovirus; DC, dendritic cells; DD, death domain; FDC, follicular dendritic cell; HHV6, human herpesvirus 6; HSV, herpes simplex virus; IκB, Inhibitors of κB; IKK, IκB kinase complex; IL, interleukin; LCMV, lymphocytic choriomeningitis virus; LIGHT, LT-related inducible ligand that competes for glycoprotein D binding to herpesvirus entry mediator on T cells; LMP1, latent membrane protein 1; LT, lymphotoxins; MMM, metallophilic macrophages; MS, multiple sclerosis; MZM, marginal zone macrophages; PP, Peyer's patches; TNF, tumor necrosis factor; TRADD, TNFR associated DD; TRAFs, TNFR receptor-associated factors.

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