Cytokine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Lymphotoxin in physiology of lymphoid tissues – Implication for antiviral defense

Ekaterina P. Koroleva [a], Yang-Xin Fu [b], Alexei V. Tumanov [a,*]

[a] Department of Microbiology, Immunology, and Molecular Genetics, University of Texas School of Medicine, UT Health Science Center, San Antonio, TX, USA
[b] Department of Pathology, The University of Texas Southwestern Medical Center, Dallas, TX, USA

ARTICLE INFO

Article history:
Received 2 June 2016
Received in revised form 17 August 2016
Accepted 19 August 2016
Available online xxxx

Keywords:
Lymphotoxin
Lymphotoxin beta receptor
Antiviral immunity
Lymphoid organs
Type I interferon

ABSTRACT

Lymphotoxin (LT) is a member of the tumor necrosis factor (TNF) superfamily of cytokines which serves multiple functions, including the control of lymphoid organ development and maintenance, as well as regulation of inflammation and autoimmunity. Although the role of LT in organogenesis and maintenance of lymphoid organs is well established, the contribution of LT pathway to homeostasis of lymphoid organs during the immune response to pathogens is less understood. In this review, we highlight recent advances on the role of LT pathway in antiviral immune responses. We discuss the role of LT signaling in lymphoid organ integrity, type I IFN production and regulation of protection and immunopathology during viral infections. We further discuss the potential of therapeutic targeting LT pathway for controlling immunopathology and antiviral protection.

1. Introduction

Lymphotoxin-alpha (LTα, TNFSF1), soluble homotrimeric cytokine, is a member of tumor necrosis factor (TNF) superfamily and was originally identified as a product of lymphocytes that was capable of exerting cytotoxic effects on tumor cells *in vitro* (for a recent review see [1,2]). LTα3 homotrimer binds to TNF receptor 1 (TNFRSF1A) and TNF receptor 2 (TNFRSF1B) with high affinity, but it has less activity in driving TNFR signaling than TNF itself. LTα forms a heterotrimer with LTβ (TNFSF3), and this membrane-bound heterotrimer signals specifically through LTβR (TNFRSF3) [3,4]. Surface LT is expressed by B and T lymphocytes, natural killer cells, innate lymphoid cells (ILCs), and dendritic cells (DCs), whereas LTβR is mainly expressed by non-lymphocyte populations, such as epithelial cells, stromal cells, DCs and macrophages [3,5,6]. Therefore, this cytokine-receptor pair interaction serves as a bridge between lymphoid cells and non-lymphoid cells, including stromal and parenchymal cells. LIGHT (TNFSF14) is another LTβR ligand that is predominantly expressed by T cells, DCs, and macrophages [3,4,7].

Genetic disruption of LT signaling in mice results in a complex phenotype. Mice with inactivated *lta*, *ltb* or *ltbr* genes lack lymph nodes (LN) and Peyer's patches (PP) and display disrupted microarchitecture of the spleen, thymus and other lymphoid organs (for a review see [8,9]). Due to defects in lymphoid organ development and maintenance these mice display multiple immune abnormalities and impaired immune response to various infections (for a review see [10]). Lymphoid organ defects associated with the lack of components of LT signaling in mouse models are summarized in Table 1. Although the role of LT in lymphoid organogenesis is well defined, the contribution of LT pathway to homeostasis of lymphoid organs during the immune response to viruses is less understood and is the focus of this review.

2. Lymphotoxin signaling promotes lymphoid organ integrity for antiviral protection

The principle function of secondary lymphoid organs (SLO) is to provide microenvironment for interaction between antigen-presenting cells and rare pathogen-specific lymphocytes for the induction of an efficient antiviral immune response (for reviews see [33–35]). SLO also reduce virus spreading by strategically localized cells producing various immune mediators, such as type I interferons (IFNs). Finally, SLO provide the necessary factors for the survival and differentiation of lymphocytes. Since the discovery that mice with genetic inactivation of LT or LTβR bear major defects in the development and structure of lymphoid organs (for review see [3,8,27], and Table 1) these mice become an irreplaceable animal model to study antiviral immune responses. Growing numbers of papers demonstrating unique requirement for LT signaling in antiviral immunity will be discussed in this chapter.

* Corresponding author.
E-mail address: tumanov@uthscsa.edu (A.V. Tumanov).

http://dx.doi.org/10.1016/j.cyto.2016.08.018
1043-4666/

Table 1
Mice with specific inactivation of components of LT pathway demonstrate defects in lymphoid organ development and structure.

Mutant strains	Spleen			LN			GALT		NALT	Thymus	References
	B cell follicles	MZM, MMM	FDC	Structure	mLN	pLN	PP	ILF			
Lta$^{-/-}$	–	–	–	–	–	–	–	–	+/–	Abnormal	[11–16]
Ltb$^{-/-}$	–	–	–	Abnormal	+/–	–	–	–	+/–	Abnormal	[14,16–18]
Ltbr$^{-/-}$	–	–	–	–	–	–	–	–	+/–	Abnormal	[13,16,19–22]
Light$^{-/-}$	+	+	+	+	+	+	+	+	ND	Normal	[23]
B-*Ltb*$^{-/-}$	–	+/–	–	Abnormal	+	+	+/–	+	ND	ND	[24–26]
T-*Ltb*$^{-/-}$	+	+		+			+	+	ND	ND	[24,26]
B,T-*Ltb*$^{-/-}$	–	–	–	Abnormal	+	+	+/–	+	ND	ND	[26,27]
RORγt-*Ltb*$^{-/-}$	+	+	+	+	+	–	–	–	ND	ND	[6,28]
RORγt-*Lta*$^{-/-}$	+	+	+	–	–	–	–	–	ND	ND	[28]
VE-*Ltbr*$^{-/-}$	ND	ND	ND	Abnormal	+	+/–	+/–	ND	ND	ND	[29]
Ccl19-*Ltbr*$^{-/-}$	+	+	+	Abnormal	+	+	+	+	ND	ND	[30,31]
Tagln-*Ltbr*$^{-/-}$	+	+	+	+	+	+	ND	ND	ND	ND	[32]

pLN-peripheral lymph node, mLN-mesenteric lymph node, PP-Peyer's patches, NALT-nasal-associated lymphoid tissue, FDC-follicular dendritic cells, MZM-marginal zone macrophages, MMM-metallophilic macrophages, ND-not determined, – absent, + present, +/– reduced.

The specific outcomes of viral infections in mice deficient with components of LT signaling pathway are summarized in Table 2.

Several studies which utilized LTα-, LTβ- or LTβR-deficient mice demonstrated that overall antiviral cytotoxic T-cell immune responses were impaired, and the clearance of the virus was slowed down or inhibited in various models of systemic viral infections, such as vaccinia virus [36], lymphocytic choriomeningitis virus (LCMV) [36–38], herpes simplex virus (HSV) [39] or Theiler's murine encephalomyelitis virus (TVEM) [40]. Adoptive transfer experiments demonstrated that LT-deficient environment rather than LT-deficient splenocytes is responsible for aberrant early replication of LCMV in the spleen and defective antiviral immune responses [38,41] Similarly, since treatment with LTβR-Ig did not impair immunity against TVEM in adult mice [40], it was suggested that changes to the splenic and lymph node architecture, but not the LT signaling during infection, were critical for clearing the

Table 2
Role of LT signaling in animal models of viral infections.

Virus	Model	Outcome	Ref
Vaccinia	*Tnf.Lta*$^{-/-}$	Attenuated primary CTL responses	[36]
LCMV	*Tnf.Lta*$^{-/-}$	Reduced primary and secondary CTL responses	[36]
LCMV	*Ltb*$^{-/-}$	Severely diminished CTL responses, delayed clearance of the virus	[37]
LCMV	*Lta*$^{-/-}$, *Tnf.Lta*$^{-/-}$	Impaired initial virus replication in the spleen	[41]
LCMV	*Lta*$^{-/-}$	Impaired CD8$^+$ T-cell responses, impaired clearance of the virus	[38]
LCMV	*Ltb*$^{-/-}$, B-*Ltb*$^{-/-}$, T-*Ltb*$^{-/-}$, TB-*Ltb*$^{-/-}$	Delayed virus clearance in TB-LTβ mice, persistent infection in LTβ$^{-/-}$ mice	[26]
LCMV	LTβR-Ig treatment of WT mice, transfer of LTβ-deficient B-cells	LTβ on B-cells promotes LCMV-induced pLN remodeling	[71]
LCMV	B-*Ltb*$^{-/-}$, *Ltbr*$^{-/-}$	Impaired IFN-I production due to insufficient early virus replication but normal CD8$^+$ T-cell responses	[72]
LCMV-13	LTβR-Ig treatment of NZB mice	Increased mice survival, reduced specific CD8$^+$ T-cell responses	[117]
MHV-68	*Lta*$^{-/-}$	Slightly delayed virus clearance	[100]
MHV-A59	Ccl19-*Ltbr*$^{-/-}$	Increased body weight loss and viral titers	[30]
TMEV	*Lta*$^{-/-}$, *Ltbr*$^{-/-}$, LTβR-Ig treatment in C57Bl6 mice	Increased mortality, impaired virus-specific CTLs, reduced demyelination. LTβR-Ig treatment failed to increase susceptibility.	[40]
MCMV	*Lta*$^{-/-}$, LTβR-Fc transgenic mice	Increased susceptibility, accelerated mortality	[52]
MCMV	*Lta*$^{-/-}$, *Ltb*$^{-/-}$, *Ltbr*$^{-/-}$, LTβR-Fc; anti-LTβR agonistic treatment of *Lta*$^{-/-}$ mice	Increased mortality, impaired IFN-β induction Induction of IFN-β, increased survival of mice	[54]
MCMV	*Ltbr.Rag*$^{-/-}$ *Ltb.Light*$^{-/-}$, B-*Ltb*$^{-/-}$	Reduced early IFN-I responses in spleen	[55]
VSV	*Ltb*$^{-/-}$, B-*Ltb*$^{-/-}$, T-*Ltb*$^{-/-}$, TB-*Ltb*$^{-/-}$	LTβ$^{-/-}$ mice succumb to infection. Reduced virus capture in MZ of B-LTβ mice	[26]
VSV	*Ltbr*$^{-/-}$	Decreased early virus titers in the spleen, impaired CD8$^+$ T-cell responses, increased mortality	[59]
VSV	LTβR-Ig treatment, BM transfer from B-*Ltb*$^{-/-}$ to WT mice	Increased mortality after s.c. infection due to inability to replicate virus in SCS macrophages to produce IFN-I, leading to fatal invasion of intranodal nerves	[25]
VSV	B-*Ltb*$^{-/-}$	Reduced IFN-I production early after infection, reduced virus-neutralizing antibodies	[61]
HSV	*Lta*$^{-/-}$	Increased susceptibility to virus-induced encephalitis, defective CD8$^+$ T-cell responses	[39]
HSV	LTβR-Ig-treated *Rag1*$^{-/-}$ mice	Delayed development of lesions and increased survival	[44]
Influenza virus A (H1N1)	*Lta*$^{-/-}$, SLP mice (splenectomized *Lta*$^{-/-}$ mice reconstituted with BM from WT mice)	Increased susceptibility of LTα$^{-/-}$ mice to infection, delayed, but effective primary and memory CD8$^+$ T-cell and antibody responses. Increased resistance of SLP mice to infection compared to WT mice.	[103,105,106]
Influenza virus A (H3N2)	*Tnf.Lta*$^{-/-}$	TNF and LTα promote loss of bone marrow derived B cells during infection	[120]
HCV	FL-N/35 HCV transgenic mice	Increased LTβ expression in tumors of HCV-transgenic mice	[95]
HBV	Agonistic anti-LTβR antibody to HBV-transgenic mice	Reduced viremia and HBV core protein expression in the liver	[80]
Rotavirus	*Lta*$^{-/-}$ *Ltbr*$^{-/-}$ > WT BM transfer	Delayed IgA production and clearance of intestinal virus Normal viral clearance, increased numbers of IFN-γ producing T cells in intestine	[121] [122]
SIV	Rhesus macaques sooty mangabeys	Loss of FRCs and IL-7 in lymph nodes correlated with decreased numbers of LTβ expressing CD4$^+$ T cells	[123,124]

Please cite this article in press as: E.P. Koroleva et al., Lymphotoxin in physiology of lymphoid tissues – Implication for antiviral defense, Cytokine (2016), http://dx.doi.org/10.1016/j.cyto.2016.08.018