Review

Structural and biological features of the TNF receptor and TNF ligand superfamilies: Interactive signals in the pathobiology of Hodgkin’s disease*

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Summary

Members of the TNF receptor superfamily are type I membrane glycoproteins with limited homology (overall homologies: 25%-30%) in the extracellular domain containing variable numbers of cysteine-rich repeats. In contrast, the TNF ligand superfamily members (with the exception of LT-α) are type II membrane glycoproteins with limited homology to TNF (overall homologies: 20%) in the extracellular region. TNF and LT-α are trimeric proteins and are composed of β-strands forming a β-jellyroll. The homology of the β-strand regions for the TNF ligand superfamily members suggests a similar trimeric or multimeric complex formation for the other members. A genetic linkage, as evidence for evolutionary relatedness, is also found by chromosomal cluster for CD30, CD120b, 4-1BB and OX40L to 1p36; CD27, CD120a and TNFR-RP to 12p13; TNF, LT-α and LT-β to 6p21; CD27L and 4-1BB to 19p13; CD95L and OX40L to 1q25. TNF, LT-α and LT-β and their receptors (CD120a, CD120b, TNFR-RP) interact in a complex fashion. Other family members, however, show a one ligand/one receptor binding principle. Signals can also be transduced through at least some of the ligands. TNF superfamily ligands are involved in induction of cytokine secretion, upregulation of adhesion molecules, activation antigens and costimulatory proteins, all known to amplify stimulatory and regulatory signals that occur during immune responses. On the other hand, differences in the distribution, kinetics of induction and requirements for induction support the view of a defined role for each of the ligands for T-cell-mediated immune activities. The shedding of members of the TNF receptor superfamily could limit the signals mediated by the corresponding ligands, as a functional regulatory mechanism. Induction of cytotoxic cell death is another common functional feature of this cytokine family (TNF, LT-α, CD30L, CD95L and 4-1BBL). Further studies have to identify unique versus redundant biological and physiological functions for each of the TNF superfamily ligands.

In addition to other cytokines primary H-RS cell frequently express at least TNF, LT-α, CD27L and CD30L, but not CD40L. Furthermore, H-RS cells express several TNF receptors, such as CD30, CD40, CD95, CD120a, CD120b and 4-1BB. The TNF-like ligands might support growth and activation of HD-associated tumor cells and/or interact with surrounding reactive bystander cells, particularly T-cells. The different interactions between H-RS cells and surrounding reactive bystander cells are part of the pathobiology of HD. Detailed functional analysis have to confirm the predicted biological activities of TNF, LT-α, CD27L, CD30L, CD40L, CD95L, 4-1BBL and gp34/OX40L for the H-RS cell/T-cell interactions with impact on tumor growth and pathogenesis of HD. TNF and LT-α/CD120a and CD120b, CD30/ CD30L, and CD40/CD40L are clearly critical elements in the deregulated network of interactive signals between H-RS cells and surrounding bystander cells with membrane-associated and cytokine-mediated events. Several TNFR superfamily members are also candidates for novel treatment protocols, including CD30 and CD40.

Key words: Hodgkin disease, ligands, pathogenesis, receptors, TNF

Discovery of the TNF receptor and TNF ligand superfamilies

The tumor necrosis factor (TNF)/nerve growth factor (NGF) receptor superfamily are formed by cysteine-rich repeats in the extracellular region (reviewed in [1]). The TNF/NGF receptor superfamily contains at least ten different membrane proteins and several viral open reading frames encoding TNFR-related molecules. The low affinity NGFR p75 was the first receptor of this family to be cloned. Subsequently, cloning of two specific receptors for TNF (CD120a/TNFR-type I p60 and CD120b/TNFR-type II p80) showed that they were related to the NGFR. The type-I-transmembrane TNF/NGF receptor superfamily also contains the TNFR-RP (TNFR-type III), CD27, CD30, CD40, CD95 (FAS/APO-1), 4-1BB, and OX40. The average homology of the cysteine-rich, extracellular ligand-binding region between the members of the TNFR superfamily is in the range of 25%-30%. The NGFR p75, CD120a, CD120b, and CD95 show a broad tissue distribution, while CD27, CD30, CD40, 4-1BB,

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and OX40 are mainly expressed within the lymphoid/hematopoietic system (reviewed in [1, 2]). Recently, ligands for all of these receptors have been cloned and grouped into two cytokine superfamilies. First, the neurotrophins (NT) are basic, NGF-like dimeric soluble molecules (NGF ligand superfamily) and include NGF, BDNF, NT-3, NT-4 and NT-5 (reviewed in [4]). Second, the TNF ligand superfamily contains acidic, TNF-like molecules with around 20% sequence homology in the extracellular domains, mainly membrane-bound forms with biologically active trimeric/multimeric complexes [1, 2]. The TNF ligand superfamily is formed by TNF, LT-α, LT-β, CD-27L, CD30L, CD40L, 4-1BBL, CD30L, and CD95L (FASL). Soluble forms have only been detected so far for TNF, LT-α, CD30L, CD40L and CD95L. TNF-like molecules are involved in regulation of cell proliferation, activation and differentiation including control of cell survival or death by apoptosis or cytotoxicity (summarized in [1, 2]).

The TNR receptor superfamily

The TNF receptor superfamily consists, at present, of 10 transmembrane glycoproteins, including NGFR p75, TNFR-RP, CD27, CD30, CD40, CD95, CD120α, CD120β, 4-1BB and OX40 [1]. The characteristic pattern is found within the extracellular, ligand-binding domain formed by cysteine-rich 40 residue repeats with 25%-30% homology [1, 2]. The majority of conserved positions are cysteine residues. The cysteine-rich repeats reflect the characteristic structural domain of the TNF/NGF receptor family. The largest variation in structure is present within the region between the C-terminus of the membrane proximal domain and the transmembrane region ( spacer region) with 8 residues in CD95 to 70 residues in CD27 [2]. Overall, this family of glycoproteins shows a relatively low level of sequence conservation despite sharing a common fundamental structure. The selection pressure driving rapid divergence of the TNF receptor family members may well arise from subversion by pathogens [1]. Thus, a number of TNR viral open reading frames (e.g., SFV-T2, va53, SalF 19R, MYX-T2, G4R, crmB) have been characterized and found to be soluble TNF binding proteins capable of blocking TNF action with attenuating host immune and inflammatory responses (reviewed in [1, 3]). Comparison of the cytoplasmic sequences of the receptors showed considerably more diversity than the extracellular regions [2]. No evidence of any underlying shared structure has been detected so far, but some elements have been identified to be shared between subsets of family members. Thus, CD120α and CD95 share the so-called ‘death domain’ and 4-1BB and CD27 a truncated cytoplasmic tyrosine kinase site, originally found within CD4 and CD8 (summarized in [5]). The signal pathways to which the more recently characterized family members (CD27, CD30, CD40, CD95, 4-1BB, and CD95) might couple remains to be determined, but a diverse set of signaling cascades have been identified for the TNF receptors (CD120α and CD120β) [6]. It is of interest that the recently identified TRAF (TNF receptor-associated factor) molecules (TRAF-1 to -4) seem to bind to the cytoplasmic domains of several TNF receptors and indicate an at least partially shared signaling cascade activated through the cytoplasmic domains [7-10]. Most of the TNF receptor superfamily members exist also in a soluble form, released by proteolytic cleavage (e.g., CD27, CD30, CD40, CD95, CD120α, CD120β) or through alternative splicing (e.g., 4-1BB, CD95) [2]. The overall structures of the TNF-R superfamily members and two TNR-like viral gene products (e.g., PV-A53R and PV-T2) are shown in Figure 1.

The TNF ligand superfamily

The TNF ligand superfamily are formed by nine members and represent counterparts for the members of the TNF receptor superfamily (e.g., TNF, LT-α, LT-β, CD27L, CD30L, CD40L, 4-1BBL, OX40L, and OX40) [1, 2]. In contrast, NGF, the ligand for the low affinity NGF receptor, is structurally unrelated to the TNF superfamily of ligands. The crystal structures revealed that TNF and LT-α, but also CD120α molecule form a trimeric complex [11]. The complex contains one LT-α/TNF homotrimer and one receptor trimer. Similarly, CD40L forms a trimeric complex [12]. It is of interest that the second form of lymphotoxin (LT-β) has been found, unlike LT-α (only entirely secreted protein), as a membrane-anchored molecule, which uses TNF-RP as a specific receptor [13, 14]. LT-β is formed as a heterotrimERIC complex. The overall structural features of the TNR-like ligands are shown in Figure 1. The extracellular regions of these ligands are highly diverse, but contain a typical, around 20% sequence homology [2]. Sequence alignments demonstrated a characteristic pattern of sequence conservation with nine short regions within the extracellular domain (Figure 1). Thus, the ligand family has diverged as rapidly as the receptors. Several of the ligand superfamilies members have moderate sized cytoplasmic regions, and at least some are capable, when engaged by their receptors, of delivering signals (e.g., CD27L, CD30L, CD40L, OX40L, 4-1BBL) [2]. The signaling cascade is presently unknown. The initial biological active form of the TNR-like ligands are membrane-bound type II glycoproteins (exception: LT-α) and also naturally occurring soluble forms have been found for TNF, CD30L, CD40L and CD95L, but not CD27L, 4-1BBL and LT-β.
**Figure 1.** Schematic presentation of the members of the TNF receptor and TNF ligand superfamilies. Shown are the ten members of the TNF receptor superfamily and two examples of viral open reading frames (PV-A53R, PV-T2) (left panel). The characteristic cysteine-rich repeats (homology region) are shown as sequestered open boxes with the cysteine residues indicated by lines within the extracellular domain. The nine members of the TNF ligand superfamily are shown at the right panel, where the extracellular homologous C-terminal regions are indicated by open boxes and non-homologous sequences by lines. LT-α, TNF and CD40L are shown as homotrimers, where the membrane-anchored LTαLTβ complex forms heterotrimers. Pro-TNF, CD30L, CD40L and CD95L can be proteolytic cleaved for the release of soluble forms (▼ indicates cleavage sites). Lines with arrows indicate the transduction of biological signals. NGF is a basic soluble dimeric molecule and the prototype of the NGF ligand superfamily. NGF has no homology to the TNF ligands and is not included.

**Characteristic biological activities of the members of the TNF ligand superfamily**

The nine TNF-related cytokines show distinctive but overlapping cellular responses involving cell proliferation, activation and differentiation (e.g., cytotoxic signals, induction of proliferation and differentiation, cellular activation) [1]. Biological activities related to T-cell-mediated immunity are a unique feature for the TNF ligand superfamily. All ligands and receptors, without exception, are expressed on activated T-cells and mediate proliferative costimulation [1]. An autocrine T-cell activation and growth loop seems to be a common feature. The induction of each ligand expression shows unique kinetics indicating different roles for each of these ligands in the T-cell activation [15]. B-cell proliferation and Ig secretion is induced by at least TNF, LT-α and CD40L [3]. Further, several members participate in the T-cell-dependent help for B-cells, which are known to express CD27, CD30, CD40, CD95, CD120a, CD120b and 4-1BB [16]. TNF, CD30L and 4-1BBL are also abundantly expressed by activated macrophages [2]. Signals generated by TNF superfamily ligands in target cells are productively coordinated with accessory molecule expression (e.g., LFA-1, ICAM-1, B7 ligands) and induce cellular aggregation and activation [2, 3]. It has been shown that at least through CD27L, CD30L, CD40L and 4-1BBL signals can costimulate activated T-cells [2]. The ability to induce cell death (necrosis and/or apoptosis), is another unique feature of this family and is presently established for TNF, LT-α, CD30L, 4-1BBL and CD95L [1]. CD95 transduces apoptotic (programmed) cell death and CD95/CD95L interaction appears to be part of the T-cell repertoire formation (peripheral T-cell tolerance) [17, 18]. Interestingly, the cytoplasmic domains of the CD120a and the CD95 molecules contain the 'death domain', which is required for signal transduction involved in mediating the cytotoxic effects [19, 20].

Essential roles of several members of the TNF receptor or ligand family have been confirmed by naturally occurring or induced mutants that abolish the functional expression of the individual receptor/ligand protein. Naturally occurring inactivating mutations of the CD95 receptor (lpr mice) and the CD95L (gld
mouse) cause similar lymphoproliferative diseases with lymphadenopathy and autoimmune disease, suggesting a failure of the immune system to eliminate autoreactive T-cells [21]. CD40 and CD40L knock-out mice confirm the critical role of CD40L for T-cell-dependent B-cell help which are impaired through mutations of CD40L causing the X-linked immunodeficiency hyper-IgM with high levels of IgM and low levels of IgG (block for Ig isotype switching) [22]. Experimental deletion of the CD120a gene in mice causes immunodeficiency with severely impaired clearance of bacterial pathogens and rapid death caused by infection, but resistance to the lethal effect of lipopolysaccharides (LPS) [23, 24]. Lack of the CD120b gene showed only a minimal phenotype with modest resistance to the lethal effect of TNF. In addition, functional ablation of TNF and LT-α by overexpression of a neutralizing recombinant TNFR molecule in mice show pronounced LPS and TNF resistance with a comparable phenotype as seen for the homozygous deletion of the CD120a gene [25]. Further, the deletion of the LT-α gene results in a distinctive phenotype with the absence of structured lymph nodes and disordered splenic architecture [26]. Overall, several TNF-like ligands play critical roles for lymphoid and thymic development. T-cell-mediated immune responses, T-cell-dependent help for B-cells and humoral B-cell activity.

### Involvement of several members of the TNF receptor and ligand superfamilies in the pathobiology of HD

HD is characterized by the presence of the malignant mononucleated Hodgkin and multinucleated Reed–Sternberg (H–RS) cells (usually less than 1%–2% of the total tumor cell mass) embedded in an abundance of reactive cells including lymphocytes, histiocytes, eosinophils, plasma cells, stromal cells. Primary and cultured H–RS cells express a heterogenous panel of cytokines and cytokine receptors, which correlate with the typical clinical and pathological presentation of HD (reviewed in [27]).

The CD70 antigen (CD27L) is expressed by many peripheral T- and B-cell lymphomas (50%–70% of cases positive) and the strongest expression is found on H–RS cells of HD (96%–100% of cases positive) [2, 28]. Frequently, expression of the CD70 protein is associated with expression of other activation antigens, particularly CD25 and CD30. CD70 is present on activated lymphocytes, but not on monocytes, neutrophils or dendritic cells [29]. CD27 is expressed by medullary thymocytes, most peripheral blood T-cells, a subset of mature B-cells and NK cells [29]. CD27 expression on T-cells is associated with the helper phenotype (CD45RA+) [30]. Activation of T-cells results in up-regulation of CD27 cell surface expression and in the release of the soluble 28–32 kD form of CD27 (sCD27) [31]. The CD27L causes costimulation for T-cell proliferation, generation of cytokotoxic T-cells and enhanced cytokine secretion, but its functional significance for thymocytes and B-cells remains unclear [32]. Most HD-derived cell lines express CD27L, but not CD27 [2]. At the present time no functional correlation to defined pathophysiological presentation profiles has been established for HD, but an involvement within the typical cellular activation seems possible.

HD-derived cell lines were used to raise monoclonal antibodies which are able to stain H–RS cells in tissue sections. Ki-1, the first CD30 MoAb, was described to react uniquely with primary and cultured H–RS cells and a small lymphoid cell population in reactive tonsils [33, 34]. Subsequent studies have shown that the CD30 antigen was neither cell lineage-restricted nor specific for H–RS cells. CD30 expression is also detectable for most blasts appearing during infectious mononucleosis, subset of mitogen- or antigen-activated PBTs, Epstein–Barr virus (EBV)-immortalized B-cells, human T-lymphotropic virus types I and II (HTLV-I, -II) infected lymphocytes and human NK cell clones [35, 36]. The phosphorylated 120 kD CD30 membrane glycoprotein is restricted to CD4+ and CD8+ T-cell clones producing Tγ-2-type cytokines such as IL-4 and IL-5 [37]. Furthermore, CD30 has also been detected on some embryonal carcinomas, nonembryonal carcinomas, malignant melanomas, mesenchymal tumors, some myeloid cell lines and decidual cells [36]. CD30 protein and mRNA expression have been found on most HD-derived cell lines (exception: HD-MyZ and SUP-HD1) [27]. The CD30 antigen is detectable on the majority of H–RS cells of most HD cases, with the exception of the lymphocyte-predominant (LP) subset [38]. The asso-

| Table 1. Expression of several members of the TNF receptor and ligand superfamilies on cultured and primary H–RS cells |
|-----------------|-----------------|-----------------|
|                  | Cultured H–RS cells | Primary H–RS cells |
| 1. TNF receptors |                 |                  |
| CD27            | –                | –                |
| CD30            | +++              | +++              |
| CD40            | +++              | +++              |
| CD95            | +++              | +++              |
| CD120a (TNFR type I) | + | + |
| CD120b (TNFR type II) | + | + |
| TNFR-RP (TNFR type III) | – | N.D. |
| 4-1BB           | ++               | ++               |
| OX40            | N.D.             | N.D.             |
| 2. TNF-like ligands |       |                  |
| LT-α            | +++              | +++              |
| LT-β            | –                | N.D.             |
| TNF             | +++              | +++              |
| CD27L           | +++              | +++              |
| CD30L           | –                | +                |
| CD40L           | –                | –                |
| CD95L           | N.D.             | N.D.             |
| 4-1BBL          | N.D.             | N.D.             |
| OX40L           | N.D.             | N.D.             |

N.D. – not determined. Data are presented semiquanitatively with – no expression; + weak; ++ moderate and +++ strong protein and/or mRNA expression.
cation between CD30 expression and HD has proven to be a useful pathological and clinical marker. The CD30 surface protein is suitable in HD patients for immunomaging and immunotherapy using immunotoxins [35]. A 85 kD sCD30 molecule is detectable and high sCD30 serum levels are found in the majority of HD cases preferentially in advanced disease states, bulky tumors, and/or presence of constitutional B-symptoms [39]. The serum levels of sCD30 are an independent prognostic factor and seem to be a useful 'tumor marker' for HD. The CD30L is a 26–40 kD type II membrane glycoprotein, mainly expressed on activated T-cells and monocytes/macrophages, but also on granulocytes, subset of B-cells and some Burkitt's lymphoma cell lines [36]. CD30L expression has been detected in all subsets of activated T-cells [15]. CD30L costimulates T-cell proliferation, cytokine secretion (IL-2, IFN-γ and TNF, but not IL-4) and surface expression of activation antigens (CD54/ICAM-1, CD80/B7-1, CD86/B7-2) [15]. CD30L is involved in antigen-induced T-cell activation and proliferation and could play a pathogenic role in several immunologic diseases associated with overexpression of TNF-α-type cytokines (e.g., systemic lupus erythematosus, atopic disorders, Omenn's syndrome, HIV infection) [36, 37].

All HD-derived cell lines failed to express CD30L on the mRNA and surface protein level, but in contrast primary H−RS cells showed weak reactivity for CD30L that appeared to be independent of the histological subtype [40, 41]. Recombinant CD30L was mitogenic for the HD-derived cell lines HDLM-2 and L-540, but not for KM-H2 and L-428 [40]. Further, CD30L enhances IL-6, TNF and LT-α secretion and surface expression of CD54 and B7 ligands (CD80 and CD86) by the HD-derived cell lines [42]. CD30L thus seems to be another cytokine-like molecule involved in the deregulated cytokine and activation cascade, characteristic for HD. Taken together, the overexpression of the cytokine receptor CD30 on most H−RS cells is an important clinical, biological and pathological marker for HD, but its role for the oncogenesis of HD is still poorly understood.

The 50 kD CD40 glycoprotein is expressed on a variety of cell types including normal, virally-transformed and malignant B-cells, but also monocytes, activated T-cells, follicular dendritic cells, interdigitating reticulum cells, thymic epithelium, and some epithelial carcinomas [3]. The 33 kD CD40L is expressed, as a type II membrane glycoprotein, mostly on activated CD4+ T-cells, but also on some CD8+ T-cells, mast cells and stromal cell lines, and basophils [3]. A soluble form of CD40 and CD40L has been found in the supernatant of activated B-cells and T-cells, respectively [43, 44]. CD40 mediates proliferation of B-cells, induction of Ig secretion in the presence of other cytokines, rescue of germinal center centrocytes from apoptosis, enhancement of cytokine release, upregulation of surface antigens (LFA-1, B7 ligands, CD23 and CD54) with involvement in both homotypic and heterotypic cell adhesion and costimulation [3]. CD40L also induces tumoricidal activity of monocytes, costimulates T-cell proliferation and surface expression of CD25, CD69 and CD40L itself [45, 46]. Further, CD40L can transduce signals on its own [47]. Most of the HD-derived cell lines express CD40 at the mRNA and protein level, but do not express CD40L mRNA and protein [48]. Similarly, strong expression of CD40 by primary H−RS cells was found in most HD cases (95% of cases positive), independent of the histological subtype [48−50]. Primary H−RS cells did not express CD40L, but scattered lymphoid cells in close relation to the CD40+ H−RS cells were CD40L positive [48, 51]. In vitro rosetting of CD40L+ activated CD4+ T-cells to cultured CD40+ H−RS cells is caused in part through the CD40/CD40L interaction [50]. CD40L increased colony formation of cultured CD40+ H−RS cells in a soft agar system by 50%, but failed to show mitogenic activity [48, 50]. CD40L induced IL-8 secretion and enhanced IL-6, TNF and LT-α from cultured H−RS cell lines [48]. In addition, CD40L upregulated the surface expression of activation antigens (CD54, CD80, CD86), all of which are overexpressed on primary H−RS cells and caused a 40%−60% reduction of the CD30 surface expression with enhanced release of sCD30 [48]. Overall, CD30L and CD40L share many pleiotropic biological activities on H−RS cells, such as enhanced cytokine secretion and surface antigen expression and are elements in the unbalanced cytokine network and cell contact-dependent activation cascade typical for HD [2].

The CD95 molecule mediates cytolytic activity as a cell-surface receptor participating in the immune response or tumor development [17]. CD95 expression is broadly detectable, primary and cultured H−RS cells included [2]. Particularly, virallytransformed cells express high levels of functional CD95. The 31 kD CD95L is another type II transmembrane protein, but also exists in soluble form with similar biological activities [52]. Freshly isolated T-cells show costimulatory activity mediated through CD95, but chronic activated T-cells undergo apoptosis [53]. The CD95+/H−RS cells (HDLM-2, KM-H2, L-428 and L-540) become apoptotic following treatment with CD95 MoAbs or soluble CD95L [54]. Other cytokines, including CD40L, are able to enhance CD95 surface expression and CD95L-mediated apoptosis on these cells [54]. HD patient contain in their serum elevated sCD95 levels with correlation to stage and clinical symptoms, which might be involved in the deregulated T-cell-dependent immune response of HD patients [54]. In general, CD95 can transduce a dual role with stimulatory or inhibitory/cytotoxic signals depending on the target cells and their activational stage. The CD95/CD95L system might thus play a role in tumor progression of HD patients.

The 33 kD 4-1BB molecule was isolated from activated T-cells and is mainly expressed on CD4+ and CD8+ activated T-cells and thymocytes [55]. The 4-1BB ligand was identified on activated T-cells,
stromal cells, activated macrophages, EBV-transformed B-cells, some tumor and leukemia cell lines, but also a variety of tissues such as brain, placenta, lung, skeletal muscle and kidney [56]. 4-1BBL co-stimulates T-cell and thymocyte proliferation, but other biological activities need to be identified, which are indicated by the wide distribution pattern of 4-1BB and 4-1BBL [56]. It is of interest that 4-1BB is involved in activation-induced cell death (AICD) of T-cells and could play an autocrine role in T-cell activation [56]. Further, 4-1BBL also acts as a signal-transducing molecule [57]. Primary HD cases have not been analyzed for 4-1BB and 4-1BBL expression, but a series of HD-derived cell lines also express 4-1BBL [58]. The functional and pathological significance of 4-1BB expression needs to be examined.

The OX40 molecule is found on the cell surface of activated T-cells mainly of the CD4+ phenotype [59]. OX40 is a strictly activation-associated antigen [60]. In lymphoid tissues OX40 expression was detected on cells scattered in the interfollicular zone, follicular mantle zone and also in the germinal centers [60]. HD cases showed reactivity only for a few H-RS cells, but T-cells resetting around H-RS cells were strongly positive [60]. The OX40L has been cloned and found to be identical with gp34, a protein expressed on HTLV-1 infected human leukemic T-cells [61, 62]. OX40L is selectively expressed on activated CD4+ and CD8+ T-cells, HTLV-1-transformed cell lines, stimulated B-lymphoblastoid cell lines and THP-1 cells, but not B-cells. As part of the T-cell-dependent immune response OX40L costimulates T-cell proliferation and cytokine production (e.g., IL-2, IL-4) [61]. OX40L expression has not been investigated on cultured or primary H-RS cells. The association of the OX40/OX40L system with the virally induced pathogenesis and/or tumorigenesis of lymphomas, particularly in the context of viral transformation (e.g., EBV, HTLV, HIV) is of interest.

TNF was originally defined by its antitumor activity, but is overall a major mediator for inflammation and cellular immune responses [63]. TNF has cytotoxic activities and induces cachexia with profound effects on general cellular metabolism and development of weight loss, fever, acute phase reaction, infection, or neoplasia. TNF enhances the proliferation of T-cells, modulates T-cell receptor expression, enhances natural killer cell activity, and regulates human B-cell function. TNF has also marked effects on neutrophils, eosinophil recruitment, monocyte/macrophage activation, fibroblast growth stimulation and endothelial cell/leukocyte interactions. TNF is broadly expressed and found on cells such as monocytes/macrophages, lymphocytes, and fibroblasts. Furthermore, the LTs are cytokines structurally related to TNF with approximal 40% sequence homology, the same chromosomal localization and trimer structure [13]. LTs are expressed mainly by T-cells, but also some EBV-transformed B-cell lines and tonsil B-cells [13]. LT-α has similar inflammatory and immunomodulatory activities as TNF. LT-α has a clear role in the lymphoid development, but the function of the LT-β remains unclear [26]. Receptors for TNF and LT are expressed at low levels on most tissues. Three distinct receptors have been shown to bind TNF, LT-α and LT-β [1]. The CD120a and CD120b proteins bind both TNF and LT-α with similar affinities and kinetics [6]. The heterotrimer LT-β binds specifically to TNFR-RP [14]. Soluble forms of CD120a and CD120b have been identified in the serum of normal individuals and tumor patients, including HD patients [64]. Expression of TNF and LT-α protein and mRNA have been reported for a series of HD-derived cell lines [27]. Similarly, TNF expression of H–RS cells was demonstrated in primary tissue from HD patients using immunohistochemistry and/or in situ hybridization (54% of cases positive) (reviewed in [2]). Further, immunoreactivity for TNF was seen for histiocytes. In addition, abundant LT-α expression was found on primary H–RS cells in 80% of HD cases [28, 65]. The LT-α signals were usually of higher intensity and present in larger proportions of H–RS cells than the TNF signal [28]. TNF and LT-α mRNAs were also found in some lymphoid cells. Most HD-derived cell lines express low levels of CD120a and CD120b on their surface or at the mRNA level [2]. The TNFR-RP protein is absent on cultured H–RS cells. Immunohistochemical studies demonstrated expression of CD120a in 25% and CD120b in 50%, respectively, of HD cases [66]. The functional role of TNF and LT-α in the pathogenesis of HD, including autocrine growth control for H–RS cells remains unclear. Recombinant CD30L and CD40L are able to induce the secretion of TNF and LT-α from H–RS cells [42]. It is of interest that HD patients have elevated TNF serum levels (62% of HD patients), which is correlated to disease stage and the presence or absence of B-symptoms [64]. Along with other immune mediators such as IL-1 and IL-6, TNF might be involved in the development of B-symptoms and/or metabolic wasting.

References

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