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TNF superfamily: costimulation and clinical applications

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Abstract

The molecules concerned with costimulation belong either to the immunoglobulin (Ig) or tumor necrosis factor (TNF) superfamilies. The tumor necrosis superfamily comprises molecules capable of providing both costimulation and cell death. In this review we briefly summarize certain TNF superfamily receptor-ligand pairs that are endowed with costimulatory properties and their importance in health and disease.

1. Introduction

Clonal expansion of T cells requires both a ligand which engages its receptor (TcR) and a functionally defined second signal (also called a co-stimulatory signal). The participation of a costimulatory signal in T cell activation is of paramount importance as it results in two potential outcomes, activation or clonal anergy (Jenkins, 1992; Mueller et al., 1989). The two different outcomes of antigen recognition, by T cells, are first explained by the dual signal model of T cell activation by Bretscher and Cohn (1970). The nature or identity of this accessory signal was initially thought to be a soluble factor but later studies have established that it is a cell surface- derived event and occurs during cognate interaction between an antigen presenting cell (APC) and partnering T cell (Jenkins and Johnson, 1993).

Based on their molecular structure, the costimulatory molecules have been divided into two major groups belonging either to the immunoglobulin (Ig) or to the tumor necrosis factor (TNF) superfamily. The members of the TNF superfamily have distinctive cytoplasmic death domains and can induce apoptosis as well as receptors with no apparent homology in the cytoplasmic tail. This latter group of receptors is involved in gene activation and anti-apoptotic signaling.

The inventory of the TNF superfamily is increasing rapidly (Fig. 1) and it is impossible to cover all aspects of this superfamily in a short chapter. In this chapter, as well as briefly summarizing key features about this superfamily, we describe how the well-characterized members of this family concerned with positive immune regulation are coordinated (Fig. 2) and their role in clinical applications.

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CD27-CD70

CD27, a type I disulfide-linked glycoprotein, was discovered more than a decade ago on human resting peripheral blood T cells and medullary thymocytes. Both in humans and mice, CD27 is expressed on naive and memory-type T cells, antigen-primed B cells, and subsets of natural killer (NK) cells (Borst et al., 2005). The CD27 ligand CD70 is transiently and stimulation-dependently expressed on T, B, and dendritic cells (Lens et al., 1997) and constitutively on APCs in the murine intestine (Laouar et al., 2005). Interestingly, CD27 is also expressed by many T cells presumably to modulate the effects of CD70 on B cells by acting as decoy receptors (Hendriks et al., 2000; Kobata et al., 1995).

CD27 costimulation of anti-CD3 primed $CD4^+$ T cells promotes cell division, enhances $BcL\text{-}_{xL}$, and promotes IFN-γ induction (van Oosterwijk et al., 2007). CD27-CD70 signals are important in the terminal differentiation of B cells into antibody-secreting plasma cells (Agematsu et al., 1998; Jacquot et al., 1997; Nagumo et al., 1998). Modulation of the in vivo CD27-CD70 pathway by appropriate agonistic antibodies elicits important functions.

Administration of agonistic anti-CD27 mAbs given without a DC maturation signal completely protects tumor-bearing mice and provides a highly potent reagent for boosting antitumor T-cell immunity (French et al., 2007). Interestingly, triggering CD27 by its ligand CD70 impedes neutralizing antibody production and leads to persistence of lymphocyte choriomeningitis virus (LCMV) infection (Matter et al., 2006). Treatment with an anti-CD70 antibody has been reported to induce long-term survival of organ allografts in CD28-deficient mice by inhibiting the activation of effector and memory $CD8^+$ T cells (Yamada et al., 2005). This finding suggests that the CD27/70 pathway might be an important target for inhibiting rejection resistant to the blockade of conventional costimulatory molecules. Patients with Waldenstrom macroglobulinemia (WM), a B-cell malignancy characterized by an IgM monoclonal gammopathy and bone marrow infiltration with lymphoplasmacytic cells, show elevated soluble CD27 which serves as a marker of disease and as a target in its treatment (Ho et al., 2008). Inb addition, treatment with engineered anti-CD70 Ab has shown promise as anti-tumor agent (McDonagh et al., 2008; Grewal, 2008).

A salient feature of CD27 is its existence in a soluble form. In vivo levels of serum and urine sCD27 correlate with tumor load in patients with leukemia and lymphoma (Lens et al., 1998; van Oers et al., 1993). High soluble levels of CD27 have also been noted in the synovial fluid of rheumatoid arthritis patients and cerebrospinal fluid of multiple scleorosis patients (van Oers et al., 1993). Although CD27 lacks intrinsic kinase activity (Loenen et al., 1998), the C-terminal region associates with TRAF2 and 5 that link to NIK and JNK signaling pathways involving the transcription factors NF-κB and Jun (Loenen et al., 1998). Engagement of CD27 induces a signaling cascade, resulting in activation of NF-κB, promotion of cell survival, and increased T cell effector function (Akiba et al., 1998a; Borst et al., 2005) (Fig. 3). Continuous CD27 signaling, however, leads to T cell depletion (Tesselaar et al., 2003).

Deletion of endogenous CD27 show impaired T cell responses to viral infection (Hendriks et al., 2000), but playing a role in germinal center formation (Xiao et al., 2004). Elimination or blockade of the CD27-CD70 pathway with CD27-deficient mice or blocking with anti-CD70 antibody resulted in improved neutralizing antibody responses and clearance and reduction of viral titers, respectively (Matter et al., 2006).

CD30-CD153

CD30, originally identified in 1982 on tumor cells of Hodgkin's lymphoma (Schwab et al., 1982), also called Ki-1, is a membrane glycoprotein consisting of two chains with a molecular weight of 120 and 105 kDa. It is expressed by a subset of activated T cells (both $CD4^+$ and

CD8$^+$), NK, and B cells and is constitutively expressed in decidual and exocrine pancreatic cells with maximum expression on CD45RO$^+$ memory T cells (Annunziato et al., 2000). CD30 expression has been noted on CD4$^+$CD8$^+$ medullary thymocytes, indicating an important role of CD30/CD153 interactions in the thymus.

CD30 ligand (CD30L; CD153) is 26–40 kDa protein cloned in 1993 and is present on a variety of cells including activated T cells, macrophages, resting B cells, granulocytes, eosinophils, and neutrophils (Smith et al., 1993). Expression of CD153 was also noted on the outer wall of Hassall's corpuscles and in placenta (Romagnani et al., 1998). As noted in the case of CD27, the soluble form of CD30 (~85/88 kDa) is generated when membrane-bound CD30 protein is cleaved by zinc metalloproteinase (Hansen et al., 1995). Interestingly, soluble CD30 (sCD30) shedding can be found in several neoplastic and reactive diseases (Del Prete et al., 1995; Falini et al., 1995; Pizzolo et al., 1994; Pizzolo et al., 1997; Romagnani et al., 1995) but the significance of sCD30 is not clear. In atopic dermatitis, CD30$^+$ infiltrating T cells in lesions, elevated sCD30 levels, and increased number of circulating CD30$^+$ cells were reported (Dummer et al., 2003). Similarly, elevated sCD30 levels and CD30 on BAL $\gamma\delta^+$ T cells were noted in atopic asthma (Heshmat and El-Hadidi et al., 2006). Soluble CD30 was also noted in rhinoconjunctivitis (Bengtsson, 2003). Increased CD30 was also noted in patients with Grave's disease and Hashimoto's thyroiditis (Okumura et al., 1997).

In vitro signaling of CD30 has costimulatory effects on lymphoid cells (Gilffilan et al., 1998). Signaling via CD30 augments proliferation under certain circumstances, but in other cases potentiated apoptosis (Telford et al., 1997) (Fig. 4). In the case of human lymphomas, CD30 signaling reveals reduced proliferation (Lee et al., 1996). Reports available also suggest that CD30 signals regulate Fas-independent apoptosis in CD8$^+$ T cells (Telford et al., 1997). The CD30 cytoplasmic tail interacts with TRAFs 1, 2, 3, and 5, inducing NF-κB (Aizawa et al., 1997; Duckett and Thompson, 1997; Duckett et al., 1997; Gedrich et al., 1996; Lee et al., 1996a).

An important role for CD30 in the protection against autoimmune disorders has been reported (Kurts et al., 1999). Unmodified anti-CD30 antibodies as well as anti-CD30-based bispecific antibodies, immunotoxins, and radioimmunoconjugates have been examined in pre-clinical trials and clinical studies. Administration of anti-CD30 coupled to ricin A-chain immunotoxin (Ki-4.dgA) in patients with refractory CD30$^+$ Hodgkin's and non-Hodgkin's lymphoma demonstrated only a moderate efficacy (Schnell et al., 2002). The increased expression of CD30 on some neoplasms versus its limited expression on normal tissue makes it an excellent target for antibody therapy. CD30-CD30L interaction also is implicated in the induction of Th2 type immunity (Bowen et al., 1996) but a blockade of CD153 could not abrogate the Th2-directed murine Leishmaniasis (Akiba et al., 2000).

CD30 deficient mice show no abnormality in peripheral immune responses but have a defect in the activation-induced death of thymocytes (Amakawa et al., 1996). MHC class-I and class-II disparate skin and heart grafts are rejected much faster in CD30-deficient mice compared with wild-type mice (Beckmann et al., 2001).

CD134-CD134L

CD134 (OX40), one of most important and widely studied TNF superfamily members, was originally described as a cell surface antigen found on activated rat T cells (Paterson et al., 1987). OX40 is transiently expressed following T cell ligation of the TCR and its ligand OX40L (CD252) is expressed on APCs and endothelium. Although CD134 is present on a variety of cells, its role in T cell activation has been thoroughly investigated (So et al., 2008; Sugumura et al., 2004; Weinberg et al., 2002). The ligand for CD134 (CD134L) was originally termed

glycoprotein 34 (gp34) and was identified on human T-leukemia virus type 1 transformed cells (Akiba et al., 1998).

Signals via OX40 are co-stimulatory in nature (Watts, 2005) and support late immune responses, enabling effective long-lasting T cell response (Croft, 2003; Salek-Ardakani and Croft, 2006; Weinberg et al., 2004) leading to T cell division, survival, and cytokine induction (Gramaglia et al., 2000; Maxwell et al., 2000; Rogers et al., 2001; Weinberg et al., 1998, 1999) (Fig. 5). The validity of these findings was further substantiated by the determination that in OX40-deficient mice the T helper responses were greatly diminished, while the B cell and CTL responses remained unaffected (Kopf et al., 1999). Also, studies with OX40-Ig fusion protein demonstrate decreased T cell responses under the conditions tested (Weinberg et al., 1999). On the other hand, OX40 signals inhibit Treg cell development and function (So and Croft, 2007; Kroemer et al., 2007; Watts et al., 2005). Signals via OX40 are relayed throughTRAF2, TRAF3, and TRAF5, resulting in NF-κB activation (Arch and Thompson, 1998; Kawamata et al., 1998).

The importance of the OX40-OX40L pathway in health and disease has been extensively explored (Hori, 2006; Kaleeba et al., 1999; Weinberg et al., 1996, 2005). The first description of enhanced responses through exploitation of the OX40-OX40L pathway was made using OX40L fusion proteins and anti-OX40 mAbs in a tumor model (Pan et al., 2002; Weinberg et al., 2000). OX40 dependent costimulation enhances EAE and is involved in promoting atherosclerotic disease (Gotsman et al., 2008). The role of OX40 signaling is important for allograft response (Demirci and Li, 2008), anti-viral responses (Bertram et al., 2004), and autoimmune processes and cancer (Redmond and Weinberg, 2007). The significance of the OX40 pathway is also explored in allergic reactions (Kroczek and Hamelmann, 2005). Allergen-sensitized and challenged OX40L-deficient mice showed decreased airway hyperactivity, Th2 cytokine production, and serum IgE levels (Aresides et al., 2002).

Besides its role in costimulation of CD4 cells, OX40/OX40L interactions are closely involved in effector functions as well. For example, OX40L crosslinking supported B cell stimulation and antibody production (Stuber et al., 1995), and elevated dendritic cell effector functions (Ohshima et al., 1997). Interfering with this association can inhibit both primary and secondary IgG responses (Stuber and Strober, 1999).

CD137-CD137L

Another important and extensively studied member of the TNF superfamily is the CD137 (4-1BB)-CD137L (4-1BBL) (Vinay and Kwon, 2006a). CD137 was initially discovered in screens for receptors on activated mouse lymphocytes (Kwon and Weissman, 1989). The CD137 is not detected (<3%) on resting T cells and T cell lines. However, when the T cells, in the presence of APCs, are stimulated with a variety of agonists (plate-bound anti-CD3, concanavalin A, phytohemagglutinin, IL-2, IL-4, anti-CD28, PMA, ionomycin alone or in combinations) CD137 upregulates and maintains its expression (Pollok et al., 1993). Interestingly, expression of CD137 is detectable on $CD11c^+$ dendritic cells and $CD4^+CD25^+$ Tregs of naïve mice (McHugh et al., 2002; Wilcox et al., 2002). In vitro the CD137 signal provides costimulatory signals to T cells and shows preference for CD8 over CD4 T cells, leading to cellular proliferation, IL-2 production, and increased expression of survival genes (Vinay et al., 2006b). Signals by CD137 are relayed through TRAF1, 2, and 3, which interact with the cytoplasmic domain of CD137; mutation analysis showed the involvement of the runs of acidic residues in the cytoplasmic domain of CD137 (Jang et al., 1998). Jang et al (1998) and Arch and Thompson (1998) reported that CD137 cross-linking induces activation of NF-κB and is inhibited by dominant negative TRAF2 and NF-κB-inducing kinase (NIK). CD137 is secreted in soluble form in sera and lymphocyte secretions in patients with rheumatoid

arthritis (Michel et al., 1998). CD137 shares this feature with certain other receptor forms, such as TNFR, NGFR, CD27, CD30, and CD95.

Interestingly, in vivo administration of agonistic antibodies supports robust $CD8^+$ T cell expansion and shrinking of CD4 and B cell numbers and humoral immunity (Vinay et al., 2006b). In depth analysis revealed increased in vivo production of IFN-γ, TNF-α, and TGF-β in anti-CD137 treated animals to be perpetuators of dampened CD4 and humoral responses (Niu et al., 2007; Menoret et al., 2006; Myers et al., 2005; Sun et al., 2002; Vinay et al., 2006c). Others have advocated that in vivo anti-CD137 Abs increase IFN-γ in $CD8^+$ T cells, which in turn upregulate indoleamine 2,3-dioxygenase (IDO) in competent APS which when interacting with $CD4^+$ T cells, bring about their destruction (Choi et al., 2006; Seo et al., 2004) (Fig. 6). Seo et al. (2004) have demonstrated that anti-CD137 mAbs expand a novel $CD11c^+CD8^+$ population expressing high levels of IFN-γ and adoptive transfer of these $CD11c^+CD8^+$ T cells into susceptible mice ameliorate arthritis. Agonistic anti-CD137 Abs has potent antitumor properties and increases transplant survival and antiviral properties (Croft, 2003; Vinay et al., 2006c).

CD40-CD154

The CD40 pathway remains the most extensively studied TNF superfamily members. The amount of research data available and its success as a therapeutic agent are too vast to cover in this review. CD40 was first identified in 1985 on B cells (Paulie et al., 1985). CD40 received its definition at the 3rd International CD Workshop (Stamenkovic et al., 1989). CD154 (CD40L, gp39, T-Bam or TRAP) is an activation-induced molecule present on $CD4^+$ T cells, monocytes, DCs, and a small proportion of $CD8^+$ cells (Schonbeck and Libby, 2001). The role of CD40 in the regulation of B cell biology is well documented (D'Orlando et al., 2007; Quezada et al., 2004). Besides B cells, CD40 is also present on a variety of antigen-presenting cells; non-antigen-presenting cells including dendritic cells; follicular dendritic cells; monocytes; macrophages; mast cells; fibroblasts; epithelial cells; vascular smooth muscle cells and endothelial cells; and as a functional molecule on $CD4^+$ T cells (Grewal and Flavell, 1998; Munroe et al., 2007) (Fig. 7).

CD4-CD154 interactions mediate one of the most effective APC-activating signals. Signaling via the dendritic cell CD40 molecule upregulates expression of CD80 and CD86, and induces IL-12 secretion (Cella et al., 1996; Ridge et al., 1998; Schuurhius et al., 2000). Signaling via CD40 activates NF-κB (Lalmanach-Girard et al., 1993; Berberich et al., 1994) and rescues BCR-induced cell death (Schauer et al., 1996). Moreover, the CD40-CD154 pathway is central to germinal center formation and Ig isotype switch as validated by studies using $CD40^{-/-}$ mice (Kawabe et al., 1994).

In vivo, CD40 ligation supports $CD4^+$ and $CD8^+$ T cell growth, resulting in increases in tumor protection and alteration of steady-state tolerance into immunity (Bonifaz et al., 2002; Clarke, 2000; Diehl et al., 1999; French et al., 1999; Lefrancois et al., 2000; Mackey et al., 1998; Toes et al., 1998). On the other hand, the CD40-signaling blockade, mainly through anti-CD40L Ab, inhibits T cell activation and results in tolerance, e.g., to transplants, and control of some autoimmune diseases (Diehl et al, 2000; Iwakoshi et al., 2000). Blockade of the CD40-CD154 pathway has been proven beneficial in transplantation (Bishop, 2002; Mungara et al., 2008; Nathan et al., 2002) and autoimmune diseases (Toubi and Shoenfeld, 2004).

GITR-GITRL

The glucocorticoid-induced tumor necrosis factor receptor (GITR) family-related gene was cloned first from dexamethasone-treated murine T cell hybridoma (3DO) cells using a differential display technique (Nocentini et al., 1997, 2000a). Two groups identified that a

novel 25 kDa protein named activation-inducible protein of the TNF receptor (AITR) is the human homolog of the murine GITR (Gurney et al., 1999; Kwon et al., 1999). The AITR, which has 55% identity with murine GITR at the amino acid level, is activated by transducing signals through a TRAF2-mediated mechanism. The expression of AITR is inducible by PMA and ionomycin, anti-CD3 plus anti-CD28 monoclonal antibodies. It is detected as a 1.25 kb mRNA in lymph nodes, PBLs and weakly in the spleen and colorectal adenocarcinoma cell line (SW 480) (Kwon et al., 1999). GITR is a 228 amino acid type I transmembrane protein characterized by three cysteine pseudorepeats in the extracellular domain. It is similar to CD137 in the intracellular domain. The full-length GITR cDNA revealed a 1005 bp long sequence. Northern blot analysis suggested that GITR mRNA is about 1.1 kb long. Subsequent studies showed at least three spliced variants of GITR (Nocentini et al., 2000b).

GITR is not detectable in freshly derived lymphoid tissues (including thymocytes, spleen, and lymph node T cells), liver, kidney, and brain and T cell hybridoma 3D0. However, low levels of GITR mRNA were detected by competitive RT-PCR in T cell hybridoma, thymocytes, spleen, and lymph node T cells. GITR expression in T cells was found to increase 4- to 8-fold upon treatment with immobilized anti-CD3 and Con A and PMA. However, the induction of kinetics were slow with no increase before 6 h (Nocentini et al., 1997). The murine GITR ligand was cloned and characterized in 2003 (Kim et al., 2003). These authors demonstrated that GITRL is detected on immature and mature dendritic cells. In addition, GITRL binding GITR on HEL 293 cells triggers NF-κB activation and the addition of soluble GITRL prevents CD25 +CD4+ Treg-mediated suppressive activities (Kim et al., 2003).

Signaling via GITR is costimulatory in nature (Nocentini and Riccardi, 2005). McHugh et al. (2002) were the first demonstrate that GITR is constitutively expressed on $CD25^{+}CD4^{+}$ Tregs. Simultaneously, Shimizu et al. (2002 determined that GITR plays a key role in dominant immunological self-tolerance maintained by $CD25^{+}CD4^{+}$ regulatory T cells and could be a suitable molecular target for preventing or treating autoimmune disease (Fig. 8). Interestingly, macrophages were shown to express constitutively both GITR and GITRL and stimulation of these cells with recombinant soluble GITRL results in increased nitric oxide synthase, cyclooxygenase-2 protein, generated significant amounts of prostaglandin E_2, and matrix metalloproteinase 9 (Lee et al., 2003; Shin et al., 2000,2002,2003).

Signaling through GITR induces NF-κB activation mediated by TRAF4 and is inhibited by the cytoplasmic protein A20 (Esparza and Arch, 2004). Anti-GITR Ab therapy significantly increased disease severity in an EAE model (Kohm et al., 2004).

The importance of the GITR pathway has begun to be appreciated (Nocentini and Riccardi, 2005). GITR knockout mice develop normally but show increased cell proliferation, IL-2 receptor expression, and IL-2 production compared with control wild-type mice in cultures stimulated with anti-CD3 (Ronchetti et al., 2002). Patients with non-infectious uveitis show more $GITR^{+}CD4^{+}$ T cells than normal individuals (Li et al., 2003). Treatment of SJL mice with anti-GITR antibody in conjunction with proteolipid protein (PLP 131–151) significantly exacerbated clinical disease severity and CNS inflammation. On the other hand, prior depletion of $CD25^{+}CD4^{+}$ Tregs failed to result in EAE, suggesting alternative targets for the anti-GITR Ab treatment (Kohm et al., 2004). Administration of anti-GITR Ab in 3-month-old mice results in autoimmune gastritis associated with anti-parietal cell auto-antibodies (Shimizu et al., 2002). In addition, the importance of the GITR-GITRL pathway is underscored in several models including colitis (Uraushihara et al., 2003), autoimmune diabetes (Suri et al., 2003), GVHD (Muriglan et al., 2004), shock due to splanchnic artery occlusion (Cuzzucrea et al., 2004), viral infections (Dittmer et al., 2004), and cancer (Calmels et al., 2005).

HVEM-LIGHT

Herpes virus entry mediator (HVEM) was identified and cloned in 1996 as one of many entry receptors for α-herpesviruses (Montgomery et al., 1996). HVEM has a wide tissue distribution (Kwon et al., 1997) and is present on a variety of cell types including T and B cells, monocytes, and DCs (Harrop et al., 1998a; Morel et al., 2001).

LIGHT, a 29 kDa type II transmembrane protein, was identified as a ligand for HVEM (Mauri et al., 1998). Although HVEM binds LIGHT, it also binds LTα3 and LIGHT besides binding HVEM, also binds LTRβ, thus complicating the interpretations (Croft, 2003) (Fig. 9). LIGHT is expressed by several cells types, including T cells and DCs (Morel et al., 2000; Tamada et al., 2000a). LIGHT signaling leads to T cell growth and differentiation and has CD28-independent costimulatory activity (Tamada et al., 2000b). LIGHT signaling is important for $CD8^+$ T cell-mediated allo-responses (Liu et al., 2003; Scheu et al., 2002). Transgenic expression of LIGHT in T cells results in acute intestinal inflammation, increased production serum IgA, kidney IgA deposition, and exacerbation of nephritis (Wang et al., 2004).

HVEM stimulation by LIGHT leads to costimulation T cells and DC activation (Morel et al., 2000; Tamada et al., 2000a). The importance of HVEM in immune regulation was demonstrated in tumor rejection (Tamada et al., 2000b), GVHD (Tamada 2000b, 2002), autoimmune diseases (Shaikh et al., 2000; Wang et al., 2001), and atherosclerosis (Lee et al., 2001). Blockade of LIGHT was shown to hamper early T cell proliferation and cytokine secretion in MLR reaction (Kwon et al., 1997; Harrop et al., 1998b; Tamada et al., 2000a). LIGHT induces apoptosis in tumor cells expressing both LTβR and HVEM, especially when combined with IFN-γ (Mauri et al., 1998; Harrop et al., 1998a; Rooney et al., 2000). The human immunodeficiency virus-1 (HIV-1 Nef) increases expression of LIGHT, resulting in heightened cytokine activity leading to disease progression in infected individuals (Lama and Ware, 2000). Overexpression of LIGHT in MDA-MB-231 breast cancer cells suppressed tumor growth (Zhai et al., 1998).

In summary, the last few years have seen rapid growth in the numbers of members of TNF superfamily. Exploitation of the various unique biological functions of the TNF superfamily members for therapeutic use has shown promise. Further research in this area will undoubtedly unravel keys to effective therapeutic intervention in cancer, transplant survival, antiviral effectiveness, and autoimmunity.

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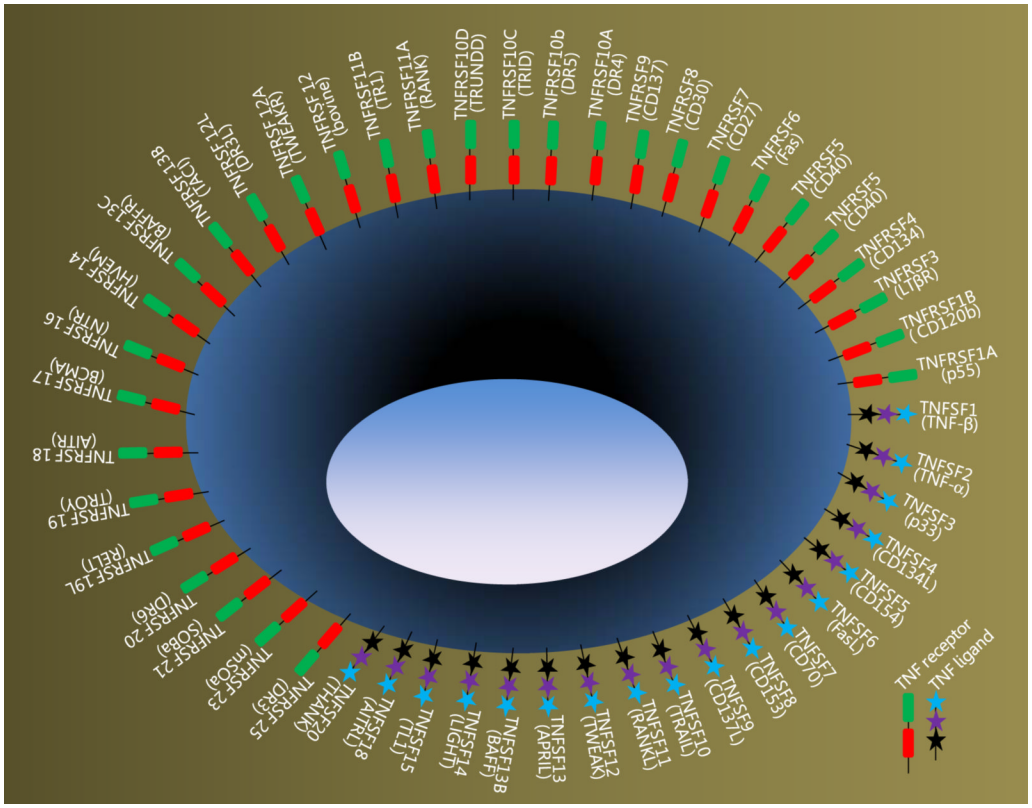

Figure 1. Schematic cartoon depicting members of TNF superfamily

Each member of the TNF superfamily is indicated by its scientific nomenclature. The description in the parentheses denotes their common name. Since the expression of a particular TNF receptors or its ligand is not exclusive to a particular cell type and sometimes present on the same cell, a generalized depiction illustrated.

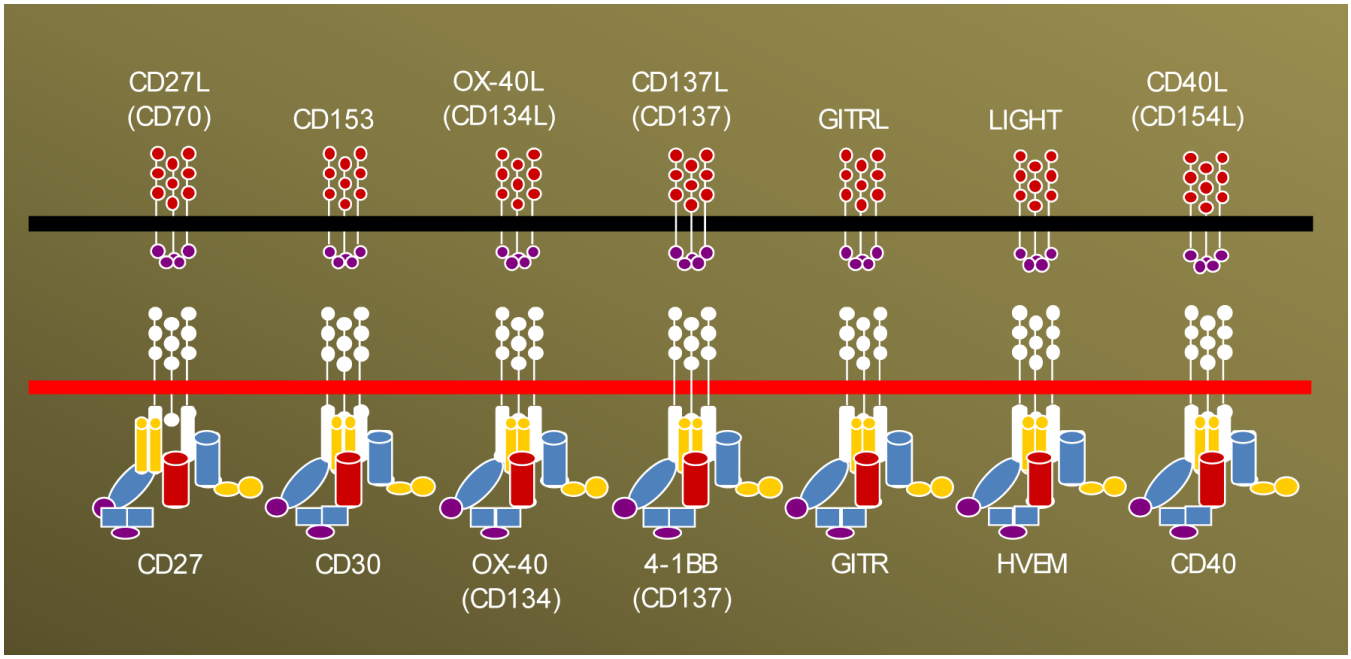

Figure 2. Schematic representation of important members of TNF superfamily

Although some the members of the family are constitutively expressed (low levels), in most cases their expression is activation dependent. The expression of given receptor or ligand is not restricted to a particular cell and can sometimes present on both T lymphocyte as well as antigen presenting cell enabling a bidirectional signaling cascade.

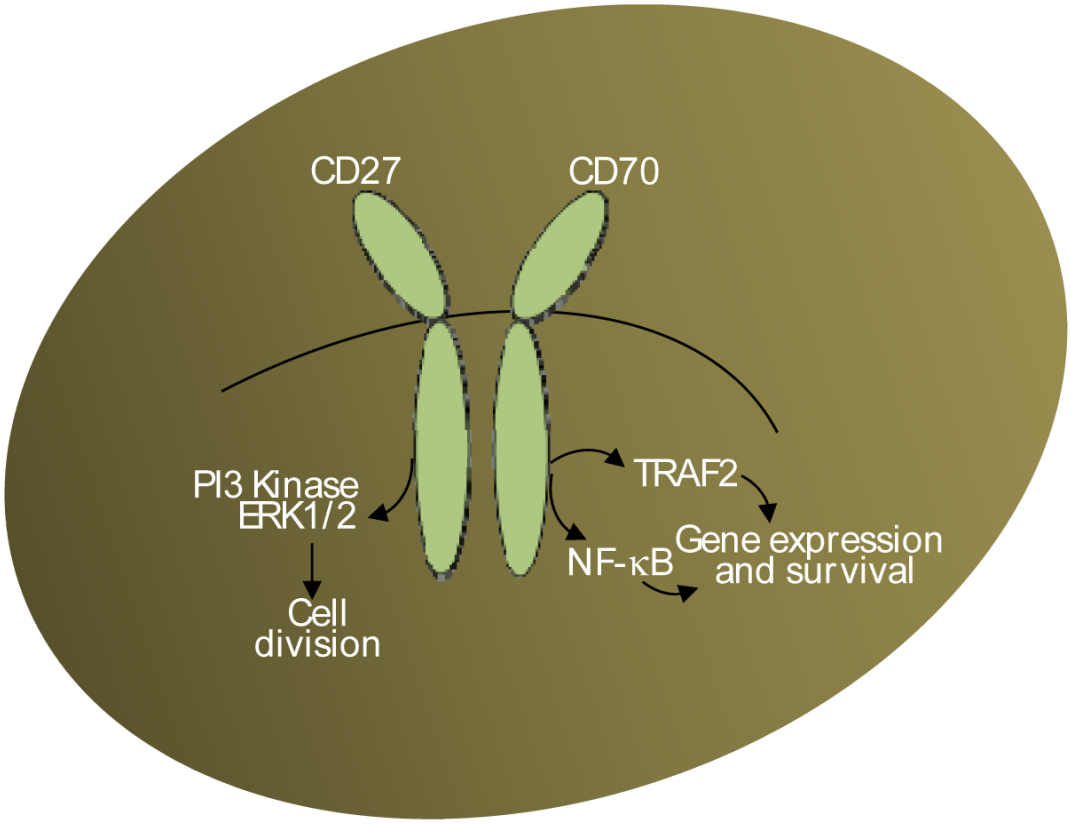

Figure 3. CD27-CD70 pathway

Signaling via CD27-CD70 pathways provides positive immune regulation. When stimulated with appropriate agonist such as anti-CD27 or anti-CD70 or cell lines made to express these molecules relay signals through TRAF2/5 resulting in long-term survival of cells via induction of NIK and NF-κB. Signals also result lead to the expression of PI3 kinase, ERK1/2, PLCγ leading to robust cell division.

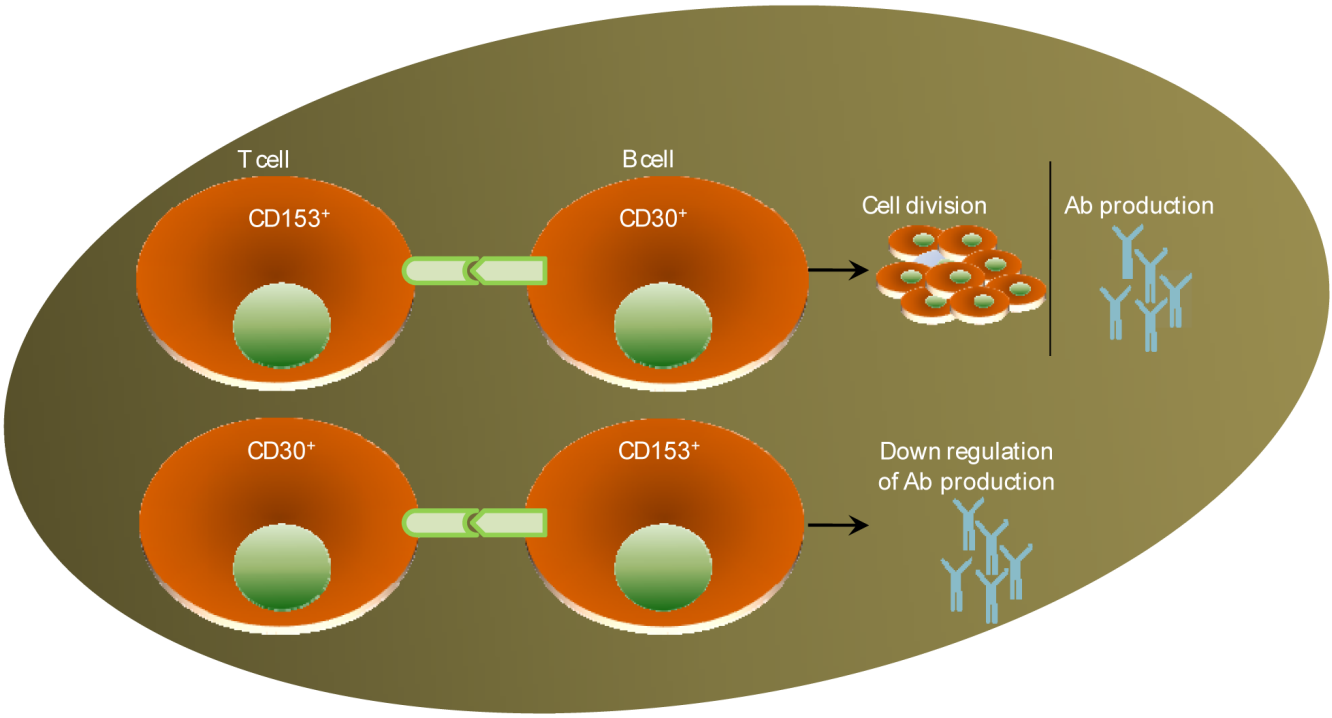

Figure 4. CD30-CD153 pathway

Expression of CD30 or CD153 is not exclusive and can be present on both T cells as well as APCs. Such variable expression pattern of CD130-CD153 results in diverse immune responses. Interaction of CD153 bearing T cell with $CD30^+$ B cell enhances survival gene expression leading cell division and increased antibody production. On the other hand, $CD30^+$ T cells interaction with $CD153^+$ B cell results in reduced Antibody production.

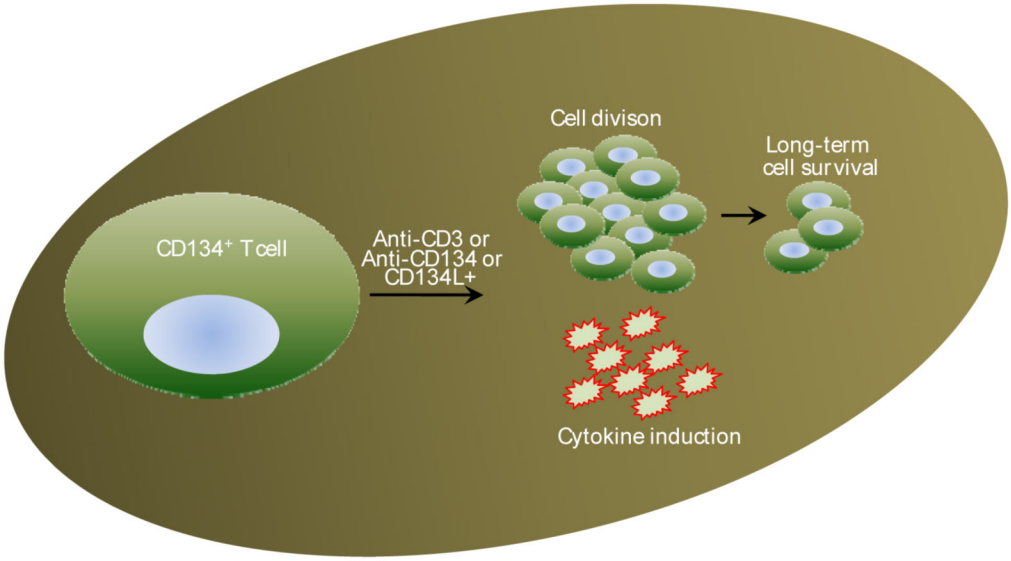

Figure 5. CD134-CD134L pathway

CD134 is transiently expressed on T cells and is known to support late immune responses. Once expressed and when stimulated via TCR or agonistic anti-CD134 mAbs or cells made to express CD134L supports cell division and IL-2 production resulting in long-term survival of memory T cells.

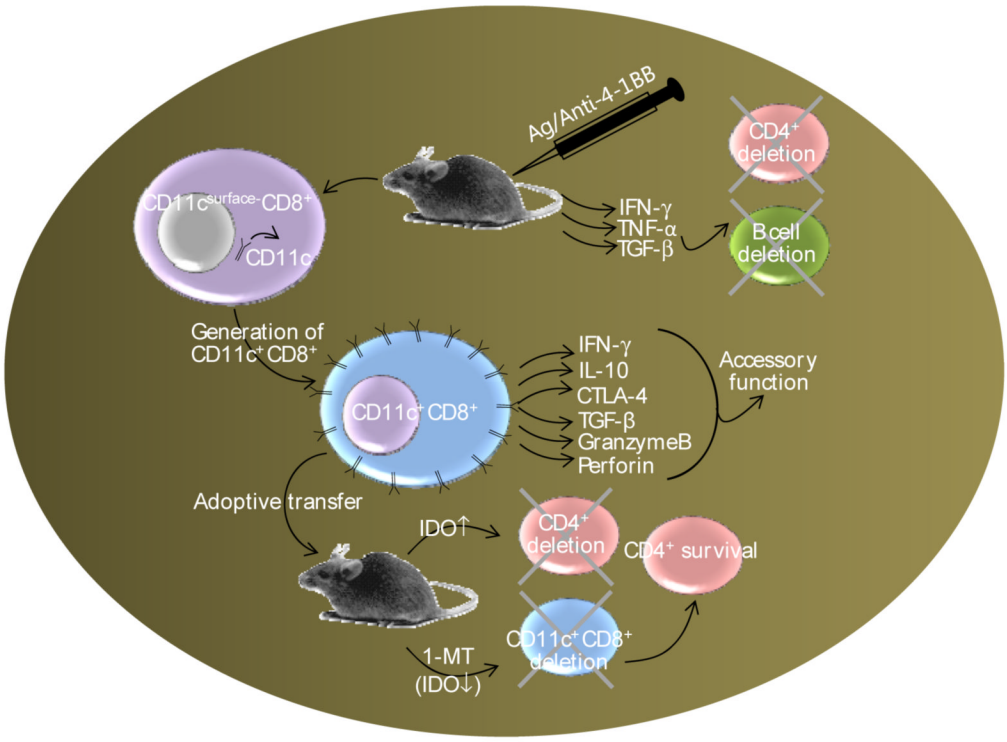

Figure 6. CD137-CD137L pathway

With a few exceptions expression of CD137 is activation dependent. There is a variability in anti-CD137-mediated signaling. While in vitro anti-CD137 stimulation supports activation of both CD4+ and CD8+ T cells, in vivo effects mediated by anti-CD137 is complex. Administration of agonistic anti-CD137 mAbs supports robust CD8+ T cell expansion and constricts CD4+ T and B cell numbers and function. This latter in vivo effect of anti-CD137 is believed to result from over expression of IFN-γ, IL-10, TGF-β, granzymeB, perforin, and CTLA-4 and expansion of a novel immunoregulatory CD11c+CD8+ T cell subset. The increased IFN-g due to anti-mediated CD11c+CD8+ T cells upregulates indoleamine 2,3-dioxygenase (IDO) in competent cells which when interact with partnering CD4+ T cells causes their deletion. This can be reversed by neutralizing IDO activity by 1-mehtyltryptophan.

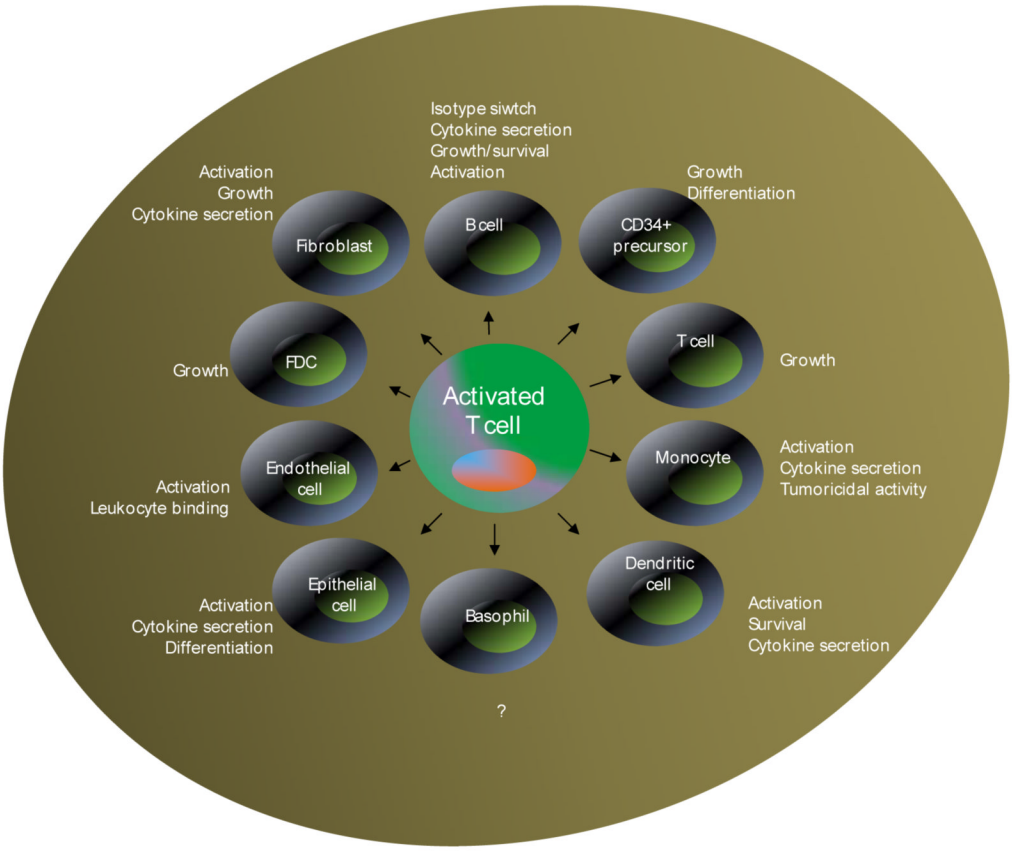

Figure 7. CD40-CD154 pathway

Expression of CD40 is widespread on a variety cells including CD4+ T cells. CD40 binds an activation induced CD154 molecule. Interaction of CD154+ CD4+ T cells with CD40-bearing cells results in the activation of partnering cells resulting in the expression of cell survival genes, cytokine induction, Ig isotype switching etc.

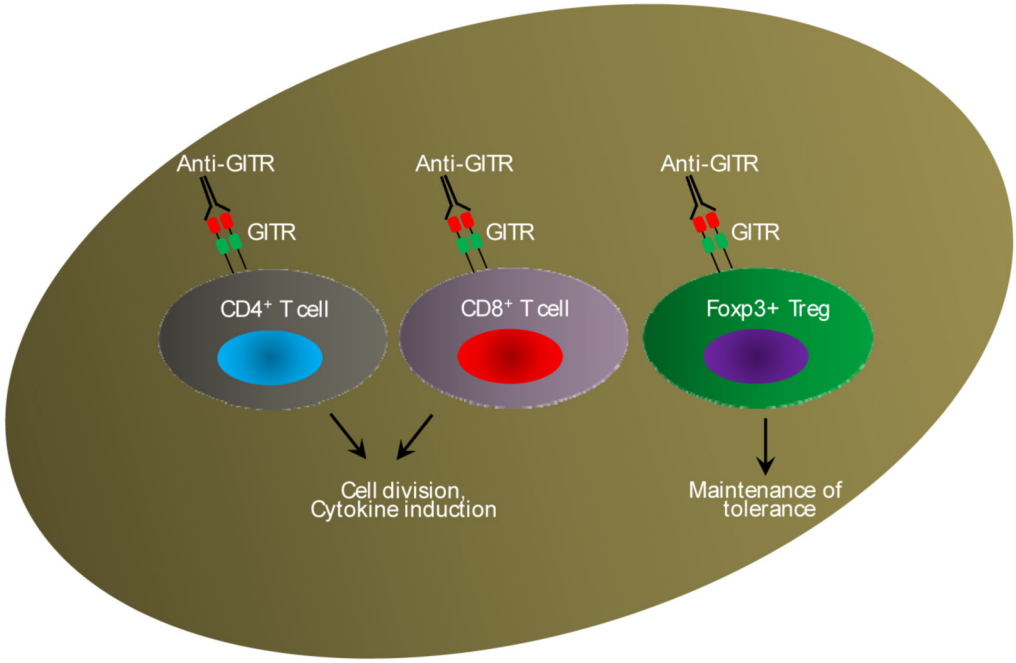

Figure 8. GITR-GITRL pathway

Expression of GITR is activation dependent with the exception of Foxp3+ Tregs which express this antigen in a constitutive manner. Signals through GITR are co-stimulatory in nature to CD4+ and Cd8+ T cells resulting cell division and cytokine induction. Importantly, GITR provides key signals to FoxP3+ Tregs to maintain immune tolerance and plays a critical role in the control of autoimmune diseases.

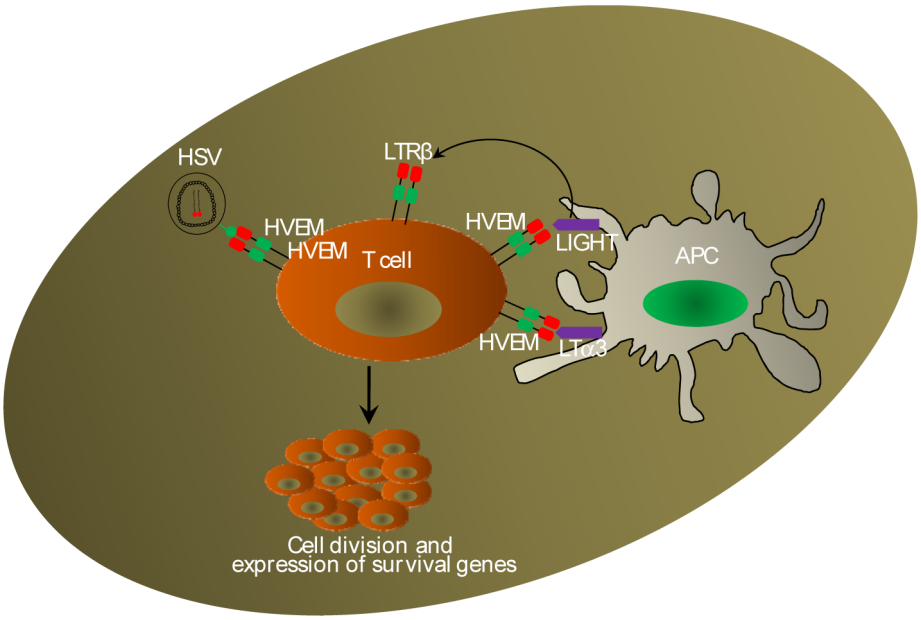

Figure 9. HVEM-LIGHT pathway

HVEM was originally identified as entry mediator of herpes virus. HVEM signaling is complex as it binds KIGHt as well as LTα3 and is further complicated as LIGHT besides binding HVEM also binds LTRβ. This complex receptor-ligand interactions as well as HSV-HVEM interplay culminate in the expression of of array of signaling molecules, type I IFNs etc.