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Current views

Receptors and ligands implicated in human T cell costimulatory processes

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ABSTRACT

It is well established that full activation of T cells that recognize antigens requires additional signals. These second signals are generated by the interaction of costimulatory ligands expressed on antigen presenting cells with their receptors on T cells. In addition, T cell activation processes are negatively regulated by inhibitory costimulatory pathways. Interaction of members of the B7 and the TNF superfamilies with members of the CD28 and TNF-R-superfamilies plays major roles in costimulatory processes. However, a large number of molecules that do not belong to these families have been reported to be involved in the generation of T cell costimulatory signals. In addition to well-defined costimulatory pathways, where both receptors and ligands are known, there are many T cell surface molecules that have been described to generate a second signal under certain experimental conditions, f.i. when ligated with antibodies. Furthermore there are several ligands that have been shown to positively or negatively modulate T cell activation by interacting with as of yet unknown T cell receptors. Here we give a comprehensive overview of molecules that have been implicated in human T cell activation processes and propose criteria that define genuine T cell costimulatory pathways.

1. Introduction

The current interpretation of the two signal hypothesis of T cell activation is a useful approximation of the stimuli that T cells require to achieve unmitigated activation under physiological conditions. It proposes that in addition to the antigen-specific signal that consists of the cognate interaction of the T cell receptor complex with the peptide–MHC complex (Signal 1), T cells depend on additional – costimulatory – signals (Signal 2) to achieve full activation. Although soluble factors like cytokines can also efficiently enhance the activation of T cells, that receive stimuli via their T cell receptor complex, the term costimulation usually describes the modification of T cell activation processes by the interaction of membrane-bound ligands with their T cell-expressed receptors.

T cell costimulatory signals are important regulators of host-protective as well as immune-pathological processes. Positive costimulatory signals are mandatory for the initiation of effective immunity and the absence of costimulatory signals results in abortive T cell response and T cell anergy [1]. Negative costimulatory – coinhibitory – pathways afford an additional layer of control that play important regulatory functions thereby contributing to the maintenance of peripheral tolerance as well as to the termination of immune responses after clearance of infections [2]. Consequently costimulatory pathways are attractive therapeutic targets in diseases that are associated with aberrant and harmful immune responses, e.g. autoimmune conditions and responses to allergens or organ grafts [3–5]. Furthermore, blocking inhibitory pathways and enhancing stimulating pathways is a promising strategy to ameliorate persistent virus infections and to enhance spontaneous or therapeutically induced immune responses to tumors [6,7].

Abbreviations: ADA, adenosine deaminase; ALCAM, activated leukocyte cell adhesion molecule; BTLA, B- and T lymphocyte attenuator; BTNL2, butyrophilin-like 2; DAF, decay accelerating factor; DC-SIGN, dendritic cell-specific ICAM-3-grabbing nonintegrin; DR3, death receptor 3; Eph, erythropoetin-producing hepatocyte; FAP, fibroblast activation protein; GITR, glucocorticoid-induced tumor necrosis factor receptor; GPI, glyco-phosphatidyl-inositol; HCV, hepatitis C virus; HSPG, heparan sulfate proteoglycan; HVEM, herpes virus entry mediator; IAP, integrin-associated protein; Ig-SF, immunglobulin-superfamily; LAG-3, lymphocyte activation gene; LAMP-3, lysosomal associated membrane protein 3; LFA, lymphocyte-function associated antigen; LPAM-1, lymphocyte Peyer's patch HEV adhesion molecule; LT, lymphotoxin; MAdCAM, mucosal cell adhesion molecule-1; MCP, membrane cofactor of proteolysis; NKG2D, natural killer group 2 member D; PADGEM, platelet activation dependent granule-external membrane protein; PD-1, programmed death-1; PSG-17, pregnancy-specific glycoprotein 17; PtdSer, phosphatidylserine; SEMA, semaphorin; SIGLEC, sialic acid binding Ig-like lectin; SIRP, signal regulatory protein alpha—possibly also beta and gamma; SLAM, signaling lymphocytic activation molecule; SRCR, receptors with scavenger receptor cysteine-rich domains; TAPA-1, target of anti-proliferative antibody-1; TIM, T cell immunoglobulin domain and mucin domain; TL1A, TNF-like ligand 1A; TM4-SF, transmembrane 4—superfamily; TM7-SF, transmembrane 7—superfamily; TNFRSF, tumor necrosis factor receptor superfamily; TNFSF, tumor necrosis factor superfamily; TRAMP, TNF-receptor-related-apoptosis-mediated-protein; TREML2, triggering receptor expressed on myeloid cells like transcript 2; VCAM, vascular cell adhesion molecule; VLA, very late antigen; VSIG4, V-set and immunoglobulin containing 4.

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Interaction of the B7 molecules B7.1 (CD80) and B7.2 (CD86) with CD28 and CTLA-4, is generally regarded as the primary costimulatory pathways and additional members of the extended B7 family – the so-called B7-homologs – can also convey potent activating or inhibitory signals to T cells. The second major group of T cell costimulatory ligands comprises members of the TNF-superfamily, which interact with their cognate receptors belonging to the TNF-receptor superfamily. Intensive research has focused on costimulatory pathways involving B7 or TNF family members and results obtained in these studies have been summarized in excellent reviews [8–12].

It is however well established that there are numerous potent costimulatory pathways involving interaction of molecules that do not belong to these molecule families, and the list of different molecules that have been reported to mediate T cell costimulation is long. Such pathways might play important roles in immune responses especially under conditions where activation of T cells via CD28 the primary costimulatory receptor, is impaired, e.g. in CD28 negative CD8 T cells or in patients treated with CTLA-4 fusion proteins.

In addition to receptors expressed on T cells that have been shown to act costimulatory upon interaction with their natural ligands expressed on antigen presenting cells (APC), a large number of T cell molecules have been categorized as costimulatory based solely on their ability to generate a second signal when ligated with antibodies. Although the effects of antibodies targeting such molecules could be therapeutically exploited for the modulation of immune responses, their physiological role as costimulatory receptors remains to be established.

1.1. Members of the B7-CD28 superfamily

The B7-CD28 superfamily is the primary group of costimulatory molecules involved in T cell costimulatory and coinhibitory processes.

The B7-CD28 superfamily comprises following receptor/ligand pairs: CD28/CTLA-4:CD80/CD86, ICOS:ICOS-L and PD-1:PD-L1/PD-L2. In addition there are two members of the B7 superfamily for which no human receptors have been identified: B7-H3 and B7-H4 [8]. The CD28/CTLA-4:CD80/CD86 pathway is the best characterized T cell costimulatory pathway. CD80 and CD86 have dual specificities for the stimulatory receptor CD28 and the inhibitory higher affinity receptor CTLA-4 [13]. CD28, which can be regarded as the most potent costimulatory receptor, promotes IL-2 production, activation of naive T cells, T cell survival and entry into the cell cycle. Engagement of CTLA-4, which is upregulated on activated T cells counterbalances the activating effects of CD28 and leads to the inhibition of cell cycle progression and IL-2 production. Recently it was shown that CD80 binds also to PD-L1 and that this interaction can down regulate murine T cell responses [14]. Specific interaction between human CD80 and PD-L1 has also been demonstrated [14–16] but to date functional consequences of this interaction have not been reported.

The ICOS-L:ICOS signaling pathway induces little IL-2 but promotes T helper cell differentiation and effector function through the production of T_H1, T_H2 and T_H17 cytokines (IL-10, IL-4, IFN-γ, IL-17 and IL-21) [17–21]. Furthermore ICOS:ICOS-L interaction is crucial for T cell dependent B cell response, B cell differentiation, germinal center formation and memory B cell development. ICOS engagement leads to upregulation of CD40L, a molecule critically involved in immunoglobulin isotype switching [22,23].

PD-L1 and PD-L2 deliver a coinhibitory signal via PD-1 to T cells thereby strongly inhibiting T cell proliferation and cytokine production [24–29]. The PD1:PD-L1/2 pathway may also play an inhibitory role in $CD4^+CD25^+$ regulatory T cells and was shown to contribute to peripheral tolerance and might have a role in preventing autoimmunity [30–34]. PD-L1 bearing tumor cell lines could be associated with increased apoptosis of $CD4^+$ and $CD8^+$ T cell clones *in vitro*. However there are also reports suggesting a costimulatory role for both PD-1 ligands [35–37]. Thus the existence of putative second receptors for PD-L1 and PD-L2 with costimulatory function on T cells has been suggested. All data suggesting an activating function of PD-L2 stem from experiments with murine T cells whereas costimulatory effects of human PD-L2 have not been described. In line with this we found that there is no evidence for a stimulatory receptor for PD-L2 on human T cells [38].

B7-H3, another member of the B7 superfamily, was originally reported to function as a T cell costimulator [39], but we and others find that B7-H3 does not enhance T cell activation and plays an important role as coinhibitory molecule [16,40–42]. Recently TREML2 was reported to serve as a costimulatory receptor for B7-H3 on murine T cells [43]. We have analysed the interaction of fusion proteins representing human B7-H3 and TREML2 with cells expressing high levels of TREML2 and B7-H3, respectively, and found no evidence for a specific interaction of these molecules [16]. Furthermore independent experiments performed in two laboratories could also not confirm a role of B7-H3 as a ligand for murine TREML2 [16,44]. Thus B7-H3 has still to be regarded as an orphan ligand.

Whereas several independent studies on B7-H4 (B7S1; B7x), another member of the extended B7 family report coinhibitory functions for murine B7-H4 [45–47], published data on the function of human B7-H4 are rare. In line with data obtained in mouse studies, Kryczek et al. reported that B7-H4 expression identifies a suppressive macrophage population in human ovarian carcinoma. They furthermore show that ectopic expression of B7-H4 in human monocytes inhibits their T cell stimulatory capacity [48]. In the first report on human B7-H4 it was however found that B7-H4 fusion proteins have a higher capacity to costimulate human T cell activation than fusion proteins representing CD80 [49].

Butyrophilins and butyrophilin-like molecules are distantly related to the B7 family and among these molecules butyrophilin-like 2 (BTNL2) was shown to have a close structural homology to B7-1 (CD80) [50]. Murine BTNL2 was shown to act as an inhibitory costimulatory ligand [51,52] and Arnett et al. demonstrated that immobilized BTNL2-fusion proteins also inhibited anti-CD3 induced proliferation of human T cells.

The macrophage complement receptor CRIg (Z39Ig) was recently identified as B7 family related protein and reported to negatively costimulate the activation of human T cells [53].

Cellular receptors that mediate T cell inhibitory effects of B7-H4, BTNL-2 or CRIg on T cells have not been identified to date.

1.2. Members of the TNF-R/TNF superfamilies

Members of the TNFR superfamily comprise the second major group of T cell costimulatory receptors. Signals from the large family of TNF-R family members have important roles, many of which are not related to immune functions. There are six receptor–ligand pairs which are generally regarded as being involved in T cell costimulatory processes: 4-1BB/4-1BBL; OX40/OX40L; CD27/CD70; GITR/GITRL; CD30/CD30L and HVEM/LIGHT [9]. Extensive studies support a costimulatory function of 4-1BB, OX40, CD27 but few reports have described such a function for human LIGHT and human CD30L. We have recently compared the capacity of TNF family members to costimulate human T cells. We found human 4-1BBL to have the most potent T cell costimulatory effects in this group. Furthermore, whereas OX40L, CD27L and GITRL readily costimulated the proliferation and cytokine production of human T cells, CD30L and LIGHT consistently failed to do so [18]. An independent study has demonstrated that 4-1BBL and CD70 but not LIGHT can costimulate cytokine production and effector function of virus