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REVIEW

The role of CD30 and CD153 (CD30L) in the anti-mycobacterial immune response

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ABSTRACT

The establishment of a protective T-cell response against mycobacterial infections involves different co-stimulatory molecules and their respective ligands. Among these molecules the Tumor Necrosis Factor Receptor Super-family (TNFRSF) and the Tumor Necrosis Factor Super-family (TNFSF) are known to be important members. This review analyzes the evidence that CD30 and CD153 (CD30L), members of the TNFRSF and TNSF, play key roles in the T cell-dependent anti-mycobacterial immune response. Mice deficient in either CD30 or CD153, or treated with antibodies blocking the effects or CD30 and CD153, and infected with *M.avium* or *M.bovis* BCG exhibit higher bacterial burden, abnormal inflammatory responses with decreased Th1 responses, this is evidenced by the reduced number of IFN-γ-producing cells. Recent evidence also showed that $CD30^+$ $CD153^+$ Tγδ cells participate in the early stages of *M.bovis* BCG infection by producing IL-17A. In humans, stimulation of T-cells with mycobacterial antigens induces CD30 expression mainly by $CD4^+$ cells; $CD30^+$ cells have been demonstrated in tissues of patients with tuberculosis (TB) and in positive tuberculin skin test reactions. In addition, the levels of soluble CD30 are increased in serum and BAL of TB patients and these levels seems to correlate with the severity of the disease. These findings suggest that CD30/CD153 interactions during the anti-mycobacterial immune response are important for the establishment and maintenance of a protective response. Further studies would be required to determine whether these molecules may be good clinical biomarkers or potential targets for immune manipulation.

Contents

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1. Introduction

The innate immunity is the first line of defence against *M. tuberculosis (M.tb)* infection, it initially controls the bacterial replication through a wide plethora of effector mechanisms; however, *M.tb* is still able to subvert them facilitating their survival and replication inside the phagosome [1]. Even though the macrophages may eventually be able to control *M. tuberculosis*, the T-cells-dependent adaptive immunity would be required to achieve an effective control of the mycobacterial replication through the formation of mature granulomas, and the production of cytokines that are capable of activating the macrophages and cytolytic molecules that kills infected cells or even directly destroy *M. tuberculosis* [2,3]. However, adequate activation of the T-cells requires recognition of their cognates antigens in the context of the Major Histocompatibility Complex (MHC) expressed by the antigen presenting cells (APC), which also provide co-stimulatory signals necessary to achieve fully activation of the T-cells [4]. CD28, which binds to CD80 and CD86 on APC, is the classical co-stimulatory molecule involved in T-cell activation; however, others molecules belonging to the TNF super-family receptors (TNFSFR), such as CD27, CD30 and CD40L are also important co-stimulants that complement or may even substitute the classical signalling by CD28 [5].

Since there is strong evidence that suggest that during active TB there are alterations in:- the antigen presentation, T-cell activation and T-cell memory processes that leads to a defective protective immune response [6,7], it is important to further understand the role of the molecules involved in the implementation and maintenance of the anti-mycobacterial T-cell response. The present review is focused on the TNFSFR molecule CD30 and its ligand CD153 (CD30L), a member of the TNFSF, which are known to play important roles in the survival, clonal expansion and maintenance of memory T-cells [8–11]. This review analyzes the information available on the participation of CD30/CD153 in the anti-mycobacterial immune response both in humans and in experimental animal models, demonstrating their active role during these infections and suggesting that the signals derived from these molecules are important for establishing an adequate cellular protective response. We also highlighted on some questions that are still not elucidated and may become important for the discovery of new biomarkers and even targets for future immunomodulatory approaches in tuberculosis.

2. TNF receptors superfamily and their ligands

TNF receptors superfamily (TNFRSF) comprises a large number of membrane proteins, including CD27, CD30, CD40, OX40, GITR (glucocorticoid-induced TNFR-related protein) and CD137 (4-1BB), which may have co-stimulatory effects on the T-cells. TNFRSF members are characterized by multiple cysteine-rich site (CRDs) in the N-terminal extracellular domain that are responsible for the interaction with their ligands [12]. The expression of TNFRSF is mainly restricted to the hematopoietic/lymphoid cells in a membrane-bound form which are all expressed on activated T-cells. However, soluble forms produced by proteolytic cleavage of CD27, CD30, TNF and LTα, and through alternative splicing of 4-1BB have been described [13]. Although the cytoplasmic domain of TNFRSF molecules vary considerably among its members, their biological functions, such as cell proliferation, activation, differentiation, induction of adhesion and co-stimulatory molecules are shared by some of them; in addition, the TNFRSF members that contain intracytoplasmic death domains (DD) are able to induce cell death as is the case of TNFR1 and CD95L[14].

The ligands for the TNFRSF belong to the TNF superfamily (TNFSF), a type II membrane glycoproteins and includes among other members: the TNF, CD153 (CD30L), CD95L(FasL), and 4-1BBL. These ligands exert their biological activity by inducing receptor multimerization on the cell surface [11,14,15].

3. CD30

CD30(TNFRSF8) is a type I transmembrane glycoprotein belonging to the TNFRSF superfamily (Table 1).The human CD30 gene located on 1p36 codes for a 120kD protein with 550 amino acids of length which comprise 362 residues of the extracellular and 188 the cytoplasmic domain [16]. The extracellular region is composed of five repeated cysteine-rich repeat units, interrupted between repeats 3 and 4 by a hinge region [17]. The cytoplasmic domain of CD30 have a TNFR-associated factor (TRAF) binding domain that interact with adaptor proteins of the TRAF family (TRAF1 and TRAF2) and mediates NF-κB activation, suggesting that CD30, like CD40, may serve as a positive regulator of T-cell function [18].

CD30 was initially described in the malignant cells of Hodgkin's disease and anaplastic large cell lymphoma (ALCL) where the over expression of CD30 results in a constitutive activation of NF-κB by a ligand-independent signaling, contributing to their abnormal growth and malignancy [19]. CD30 expression has also been reported in a small cell population in the parafollicular area of hyperplastic lymph nodes and tonsils, in activated B-cells and EBV transformed cells, T-cells infected by HTLV-1, and in a variety of non-Hodgkin's lymphomas [16,20,21]. In healthy individuals the expression of CD30 has been demonstrated in a small percentage of circulating T cells (0–2%), although some authors have reported higher percentages (3–31%), mainly on $CD8^+$ T-cells [22]. It was found that the number of CD30-positive cells increases in some reactive conditions such as infectious mononucleosis, toxoplasmosis, asthma and eczema.

CD30 is expressed on activated and memory T-cells ($CD45RO^+$), NK cells, macrophages and thymus medulla (epithelial cells and Hassal's corpuscles), but not on naïve and resting T-cells. The Mouse models was used to show that CD30 is upregulated on both $CD4^+$ or $CD8^+$ T-cells following activation with αCD3 plus and αCD28[23], but no up-regulation of CD30 occur after stimulation with αCD3 alone in 3–5 days cultures. The ability of CD28 co-stimulant to induce CD30 expression is enhanced by IL-4 [24]and IL-12[25], even in CD28 deficient TCR transgenic mice [23,24].

3.1. Soluble CD30

Shedding of CD30 from the cell membrane by TACE, a member of the "A Disintegrin and Metalloprotease", or ADAM family [26] produces a 90kD soluble CD30 (sCD30) molecule. The mechanisms that regulate the release of CD30 are not clear. Depletion or reduction of cholesterol from lipids rafts has been shown to increase the shedding of CD30 from membrane in Hodgking's lymphoma T-cell lines [27]. Velasquez et al. [28], demonstrated, in an *in vitro* allogeneic model, that the release of sCD30 was regulated by the Th1-type cytokines IFN-γ and IL-2 by an ADAM10-and ADAM17-independent mechanism, suggesting that these enzymes are not modulated by these cytokines or are not associated with shedding of membrane CD30.

The isoform of sCD30 competes with the membrane form for binding to CD153 and limits the signals mediated by the corresponding ligands resulting in a functional regulatory mechanism mediated by a serum competitor. The regulatory mechanism of sCD30 is related to the suppression of Th1-type, but not with the Th2-type immune responses. Viral CD30, a functional soluble CD30 homologue encoded by Ectromelia (mousepox) virus has been