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CD70: An emerging target in cancer immunotherapy

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ABSTRACT

Over the last decades, advances in the knowledge of immunology have led to the identification of immune checkpoints, reinvigorating cancer immunotherapy. Although normally restricted to activated T and B cells, constitutive expression of CD70 in tumor cells has been described. Moreover, CD70 is implicated in tumor cell and regulatory T cell survival through interaction with its ligand, CD27. In this review, we summarize the targetable expression patterns of CD70 in a wide range of malignancies and the promising mechanism of anti-CD70 therapy in stimulating the anti-tumor immune response. In addition, we will discuss clinical data and future combination strategies.

Contents

1. Introduction

The mutual and interdependent interaction between the cancer cells and their microenvironment is increasingly considered a crucial domain of investigation in cancer research. In this regard, immunotherapy represents a promising therapeutic modality in oncology, as evidenced by its election as Science's Cancer Breakthrough 2013 (Couzin-Frankel, 2013). Recently, much interest has been generated by the clinical results associated with inhibition of immune checkpoint proteins by antibodies directed against cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death (ligand) -1 (PD-1/PDL-1) (Rolfo et al., 2014). In this review, we will focus on the CD70–CD27 signaling pathway, emerging as an interesting new field of study to enhance anti-tumoral immune

Abbreviations: ADCC, Antibody-dependent cellular cytotoxicity; ADCP, Antibody-dependent cellular phagocytosis; CDC, Complement-dependent cellular cytotoxicity; CTLA-4, Cytotoxic T lymphocyte antigen-4; FOXP3, Forkhead box P3; HIV, Human immunodeficiency virus; IHC, Immunohistochemistry; IL, Interleukin; iTregs, Induced Tregs; LPC, Lymphoplasmacytic cells; MMP, Matrix metalloproteinase; NHL, Non-Hodgkin lymphoma; NK, Natural killer; NSCLC, Non-small cell lung cancer; nTregs, Naturally occurring Tregs; PD(L)-1, Programmed death (ligand); RCC, Renal cell carcinoma; sCD27, Soluble CD27; TCL, T cell lymphoma; TCR, T cell receptor; TGF-β, Tumor growth factor-β; TIL, Tumor-infiltrating lymphocyte; TNF, Tumor necrosis factor; TRAF, Tumor receptor-associated factor; Tregs, Regulatory T cells; WM, Waldenström macroglobulinemia.

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responses. Indeed, the discovery of CD70 expression on multiple tumor types of hematological origin and also on several types of solid tumors makes this molecule an attractive target for antibody-based immunotherapy.

CD70 belongs to the tumor necrosis factor (TNF) superfamily of molecules, consisting of over 20 membrane-bound and secreted protein ligands. This protein is a type II transmembrane glycoprotein, comprised of 193 amino acids with a molecular mass of 50 kDa. Sequence homology with other TNF superfamily members predicted the appearance of CD70 as a homotrimer leading to the understanding that interaction with CD27, its unique receptor, may involve three CD27 homodimers (Boursalian et al., 2009). Upon interaction with CD70, cytoplasmic residues of CD27 are bound to TNF receptor-associated factors (TRAFs), such as TRAF2 and TRAF5, thereby activating NFκB and c-Jun kinase pathways, leading to proliferation, survival and differentiation (Boursalian et al., 2009). Additionally, a role of CD27 in caspase-mediated apoptosis is suggested via the receptor-associated death domain-containing adaptor protein Siva (see Fig. 1) (Prasad et al., 1997). As new insights into the CD70–CD27 pathway have been gained over the last decade, we will discuss novel approaches to target this pathway in human malignancies.

2. CD70–CD27 physiology

The TNF receptor superfamily member CD27 is a tightly regulated costimulatory molecule, activated through its unique ligand CD70, enabling activation of innate and adaptive immunity. In humans, expression of CD27 is detected on thymocytes and naïve T cells, upregulated upon T cell activation and diminishing after effector T cell differentiation (Hintzen et al., 1994). In addition, CD27 is also found on central memory T cells, residing in secondary lymphoid organs (6). Despite these expression patterns, CD27-deficient mice have normal T cell development in the thymus and similar numbers of naïve T cells in secondary lymphoid organs as opposed to wild-type controls. However, depletions in the effector T cell pool and impeded memory T cells are observed (Hendriks et al., 2000, 2003). These studies indicate that CD27 triggering is neither required nor sufficient to induce effector T cell formation, but contributes to the formation of the effector T cell pool by efficient priming of T cells and the subsequent promotion of T cell survival (Nolte et al., 2009). The role of the CD70/CD27 axis in the priming of T cells was also demonstrated in a variety of immunization and infection models (Matter et al., 2005; Nolte et al., 2009). CD27–CD70 interactions were shown to induce proliferation and cytokine production by both $CD4^+$ and $CD8^+$ T cells and promote development of cytotoxic T cell responses (Lens et al., 1998). Nonetheless, CD70 knock out mice show normal CD4 T cell responses and memory CD8 T cell generation after lymphocytic choriomeningitis virus infection (Munitic et al., 2013). Instead, persistent signaling of CD27 upon lymphocytic choriomeningitis virus infection induces immunopathology and suppression of neutralizing antibodies, indicating that CD27 activity should be carefully controlled in order to prevent collateral damage (Matter et al., 2006). This is established by the strict control of CD70 expression under physiological conditions: transiently upregulated on antigen-activated T and B cells, waning following the removal of the antigenic stimulus and mainly detected in primed effector lymphocytes (Borst et al., 2005). In mature dendritic cells, CD70 expression is upregulated upon triggering of CD40 or Toll-like receptors (Boursalian et al., 2009). Thereby an intrinsic pool of CD70 is transported towards the immunological synapse with MHC-II molecules, ensuring optimal T cell stimulation (Keller et al., 2007; Kuka et al., 2013). Besides its effect on T cell development, CD27 is upregulated on B cells through antigen receptor triggering and is maintained after activation, making it a typical marker for memory B cells (Jacquot et al., 1997). Despite the fact that triggering of the CD70/CD27 axis stimulates immunoglobulin production by the promotion of plasma cell differentiation, CD27 is not absolutely required for adequate B cell responses, since deficiency does not affect isotype switching, somatic hypermutation or antibody production (Agematsu et al., 1999; Xiao et al., 2004). Moreover, in mice that constitutively express CD70 on B cells, T cells or dendritic cells, a demise of B cells in the bone marrow and secondary lymphoid organs is seen due to the chronic activation of CD27 (Nolte et al., 2009). In these mouse models, the expression of CD70 by B cells even resulted in exhaustion of the naïve T cell pool, depletion of T cells from lymph nodes and death from opportunistic infection (Tesselaar et al., 2003). As for B cells and T cells, CD27 is highly regulated on natural killer (NK) cells, the key mediators of innate immune defense mechanism. Evidence indicates that NK cells upregulate CD27 in their final developmental stage before leaving the bone marrow. However, on circulating NK cells CD27 is absent, implicating that CD27 is turned off when these cells acquire their highest effector cell potential (Vossen et al., 2008). The impact of the CD70–CD27 pathway on human NK cells is still largely unknown since CD27-deficient mice show normal amounts of NK cells with adequate function properties (Vossen et al., 2008). However, in mice that constitutively express CD70 on B cells, continuous CD70–CD27 interactions result in a severe reduction of NK cell numbers (De Colvenaer et al., 2010). Overall, CD70–CD27 interaction is crucial for the regulation of the cellular immune response leading either to improved T cell function or T cell dysfunction, whereby timing, context, and intensity of these costimulatory signals determine the functional consequence of their activity (Nolte et al., 2009). In this regard overexpression of CD70 can be observed in different auto-immune diseases, such as rheumatoid and psoriatic arthritis and lupus (Boursalian et al., 2009; Han et al., 2005; Lee et al., 2007; Oelke et al., 2004). In the next sections we will discuss the role of the CD70/CD27 axis in tumor biology as it is becoming clear that CD70 can also serve as a target for cancer immunotherapy.

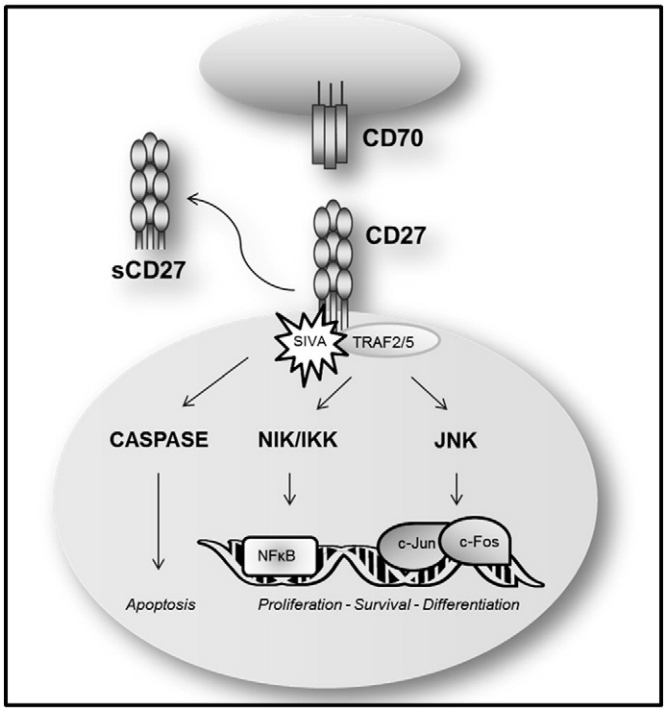

Fig. 1. CD70–CD27 pathway. Diagram showing the CD27–NFκB pathway, mediated by TRAF2, and the CD27–c-Jun kinase pathway, mediated by TRAF5, resulting in survival, proliferation and differentiation signals. On the left, cytoplasmic binding of CD27 to Siva is illustrated, leading to caspase-mediated apoptosis. NIK, NFκB inducing kinase; IKK, IkB kinase; JNK, c-jun N-terminal kinase; TRAF, TNF receptor-associated factor 2.