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The CD27–CD70 pathway and pathogenesis of autoimmune disease

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ABSTRACT

Objective: To critically examine current evidence regarding the role of the CD27–CD70 pathway in the pathophysiology of autoimmune disease with a focus on understanding the contributions of this pathway as a potential new therapeutic target for systemic lupus erythematosus and rheumatoid arthritis.
Methods: A PubMed search for articles was conducted using the following key words: ("CD27" OR "CD70") AND ("autoimmune disease" OR "systemic lupus erythematosus" OR "rheumatoid arthritis"). The search was limited to publications in English and included human and animal studies. The reference lists of identified articles were searched for further relevant citations. Publications on the list that was developed by this approach were assessed and those with relevance to CD27–CD70 pathway mediated pathophysiology in autoimmune disease were chosen for the detailed review.
Results: Data from human diseases and animal models document a major role for the CD27–CD70 receptor–ligand pair in providing signals that regulate T and B lymphocyte activation. The membrane receptor CD27 and its soluble form (sCD27) transmit co-stimulatory signals and induce activation and proliferation of T and B lymphocytes. CD70-expressing CD4 T lymphocytes are increased in autoimmune disease including systemic lupus erythematosus and rheumatoid arthritis and have been shown to produce pro-inflammatory cytokines. At the same time, preclinical evidence suggests that the outcome of CD27–CD70 signals may vary qualitatively between cell subsets and differentiation stages, especially for B lymphocytes. Blockade of the CD27–CD70 pathway has been shown to ameliorate disease manifestations in animal models including murine collagen-induced arthritis and experimental colitis.
Conclusion: Current evidence from animal models and human diseases suggests that CD27–CD70 pathway contributes to the pathophysiology of autoimmunity. Although a number of basic questions still remain open, the available findings suggest that targeting the components of this pathway could provide useful and novel therapeutic interventions.

Advances in understanding of the roles of cytokines and their receptors have, in the past 2 decades, revolutionized the treatment of autoimmune rheumatic diseases, including rheumatoid arthritis. However, many potentially important immunoregulatory pathways which contribute to pathophysiology of autoimmune diseases remain to be fully elucidated, and some of these are likely to be promising candidates for targeted therapeutic interventions. The CD27–CD70 surface ligand–receptor pair belongs to one of these pathways, and is the focus of this review.

CD27 and CD70 are ligand–counter ligand pair that has been recognized as providing stimulatory signals for T cell and B cell activation [1–3]. CD27 (TNFRSF7) belongs to the tumor necrosis factor (TNF) receptor family and is found on CD4 and CD8 T lymphocytes, NK cells, and hematopoietic stem cells [2,4–9]. CD27 is not expressed by naïve B lymphocytes but is upregulated in activated and antigen-experienced B lymphocytes [10]. Soluble CD27 (sCD27) can be cleaved from the membrane bound form on activated T lymphocytes through the action of matrix metalloproteinase [11,12]. The only characterized ligand of CD27 is CD70 (TNFSF7), a TNF superfamily member expressed on activated T lymphocytes, B lymphocytes, dendritic cells and NK cells, and also weakly on activated macrophages [4,13–15]. Thus, the CD27–CD70 interaction is primarily regulated by the expression of CD70, which is induced by Toll-like receptor (TLR), CD40, and/or antigen receptor signaling [13,16]. Similarly to other TNF family members (e.g., CD40L), CD70 is capable of retrograde signaling [17,18], and therefore CD27–CD70 interactions have bidirectional functional effects (Fig.). In this review, we summarize the evidence

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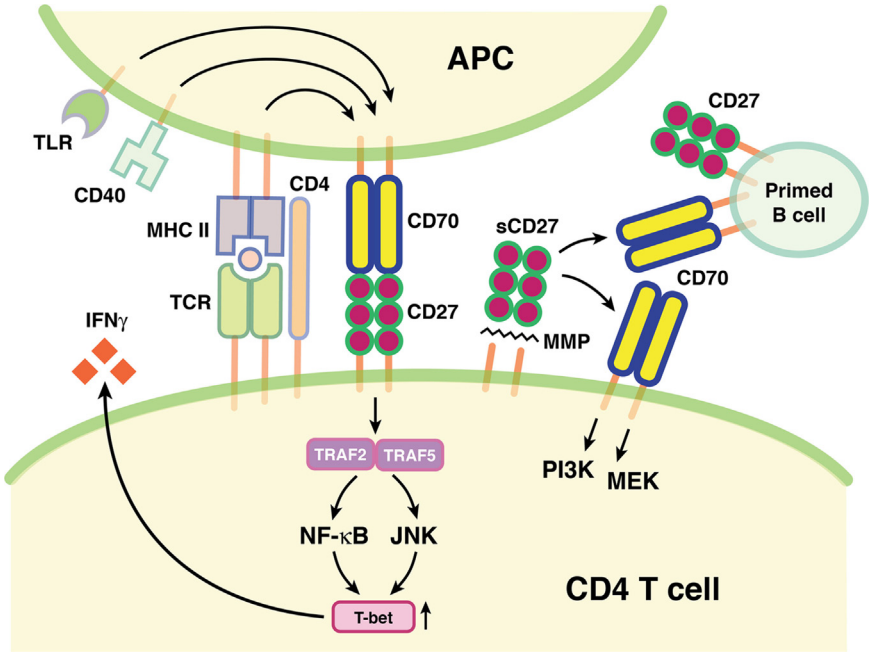

Fig. CD27–CD70 pathway in immune regulation. The CD27–CD70 pathway is a ligand–counter ligand pair that provides signals for T cell and B lymphocyte activation. The CD27–CD70 interaction is primarily regulated by expression of CD70, which is induced by Toll-like receptor (TLR), CD40 and/or, antigen receptor signaling. CD70 on activated antigen presenting cells (APCs) including dendritic cells and B lymphocytes interacts with CD27 on T lymphocytes and provides costimulatory signals in addition to T cell receptor (TCR) engagement. CD27 signals through NF-kappaB (NFκB) and c-Jun N-terminal kinase (JNK) pathways via TRAF2 and TRAF5. CD27 signaling stimulates naive CD4 T lymphocytes to differentiate into IFNγ producing T helper 1 (Th1) cells by enhancing the Th1-specific transcription factor T-bet. Soluble CD27 (sCD27) can be cleaved from the membrane bound form on activated T lymphocytes through the action of matrix metalloproteinase and binds to CD70 on T or B lymphocytes. CD70 also has signaling properties after interacting with CD27 and the phosphoinositide 3-kinases (PI3k) and MEK pathways are involved in its signaling.

supporting an involvement of the CD27–CD70 pathway in autoimmune rheumatic diseases including systemic lupus erythematosus and rheumatoid arthritis.

CD27–CD70 pathway in T lymphocyte responses

CD27 is constitutively expressed on naïve T lymphocytes, and is downregulated only after prolonged stimulation [4,19]. Its ligation by CD70 expressed on activated antigen presenting cells (APCs) including dendritic cells and B lymphocytes provides costimulatory signals in addition to T cell receptor (TCR) engagement through the NF-kappaB (NFκB) and c-Jun N-terminal kinase (JNK) pathways via TRAF2 and TRAF5 [20,21]. Thus, CD27 acts in parallel to a large array of other costimulatory molecules which promote T lymphocyte cell cycle progression, survival and cytokine production after encounter with antigen. This includes CD28, a co-stimulatory receptor of immunoglobulin superfamily member on T lymphocytes which is ligated by B7 molecules (CD80 and CD86) on APCs [22], and several members of the TNF receptor superfamily, namely OX40, 4-1BB, CD30, HVEM (herpes-virus entry mediator), and GITR (glucocorticoid-induced TNFR family related gene) [3,23].

The role of the CD27–CD70 pathway in T lymphocyte functions has been studied in several animal models. CD27-deficient mice showed impaired CD4 and CD8 T lymphocyte priming and accumulation at sites of influenza virus infection [24], and CD27 was shown to be required for efficient survival of virus-specific CD8 T lymphocytes, independently of CD28 [25]. Furthermore, CD27 signaling promoted IL-2 production and CD27-mediated survival of primed murine CD8 T lymphocytes and was shown to be dependent of IL-2 signaling in *in vitro* as well as *in vivo* studies with CD27-deficient mice [26]. Additionally, secretion of the chemokine CXCL10 by primed CD8 T lymphocytes in response to CD27–CD70 co-stimulation acted as a chemoattractant for other primed CD8 T lymphocytes [27].

Constitutive transgenic expression of CD70 on B lymphocytes in another mouse model was shown to result in CD4 and CD8 T lymphocyte expansion and age associated, CD27- and TCR-dependent differentiation into effector lymphocytes that produced interferon γ (IFNγ) [28,29]. CD27-mediated signals promoted *in vitro* proliferation and survival of human naive CD4 T lymphocytes, and, although they did not specifically induce T helper 1 (Th1) polarization, they drove higher expression of the Th1-inducing T-bet transcription factor and IL12 receptor β2 chain [30]. CD70 was also shown to be capable of inducing Th1 cell differentiation independent of IL-12 in an *in vivo* study of Leishmania major antigen presentation by CD205+ dendritic cells [31].

In a different transgenic mouse that constitutively expressed CD70 on dendritic cells in a CD27 null background, administration of OT-1 T lymphocytes together with OVA peptide without adjuvant (normally a tolerogenic signal) was able to break tolerance and elicit CD8 T lymphocyte responses and memory which was independent of CD4 T lymphocytes [32,33]. These findings suggested that CD70 signals delivered by unstimulated, immature dendritic cells might contribute to failure of tolerance mechanisms and promotion of (auto)immune responsiveness.

CD70 also has intrinsic signaling properties after interacting with CD27 [17,18]. It has been reported that the soluble form of CD27 (sCD27) contributes to T lymphocyte activation [34]. *In vitro*, sCD27 is preferentially derived from TCR-activated CD4 T lymphocytes, and blocking CD70 by anti-CD70 significantly inhibited production of sCD27. Conversely, sCD27 has been shown to stimulate up-regulation of other surface molecules including CD40L on CD4 T lymphocytes and CD25, CD70, 4-1BB on CD8 T lymphocytes [34].

In apparent contrast to the above findings, several studies have shown that the CD27–CD70 pathway may have a suppressive effect on immune responses. In a mouse model of experimental autoimmune encephalomyelitis (EAE), constitutive CD27 signals via the JNK pathway were shown to impede activity of T helper 17