

Regulation of Inflammation by Bidirectional Signaling through CD137 and Its Ligand

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Although the majority of research on CD137 has been directed to T cells, it is becoming clear that this molecule has distinct functions in other lineages of cells, including non-hematopoietic cells. In particular, emerging evidence suggests that the CD137-its ligand (CD137L) network involving immune cells and non-immune cells, directly or indirectly regulates inflammation in both positive and negative manners. Bidirectional signaling through both CD137 and CD137L is critical in the evolution of inflammation: 1) CD137L signaling plays an indispensable role in the activation and recruitment of neutrophils by inducing the production of proinflammatory cytokines and chemokines in hematopoietic and non-hematopoietic cells such as macrophages, endothelial cells and epithelial cells; 2) CD137 signaling in NK cells and T cells is required for their activation and can influence other cells participating in inflammation via either their production of proinflammatory cytokines or engagement of CD137L by their cell surface CD137; 3) CD137 signaling can suppress inflammation by controlling regulatory activities of dendritic cells and regulatory T cells. As recognition grows of the role of dysregulated CD137 or CD137L stimulation in inflammatory diseases, significant efforts will be needed to develop antagonists to CD137 or CD137L.

[Immune Network 2012;12(5):176-180]

INTRODUCTION

Inflammation probably evolved to defend against infection or irritants and also co-evolved to adapt to tissue injury and

stress (1). This view is largely based on the observation that the initiation of inflammation can be triggered by common sensors to recognize both exogenous inflammatory inducers called pathogen-associated molecular patterns (PAMPs) and endogenous danger-associated molecular patterns (DAMPs). Inflammation is a tremendous price to pay for resolution of disruption to homeostasis (2). Sustained inflammation usually leads to massive tissue destruction appearing as inflammatory diseases.

Results obtained from CD137-deficient mice indicated that CD137/CD137L interactions might be involved in inflammation in models of autoimmune disease, infection, allergy or septic shock. Initially, it was thought that decreased inflammation in CD137-deficient mice was due to defects in the functions of lymphoid cells such as T cells, NK, and NKT cells or of myeloid cells such as neutrophils. Recent studies, however, suggest that CD137 can regulate inflammation by influencing various immune cells in a negative manner. Furthermore, it has been shown that reverse signaling through CD137L is essential in amplifying inflammation. In this mini-review, I discuss hypotheses that provide appropriate explanations for inflammation mediated by CD137 or CD137L signaling.

CD137 SIGNALS IN INFLAMMATION

Observations showing that lower extents of inflammatory diseases occur in CD137-deficient mice or mice treated with

Received on September 19, 2012. Revised on October 4, 2012. Accepted on October 12, 2012.

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Keywords: CD137, CD137L, Inflammation

Abbreviation: CD137L, CD137 ligand

CD137 blockers are considered to be evidence for the involvement of CD137 signaling in inflammation mediated by CD4⁺ T cells. For example, there is a milder disease severity in the absence of CD137 signaling in various types of immunological diseases such as rheumatoid arthritis, atherosclerosis, acute coronary syndrome, autoimmune myocarditis, herpetic stromal keratitis, allograft rejection, and graft-versus-host disease (3-13). CD137 signaling stimulates CD4⁺ T cells to produce the proinflammatory cytokines, IFN- γ and TNF- α (14). NK and NKT cells also use a similar signaling pathway through CD137 in mediating sepsis and airway inflammation, respectively (15,16).

Since CD137 is expressed in myeloid lineage cells, it was predicted that CD137 signaling would control inflammation by directly regulating their cellular activities. These cells include neutrophils (17,18), mast cells (19), eosinophils (20), and dendritic cells (21,22). CD137 signaling plays a critical role in defending against some bacterial pathogens. For example, CD137-deficient neutrophils are defective in their activities for phagocytosis and radical oxygen species (ROS) production, which is correlated with the susceptibility of CD137-deficient mice to *Listeria monocytogenes* infections (17). CD137 also may be involved in the resolution phase of inflammation, since its signaling can abrogate GM-CSF-mediated anti-apoptosis in neutrophils (18). CD137 signaling has positive and negative roles in mast cells and eosinophils for allergic inflammation, respectively: 1) CD137-deficient mast cells have defects in cytokine production and degranulation triggered by IgE, suggesting that CD137 signaling mediates allergic responses through activation of mast cells (19); 2) activation of CD137 inhibits GM-CSF- or IL-5-mediated anti-apoptosis of eosinophils in atopic dermatitis patients and extrinsic asthmatics (20). In contrast, CD137 is not expressed on eosinophils of patients with intrinsic asthma and idiopathic eosinophilia, therefore implicating that the absence of CD137 signaling is associated with the accumulation of eosinophils (20).

CD137 signaling in non-hematopoietic cells plays a critical role in inflammation. For example, CD137 is expressed in vessels of inflammation sites including endothelial cells and smooth muscle cells (4,5,23). CD137 signaling in endothelial cells results in the production of cytokines and chemokines and upregulation of cell adhesion molecules. However, CD137 may be involved in breaking down inflammation by inhibiting vessel permeability (unpublished data) and smooth muscle cell proliferation (4). It is interesting that regulation of acute versus chronic inflammation is governed by genetic

background (12,24; unpublished data). For example, CD137-deficient C57BL/6 mice have more severe acute inflammation (e.g., acute graft-versus-host disease), while having less severe chronic inflammation (e.g., obesity). The reverse case is true in CD137-deficient Balb/c mice.

There is evidence showing that CD137 signaling regulates inflammation in a negative manner (25,26). Mesenteric lymph node dendritic cells express CD137 and CD137 signaling in these cells controls the development of inducible regulatory T cells in the GALT by regulating retinal dehydrogenase, an enzyme that promotes the production of retinoic acid (25). Administration of anti-CD137 mAb induces the expansion of regulatory T cells and its immunosuppressive activity (26). Our unpublished data indicate that CD137 signaling controls the regulatory activity of hepatic NK cells and subsequently influences liver ischemia-reperfusion injury. In sum CD137 seems to play a role in the induction of immune tolerance or immunosuppression.

Considering that CD137 signaling is critical in the induction of inflammation, blocking of CD137 signaling should inhibit the progression of inflammatory diseases. Numerous reports support this view (8-10,27). However, it should be careful in interpreting data that come from experiments performed in the absence of CD137 signals (28). As discussed in the next section, CD137L reverse signaling is critical in inflammation.

CD137L REVERSE SIGNALING IN INFLAMMATION

CD137L is expressed in APCs and other myeloid cells (B cells, macrophages, dendritic cells, mast cells, and eosinophils) and non-hematopoietic cells (endothelial cells, fibroblasts, and epithelial cells) (26). Evidence supporting that CD137L signals play an *in vivo* physiological role in inflammation is just being emerged, even though accumulating evidence has demonstrated the existence of CD137L signals at molecular and cellular levels. For example, CD137L signaling mediates cellular functions ranging from cell differentiation, proliferation, and survival to the production of inflammatory mediators in a variety of cells (29).

It is now becoming clear that CD137L signaling is critical in multiple phases of inflammation. Inflamed vessels express CD137 and CD137L and CD137L signaling in endothelial cells leads to the production of proinflammatory cytokines and chemokines (4,5). Further, CD137L signaling may facilitate transendothelial migration of leukocytes through upregulation of cell adhesion molecules on endothelial cells (4,5). On the

other hand, CD137L signaling increases the expression of cell adhesion molecules on monocytes and promotes their extravasation (23). Since endothelial cells express both CD137 and CD137L, CD137-CD137L interactions between endothelial cells and leukocytes may amplify inflammation such a way that endothelial cells induce sustained production of inflammatory mediators and prime leukocytes before they arrive at inflamed tissue territories. In the tissues, it seems that CD137L signaling in recruited leukocytes, residential cells and parenchymal cells also is critical in the amplification of inflammation. Macrophages express CD137L on exposure to an inflammatory environment and produce high levels of proinflammatory cytokines and chemokines in response to CD137L signals (5,30,31). In collaboration with other inflammatory inducers, CD137L signaling results in the production of inflammatory mediators in macrophages in a synergistic manner (32), an indication that CD137L signaling is an amplifier of inflammation. It is noteworthy that CD137L can sustain TLR signaling by binding to TLRs without engagement of CD137 (31). Recently, we have identified a novel inflammatory pathway involving CD137L signaling in epithelial cells (33). In kidney ischemia-reperfusion injury, CD137 expressed on infiltrated NK cells stimulates CD137L in tubular epithelial cells to produce CXCR1 and 2 that are required for recruitment of neutrophils in the kidney. Since kidney ischemia-reperfusion injury does not occur without NK cells or neutrophils, it is thought that the axis of NK cell-tubular epithelial cell-neutrophils is the major pathogenic pathway for kidney ischemia-reperfusion injury (34).

There are few reports on the roles of CD137L signaling in disease context. As mentioned above, CD137L signaling is indispensable for kidney ischemia-reperfusion injury (33). Con-

sidering that CD137L signaling is critical in inflammatory responses, it is predicted that milder inflammatory diseases will occur in the absence of CD137L signals. Indeed, we have demonstrated that blocking of CD137L can inhibit inflammatory responses and prevent mortality in *Candida albicans*-induced sepsis (unpublished data). In this model, CD137 signaling enhances the phagocytic activity of neutrophils, whereas CD137L signaling induces massive cytokine production by macrophages following *Candida albicans* infection. In this model, agonistic anti-CD137 mAb has dual beneficial effects on *Candida albicans*-induced sepsis by promoting fungal clearance by neutrophils and downregulating cytokine production by macrophages.

CONCLUSION REMARKS

Emerging evidence suggests that both CD137 and CD137L signals play an important role in the evolution of inflammation. CD137 signaling in lymphoid cells such as NK, NKT and T cells, promotes inflammation by producing IFN- γ and TNF- α . However, the outcomes of CD137 signaling in regulatory T cells and neutrophils are connected to the suppression of inflammation. CD137 signaling in regulatory T cells and NK cells induces production of immunosuppressive cytokines that directly decrease inflammation (unpublished result). CD137 signaling in neutrophils can facilitate pathogen clearance and thus contributes to rapid resolution of inflammation (unpublished results). CD137L signaling seems to always have proinflammatory actions. Fig. 1 summarizes roles of CD137 and CD137L signals in inflammation.

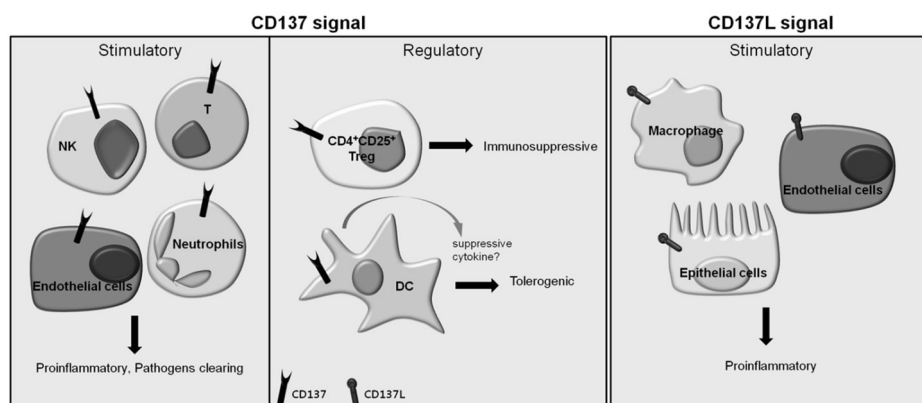


Figure 1. A schematic diagram showing a bidirectional signal transduction of the CD137 and CD137L pathway in inflammation.

CONFLICTS OF INTEREST

The authors have no financial conflict of interest.

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