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Minireview

Molecules and Cells

Reverse Signaling through the Co-Stimulatory Ligand, CD137L, as a Critical Mediator of Sterile Inflammation

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CD137 (also called 4-1BB and TNFRSF9) has recently received attention as a therapeutic target for cancer and a variety of autoimmune and inflammatory diseases. Stimulating CD137 *in vivo* enhances CD8$^+$ T cell-activity and results in strong immunosuppression in some contexts. This paradoxical phenomenon may be partially explained by the ability of CD137-stimulating reagents (usually agonistic monoclonal antibodies against CD137) to over-activate T cells and other CD137-expressing cells. This over-activity is associated with deleting pathogenic T cells and B cells or generating a tolerogenic microenvironment. Recent studies, however, suggest that the biology of CD137 and its ligand (CD137L) are more complex, mainly due to bidirectional signaling between CD137 and CD137L. For example, signaling through CD137L in non-hematopoietic cells such as epithelial cells and endothelial cells has been shown to play an essential role in sterile inflammation by regulating immune cell recruitment. One outstanding, and clinically important, issue is understanding how bidirectional signaling through CD137 and CD137L controls the vicious cycle of sterile inflammation (e.g., ischemia-reperfusion tissue injury and meta-inflammatory diseases).

INTRODUCTION

Inflammation is a highly coordinated process that probably evolved to defend against infection (Medzhitov, 2008). Recent studies, however, have demonstrated that inflammatory triggers are not restricted to viruses and microbes but also include a wide range of molecules released by stressed or damaged tissues. In either case, the main function of inflammation is to resolve disruptions to homeostasis (Barton, 2008). If infections are not resolved quickly or tissue injury is not properly repaired, tissue dysregulation leads to chronic infection or inflammatory disorders.

The inflammatory response is coordinated by a large range of mediators that form complex regulatory networks. Medzhitov (2008) has categorized these inflammatory signals into five functional groups: inducers, sensors, mediators, and effectors. Inducers of inflammation are danger signals, including microbe-derived factors, such as pathogen-associated molecular patterns (PAMPs) and virulence factors; non-microbe-derived factors, such as allergens, irritants, and toxic compounds; and endogenous inducers, such as damage-associated molecular patterns (DAMPs) and various cellular or tissue products. Sensors for inflammation recognize both exogenous and endogenous inflammatory inducers. The two typical sensors are Toll-like receptors (TLRs) and nucleotide-binding oligomerization-domain protein (NOD)-like receptors (NLRs). Inflammatory mediators originate in plasma or specific tissue resident immune cells or parenchymal cells and are converted into active forms. Alternatively, they can be produced directly in response to appropriate stimulation by inflammatory inducers (Kumar et al., 2003; Majno and Joris, 2004). Inflammatory mediators may have a variety of biochemical properties (Kumar et al., 2003; Majno and Joris, 2004), such as vasoactive amines, vasoactive peptides, fragments of complement components, lipid mediators, cytokines, chemokines and proteolytic enzymes. Inflammatory effectors are tissues and cells whose functions are affected by inflammatory mediators (Medzhitov, 2008).

Each type of inflammatory cell recruits and activates others based on sequential inputs of inflammatory inducers and mediators in the early stages of an inflammatory response (Nathan, 2002). This hierarchy of immune and tissue cells becomes obscure as immune cells are progressively recruited to sites of inflammation and each cell joins in amplifying the inflammation. Here, we discuss some of the amplification stages of sterile inflammation in the context of cell-cell interactions.

Sterile inflammation

An inflammatory response triggered by tissue damage is difficult to discern from inflammation induced by infection, since many types of tissue injuries are associated with infection. Sterile injury, however, can be caused by trauma, ischemia, and ischemia-reperfusion injury without concomitant infection. Malfunctioning cells produce a broad range of metabolites that

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have recently been recognized to induce low-grade sterile inflammation. In addition to intracellular danger signals, a number of extracellular substances have DAMP-like properties after proteolytic digestion (Rosin and Okusa, 2011). The DAMP sensors are the same receptors used by PAMPs such as TLRs and NLRs. Therefore inflammation evolved to manage both external and internal danger signals and ultimately restore homeostasis.

CD137L signaling pathways

CD137L is expressed mainly in myeloid cells (macrophages, dendritic cells, mast cells, and eosinophils) and non-hematopoietic cells (endothelial cells, fibroblasts, and epithelial cells) (Kwon, 2009). Though rare reports show that CD137L signals play a physiological role *in vivo*, accumulating evidence has shown that CD137L signals can be delivered to mediate cellular functions ranging from cell differentiation, proliferation, and survival to production of inflammatory mediators in a variety of cells (reviewed in Shao and Schwarz, 2011).

Tumor necrosis factor superfamily members commonly have a reverse signal transduction pathway, including FasL (Sun and Fink, 2007). The most thorough studies on CD137L signaling have been done in professional antigen-presenting cells. For example, CD137L binding induces B cell proliferation and immunoglobulin production (Pauly et al., 2002). In particular, prominent phenotypic changes in monocytes/macrophages follow CD137L stimulation, such as cell proliferation, production of pro-inflammatory cytokines and chemokines, and up-regulation of cell adhesion molecules, thus enhancing the inflammatory response in an autocrine or paracrine fashion (reviewed in Shao and Schwarz, 2011). CD137L signaling mediates similar activities in dendritic cells that are observable in monocytes/macrophages: cross-linking CD137L enhances the expression of co-stimulatory ligands and MHC molecules and cytokine release (Lippert et al., 2008).

Deficient CD137L signaling induces myelopoiesis (Lee et al., 2008). CD137L signaling does not regulate only hematopoiesis in myeloid cells. The absence of CD137L signaling promotes B-cell differentiation in the bone marrow. Since B lymphoma is frequent in CD137L Knockout (KO) mice, CD137L signaling seems to control peripheral B-cell differentiation (Middendorf et al., 2009). Another example inhibiting mature cell differentiation is that CD137L-deficient bone marrow macrophages have a higher capacity for differentiation into osteoclasts (Shin et al., 2006). Dysregulated immune cell differentiation caused by deficient CD137L signaling has not been associated with inflammation but unpublished results demonstrate that CD137 KO mice have severe inflammation in some organs that correlate with tissue neutrophilia. Overall, CD137L signals are likely important for cell maturation in the periphery.

As described below, CD137L signaling in non-hematopoietic cells is essential for tissue inflammation (Jeon et al., 2010; Kim et al., 2012a). Epithelial cells are the cells most commonly damaged by intracellular and extracellular insults, and therefore often initiate inflammation (Swamy et al., 2010). In renal ischemia-reperfusion injury, CD137L signals are required to recruit neutrophils (Kim et al., 2012a). The endothelial cells of vessels in atherosclerotic lesions express both CD137 and CD137L (Jeon et al., 2010; Olofsson et al., 2008). Since CD137 and CD137L signals can promote leukocyte transmigration by inducing pro-inflammatory cytokines and chemokines and by up-regulating cell adhesion molecules in endothelial cells (Jeon et al., 2010), endothelial cells seem to activate either CD137- or CD137L-expressing leukocytes during transmigration into inflammation sites. Thus, the bidirectional signaling between CD137 and CD137L provides an efficient way for endothelial cells and leukocytes to sustain mutual activation. Immune cells that stimulate CD137L on epithelial cells (presumably endothelial cells) early during inflammation are CD137-expressing NK cells (Kim et al., 2012a). Later, T cells are the major CD137-expressing cells and may engage CD137L on macrophages. Whether CD137L signaling in macrophages either increases or resolves inflammation remains to be determined.

The molecules downstream of CD137L signaling are now being identified. The cytoplasmic domain of CD137L has casein kinase phosphorylation sites (Croft, 2009), suggesting that proximal signaling may be initiated by docking adaptors binding to sites phosphorylated by a casein kinase δ (unpublished data). The downstream signaling pathway includes activation of Src tyrosine kinase, PI3K, p38 MAPK, ERK1/2, JNK, and the transcription factor NF-κB (Shao and Schwarz, 2011). Recent studies have demonstrated that AKT and mTOR/p70S6 kinases are required to up-regulate cytokines and cell adhesion molecules in monocytes following CD137L stimulation (Kim et al., 2009). CD137L can form a complex with TLRs and sustain TNF production by TLRs, which occurs independent of CD137 (Kang et al., 2007).

CD137L signals in ischemia-reperfusion renal injury

The role of CD137L signaling has been most thoroughly investigated in an animal model of renal ischemia-reperfusion injury (Kim et al., 2012a). Since epithelial cells line the surfaces of organs or internal cavities, they are particularly vulnerable to injury by pathogenic microorganisms, toxic factors and physical trauma. Epithelial damage results in changes, including secreted endogenous inflammatory inducers and mediators and altered cell surface molecules, that allow epithelial cells to interact with immune cells and other mesenchymal cells (Swamy et al., 2010). Even though progress in understanding how surface antigens on stressed epithelial cells regulate immune cells has been made, little is known about the cell surface receptors that make immune cells targets for epithelial cells. In renal ischemia-reperfusion injury, hypoxia occurs early during ischemia, followed by inflammatory responses during reperfusion. These injured cells release endogenous inducers of inflammation, including pro-inflammatory cytokines, complement products, and endogenous danger signals recognized by TLRs. In ischemic kidneys, TLR activation, cytokine stimulation, and complement activation all induce expression of multiple pro-inflammatory chemokines. The tubular epithelium is a major site of cell injury and such changes. Even though neutrophil influx is characteristic of acute inflammation, how damaged tubular epithelial cells regulate neutrophil infiltration into post-ischemic kidneys is not understood.

We observed that CD137L was constitutively expressed on tubular epithelial cells and that CD137 KO or CD137L KO mice were severely impaired in renal ischemia-reperfusion injury. The observation that stimulating CD137 using an agonistic anti-CD137 monoclonal antibody blocks rather than enhances renal ischemia-reperfusion injury suggests that reverse signaling through CD137L plays a pivotal role in renal ischemia-reperfusion injury. Indeed, engaging CD137L using recombinant CD137L-Fc fusion protein completely recovered renal ischemia-reperfusion injury in CD137 KO mice.

Other studies (Leemans et al., 2005; Wu et al., 2007) have demonstrated that TLR2 or TLR4 deficiencies in tubular epithelial cells result in severe defects in neutrophil infiltration in renal ischemia-reperfusion injury, similar to that observed in CD137 KO or CD137L KO mice. To investigate whether CD137L signals in tubular epithelial cells are involved in recruiting neutro-

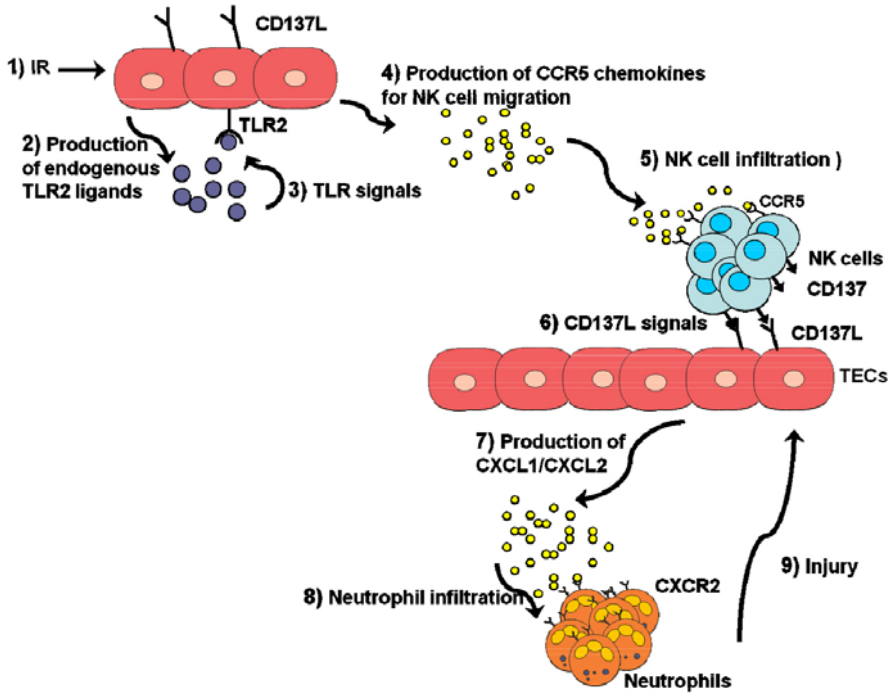

Fig. 1. The sequential pathway leading to renal ischemia-reperfusion injury. Ischemia damages tubular epithelial cells (TECs), which in turn release endogenous TLR ligands. TLR signals induce chemokine production for NK cell chemotaxis. NK cells stimulate TECs to secrete CXCR2 chemokines to recruit neutrophils. Neutrophils are the final effector cells that mediate ischemia-reperfusion renal injury.

phils in renal ischemia-reperfusion injury, we devised a system to allow CD137L signaling in tubular epithelial cells of CD137L KO mice. Implantating wild-type tubular epithelial cells under the kidney capsules of CD137L KO mice restored renal ischemia-reperfusion injury, suggesting that reduced CXCL1 and CXCL2 production in tubular epithelial cells and the consequent impaired neutrophil recruitment were associated with resistance to renal ischemia-reperfusion injury in CD137 KO or CD137L KO mice. Stimulating tubular epithelial cells with recombinant CD137-Fc protein *in vitro* rapidly releases CXCL1 and CXCL2, which induce neutrophil migration.

Bone marrow reconstitution experiments indicated that CD137 expression on hematopoietic cells was required for renal ischemia-reperfusion injury. Among hematopoietic cells, CD137-expressing natural killer (NK) cells are recruited to the kidney early in renal ischemia-reperfusion injury. The basement membrane separating tubular epithelial cells from other mesenchymal cells was disrupted rapidly after renal ischemia-reperfusion injury and NK cells approached tubular epithelial cells. Adoptive transfer of wild-type NK cells completely restored renal ischemia-reperfusion injury in CD137 KO mice. In addition, active NK cells expressing CD137 stimulated tubular epithelial cells to produce high levels of functional CXCL1 and CXCL2. On the other hand, depleting NK cells completely abrogated neutrophil recruitment into the kidney and the subsequent renal ischemia-reperfusion injury.

Since CD137 KO NK cells were recruited after renal ischemia-reperfusion injury, CD137 on NK cells and CD137L on epithelial cells should have interacted and contributed to epithelial dysregulation. Accumulating evidence has shown that TLR2 and TLR4 on tubular epithelial cells function as sensors for endogenous inflammatory inducers and play roles in cytokine and chemokine production and neutrophil infiltration (Leemans et al., 2005; Pulskens et al., 2008; Shikeoka et al., 2007; Wu et al., 2007). Therefore, the impaired neutrophil recruitment in CD137 KO mice might lie downstream of TLR signals, more specifically between influx of NK cells and neutrophil recruitment following renal ischemia-reperfusion injury. Indeed, TLR2 KO mice had defects in recruiting NK cells and neutrophils after renal ischemia-reperfusion injury (unpublished data). Injecting CCR5 antagonists inhibited NK cell recruitment, followed by defects in neutrophil infiltration and decreased ischemia-reperfusion injury (unpublished data), thus ischemia-reperfusion likely induces production of CCR5 chemokines to recruit NK cells to the injured kidney. The cells that produce CCR5 chemokines in response to endogenous TLR ligands remain to be identified, but tubular epithelial cells are candidates, considering the TLR expression pattern (Leemans et al., 2005; Wu et al., 2007). Figure 1 summarizes the sequential events leading to ischemia-reperfusion renal injury.

Our findings raise some interesting points. Injured cells (tubular epithelial cells in ischemia-reperfusion injury) seem to be major players regulating the induction of sterile tissue inflammation by sequentially recruiting NK cells and neutrophils. This mechanism is quite different from inflammation induced by infection: tissue macrophages are primarily responsible for recruiting neutrophils in response to pathogens. Thus, tissue inflammation may be directed by the sensitivity or responsiveness of tissue resident cells when exposed to danger signals (for example, injured tubular epithelial cells are more sensitive to DAMPs than kidney macrophages, which may be superior responders to PAMPs). Reports have shown that NK cells mediate renal ischemia-reperfusion injury by killing tubular epithelial cells (Zhang et al., 2008). Since renal ischemia-reperfusion injury does not occur without neutrophils (Kim et al., 2012a), the main function of NK cells seems to be recruiting neutrophils by stimulating tubular epithelial cells to secrete CXCR2 chemokines. CD137 signals, however, either enhance NK-cell effector function (cytotoxicity and cytokine production) directly (Melero et al., 1998) or play a role in activating or differentiating conventional T cells mediated by NK cells (Wilcox et al., 2002). Since CD137 signals in NK cells increased their cytotoxicity against

tubular epithelial cells (Kim et al., 2012a), NK cell-induced damage of tubular epithelial cells does not seem to result in fulminant renal ischemia-reperfusion injury. Finally, bidirectional signaling via CD137 in lymphoid cells and CD137L in myeloid and parenchymal cells, such as epithelial cells and fibroblasts, may enhance immunity. Our findings also require re-evaluating the modulating effects of anti-CD137 monoclonal antibodies or recombinant CD137-Fc fusion protein on a number of *in vivo* biological activities, considering that stimulating CD137 necessarily results in a blockade of CD137L signals and *vice versa*.

CD137L signaling in other inflammatory diseases

Obesity is associated with a number of diseases, including type 2 diabetes and atherosclerosis (Ouchi et al., 2011). CD137 KO mice were resistant to obesity-related atherosclerosis and type 2 diabetes (Jeon et al., 2010; Kim et al., 2011). CD137 expression is induced in endothelial cells in response to pro-inflammatory cytokines and that stimulating CD137 results in up-regulated cell adhesion molecules in endothelial cells (Olofsson et al., 2008). In addition, CD137 and APOE or LDLR double KO mice are resistant to atherosclerosis induced by high fat diet (Jeon et al., 2010). Atherosclerotic lesions comprise T cells expressing CD137, macrophages expressing CD137L, and endothelial cells expressing both CD137 and CD137L, suggesting that inflammation should be amplified by bidirectional signaling in this cell network.

CD137 deficiency protects against high fat-induced obesity, glucose intolerance and liver steatosis (Kim et al., 2011). The mechanism underlying this observation has yet to be determined; however in obesity, a pro-inflammatory microenvironment likely builds up in adipose tissues. Since macrophages play a key role in the inflammation in adipose tissues, the absence of CD137L signaling in macrophages may explain the decreased inflammatory response in adipose tissue of CD137L KO mice.

Even though CD137L signals play a critical role in acute and chronic inflammation, more severe inflammation occurs in some disease models in CD137 KO mice (unpublished data). These diseases include streptozotocin-induced type 1 diabetes, cisplatin-induced systemic toxicity, bleomycin-induced pulmonary fibrosis, and GVHD following total body irradiation (unpublished data). Two hypotheses can explain this phenomenon. First, CD137 or CD137L signaling may be important for regulatory cell function or may function as brake systems to prevent immune cell over-activation. For example, CD137 signals are important for expanding the immunosuppressive activity of regulatory $CD4^+$ T cells (Kim et al., 2012b). $CD8^+$ T cells release IL-13 as well as IFN-γ by CD137 signaling and agonistic anti-CD137 monoclonal antibody induces more severe hepatitis in IL-13 KO mice (Shin et al., 2008). CD137 KO mice are hyper-responsive to tumors (Choi et al., 2010), likely due to the absence of CD137L signaling in the cells responsible of forming an immunosuppressive microenvironment within the tumor (unpublished data). Second, abnormally heightened myelopoiesis in CD137 KO or CD137L KO mice may be associated with elevated inflammatory response in these knockout mice. For example, a high number of neutrophils in the liver of CD137 KO mice are relevant to severe hepatic ischemia-reperfusion injury developing (unpublished data). There is also a positive correlation between the severity of bleomycin-induced pulmonary fibrosis and the number of resident macrophages in the lung of CD137 KO mice (unpublished data).

CONCLUSIONS

Systemically identifying activities that are mediated by CD137 signals and which by CD137L signals is difficult, due to a lack of *in vivo* analytical tools. The *in vivo* physiological consequences of CD137L signaling have just emerged, since a variety of tools to specifically block CD137 or CD137L signals became available, including CD137 and CD137L KO mice, anti-CD137 monoclonal antibodies, recombinant CD137-Fc fusion proteins and cell transfer and implantation technique (Kim et al., 2012a). The experimental tools used by Kim et al. (2012a) will help to solve questions related to CD137 and CD137L bidirectional signaling, including how CD137/CD137L interactions simultaneously enhance inflammation and T-cell immunity, a particularly challenging question. Investigating the spatiotemporal expression of CD137 and CD137L in inflamed tissues (Kim et al., 2011) may reveal that CD137 and CD137L signals are involved in multiple steps of the inflammatory response, including resolving of inflammation. The molecular mechanisms of the CD137L signal transduction pathway will also provide insight into tissue inflammation.

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