Multifaceted regulation of T cells by CD44

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CD44 is a widely-expressed adhesion receptor that is associated with diverse biological processes involving migrating cells, including inflammation, angiogenesis, bone metabolism and wound healing. In the immune system, CD44 is upregulated after activation of naive T lymphocytes during their responses against invading microbes. Once an infection is cleared, elevated levels of CD44 remain on the surface of memory T cells that mediate protection against re-infection. While this has led to the use of highly sustained CD44 expression on T cells as an indicator of a previous immune response, the relevance to T-cell responses or homeostasis has been largely unexplored. Our recent studies demonstrate that CD44 selectively regulates the survival of the Th1 subset of CD4 T cells, but not other T-cell subpopulations. These findings, together with studies of CD44 in other cell types, suggest that differences in the engagement of signaling mechanisms are likely to underlie differential regulation of T-cell responses and underscore the importance of this adhesion receptor to immune cell regulation and protection against viruses and intracellular bacteria.

Introduction

CD44 is a type I transmembrane glycoprotein with a C-type lectin domain in the N-terminal domain that binds the major in vivo ligand, hyaluronic acid (HA), a glycosaminoglycan component of the extracellular matrix (ECM) involved in maintaining tissue integrity.1 Encoded by a single gene containing 21 exons, Cd44 gives rise to a family of molecules with an invariant form and at least 5 isoforms generated by alternative mRNA splicing. Although all forms of CD44 bind HA, the affinity is regulated by post-translational modifications such as glycosylation and sialylation.2,3 Most cells, including resting T cells, express the invariant form of CD44. We have not detected CD44 variants on murine CD4 T-cell subsets, including Th1, Th2 or Th17 cells.4 However, isoform expression is observed on T cells that infiltrate target tissues in various autoimmune and inflammatory diseases5,6 and transient expression of CD44 variants can occur.7 CD44 can be activated from a low to high affinity state on T cells by HA-binding itself,8,9 TCR engagement,8 and responses to cytokines/chemokines.10 Furthermore, T cell-derived IL-2, TNFα and IFNγ can regulate HA binding to monocyte CD44, highlighting the potential indirect effects that T cells may have on CD44 function on other cell types.11,12 In this review, the consequences of CD44 engagement on T-cell migration and signaling will be discussed specifically.

The Role of CD44 in T-Cell Migration

CD44 has been best characterized as an adhesion receptor engaged by migrating T cells. On activated T cells, CD44 can regulate tethering and rolling interactions with vascular endothelial cells that express HA.13 These findings demonstrate that CD44 could provide an alternative to usage of the selectin family of C-type lectins in initiating the multistep adhesion cascade that leads to the extravasation of lymphocytes from the blood via the endothelium into tissues. The CD44-dependent adhesion mechanism is likely to be most important for the mobilization of effector T cells at sites of infection and inflammation because expression of CD44 is upregulated whereas L-selectin (CD62L), the lymphocyte-expressed selectin, is downregulated. In vitro, CD44 associates with the integrin VLA-4 (α4/β1; CD49d/CD29) in the membrane of activated T cells through its cytoplasmic tail, and in vivo this receptor combination can regulate T-cell extravasation into the peritoneum after induced inflammation.14,15 The association between the two surface receptors thereby not only allows for firm adhesion, but also could provide each with access to the other’s signaling pathways, which would otherwise be unavailable. Deletion of the cytoplasmic tail of CD44 prevents firm adhesion of cells to the endothelium, highlighting the importance of the molecules’ association for T-cell extravasation. The VLA-4-ligand, VCAM-1, is induced on endothelial cells in response to inflammatory cytokines and HA synthesis and expression are also augmented. However, CD44-dependent tethering/rolling could also occur independently of HA via binding to E-selectin, which is expressed on activated endothelium.16 However, we and others have shown that CD44-independent mechanisms can also regulate effector T-cell recruitment to sites of inflammation or tumor implantation because CD44-deficiency does not impair migration.4,17 The major alternative pathway is the binding of P-selectin glycoprotein ligand-1, a selectin-ligand expressed on T cells, to E and/or P selectin, which are induced on inflamed endothelium.18,19 The relative dominance of CD44 or selectins in regulating effector T-cell migration appears to be associated with environmental cues that include the magnitude and duration of inflammation.

In addition to the well-established role of mediating T-cell extravasation, CD44 also has a crucial function in regulating
cell motility within the tissue stroma. In tissue-resident T cells, CD44 and other adhesion receptors accumulate at the trailing edge, or uropod, that is the part of the cell body that is in contact with the ECM.\textsuperscript{20,21} Interactions of ERM (ezrin/radixin/moesin) proteins with the cytoplasmic tail of CD44 can contribute to the stabilization of a polarized cell shape that is necessary for migration. ERM proteins regulate cytoskeletal organization through interactions with actin\textsuperscript{22} and are involved in the generation of the uropod of a migrating T cell.\textsuperscript{23} A recent study highlighted the importance of CD44-mediated polarity on interstitial migration in a cancer model, where anti-tumor activity of CD44\textsuperscript{17} CD8 T cells was compromised as a consequence of defective migration.\textsuperscript{24} Thus, CD44 expression in T cells in the interstitial space may be essential to maintain cell shape during active migration. As movement takes place, CD44 anchorage of the cell’s uropod to the ECM is disengaged by proteolytic activity. Cleavage of the extracellular domain (ECD) of CD44 is mediated by membrane type metalloproteinases (MT1-MMP) on responding T cells.\textsuperscript{24} In tumor cells, metalloproteinases belonging to the ADAM (a disintegrin and metalloproteinase domain) family play an important role in ECD cleavage.\textsuperscript{25} Unlike in T cells, CD44 localizes at the leading edge of the cell and is cleaved by ADAM-17, which allows for the redistribution of both molecules and movement of the cell. The resulting extension of the cell was proposed to upregulate Ca\textsuperscript{2+}-induced ADAM-10 activation in the uropod, where cleavage of CD44 and detachment from the ECM subsequently occur.\textsuperscript{26} It is unknown if ADAM-10 and -17 have similar roles in T cells, especially since CD44 seems to be primarily located in the uropod.\textsuperscript{20,22} However, through its interaction with CD49d, CD44 may gain access to the leading edge of activated, migrating T cells where it would be able to interact with ADAM-17.\textsuperscript{24}

The release of soluble CD44 ECD could regulate the ability of T cells to interact with the ECM during migration by inhibition of CD44-dependent cell-cell and cell-matrix interactions.\textsuperscript{27} Cleavage of CD44 ECD initiates the intramembrane cleavage and release of the intracellular domain (ICD) by presenilin-1/γ secretase.\textsuperscript{28,29} The resulting cytoplasmic fragment translocates to the nucleus where it may be directly or indirectly involved in gene transcription.\textsuperscript{30} At least one of the targets of the ICD is the transcriptional co-activator CBP/p300 and activation results in part in the upregulation of Cd44 itself and de novo CD44 production.\textsuperscript{28} Whether this occurs in T cells is also unknown.

Thus, CD44 can function to mediate entry of T cells to target sites, as well as cell motility within these tissues. The rapid activation and proteolytic degradation of CD44 could allow efficient cell migration and as such is crucial for the potency of T cell effector functions.

**Regulation of T-Cell Responses by CD44**

In addition to regulating adhesion during T-cell migration, it is also apparent that CD44 has underappreciated roles in regulating effector T-cell responses. CD44 appears to be the predominant HA-binding protein normally expressed by activated T cells.\textsuperscript{31} The binding of CD44 on the surface of T cells to HA on the surface of dendritic cells (DC) can promote cell clustering, suggesting a role in T cell-DC conjugate formation, which is necessary for the induction of an immune response. In addition, CD44 is shown to be recruited to lipid rafts at the immunological synapse on DCs, where it contributes to the stability of DC-T cell interactions, as well as augmentation of T-cell proliferation and cytokine responses.\textsuperscript{32} The ligand on T cells that promotes this effect has not been identified, but synthesis of HA by activated T cells has been described.\textsuperscript{31}

Although CD44 can directly regulate proliferation of various cell types,\textsuperscript{34} and ligation has been reported to enhance T-cell proliferation to TCR signaling in vitro,\textsuperscript{35,36} we have not detected a direct role in modulating T-cell expansion during an immune response in vivo.\textsuperscript{4} Although in vitro studies have suggested that CD44 can act as a co-stimulatory molecule for the production of cytokines from activated T cells, using adoptive transfer models, we have not found evidence for this function in vivo in studies of the immune responses of CD44-deficient CD4 T cells to influenza virus infection or antigen-presenting DCs.\textsuperscript{4} Furthermore, CD44-deficient CD8 T cells do not have impaired induction of immune responses after adoptive transfer to normal recipients.\textsuperscript{17} Nevertheless, we observe a function for CD44 in regulating the survival of CD4 T cells by sustaining the immune response, which is necessary for development of protective memory cells.\textsuperscript{4} This effect was observed for Th1 CD4 cells, but not for other subsets of CD4 T cells or CD8 T cells. The death of CD4 T cells responding to influenza virus infection was recapitated in CD44-deficient mice as well as by antibody-mediated blocking of HA-binding by CD44.\textsuperscript{31}

Additional studies have shown a non-redundant role of CD44 in the function of regulatory CD4 T cells (Tregs), which are essential for the prevention of autoimmunity. In vitro, Tregs from CD44-deficient mice have an impaired capacity to inhibit T-cell responses and diminished production of the cytokines, TGFβ1 and IL-10,\textsuperscript{37} which are necessary for their function. We find that CD44-deficient Tregs fail to persist after transfer in vivo (our unpublished observations). In vitro ligation of CD44 on activated wild-type Tregs promotes persistent expression of the transcription factor FoxP3, which is essential for regulatory activity.\textsuperscript{37} These functions of CD44 are shown to depend upon interactions with high molecular weight forms of HA that are found in the absence of inflammatory responses.

**Regulation of Activation-Induced Cell Death by CD44**

Regulation of cell death is an important mechanism to maintain homeostasis of antigen-reactive T cells. The generation and expansion of effector T cells during a response requires survival signals, whereas the attrition of the cells after an infection depends upon regulated cell death. There is considerable evidence that CD44 can regulate apoptosis in T cells. However, roles in both resistance and susceptibility to cell death have been described, suggesting that it participates in the control of expansion. Some of the discrepancies are likely due to differences in the T cells and model systems that have been used, particularly antibody-mediated ligation of CD44. Both agonist and antagonist
effects of CD44 can occur with induction or prevention of cell death in vitro, respectively.48-50 In vitro studies using T cells from CD44-deficient mice suggest that the absence of CD44 confers resistance to apoptosis and demonstrate that HA binding by wild-type cells elicits apoptosis.50 In vivo, the absence of CD44 or the CD44 variant, v7, ameliorates T-cell dependent induced inflammation models that include arthritis and inflammatory bowel disease,41,42 but not others such as hepatitis.51 Antibody-mediated blocking of CD44 in vivo generally has protective effects in models of chronic inflammatory disease.52 Because CD44 is so broadly expressed on cells that are engaged in inflammatory responses, it is impossible to determine if generic CD44 blocking or deletion in T cells specifically ameliorated clinical signs.

Several mechanisms by which CD44 can protect against cell death in T cells have been identified. CD44 has been shown to interact with the cytokine, osteopontin, which can provide a survival signal and protect from activation-induced cell death.53 CD44 has been found to associate with death receptor, CD95 (FAS), on apoptosis-resistant tumor cells and has been proposed to inhibit apoptosis by sequestering FAS and preventing assembly of death-inducing signaling complex (DISC) (Fig. 1A).

Our studies with the adoptive transfer model, where only CD4 T cells lacked CD44 expression, directly demonstrate a role in protection against cell death that is mediated by CD44. We have recently shown that CD44-induced Akt activation (Fig. 1B). Both calcium influx and PI3K activation are thought to depend on Lck activation and the DISC. Without DISC formation, Fas ligand (FasL) cannot engage FAS, which precludes downstream activation of caspases that would lead to apoptosis. (B) Ligation of CD44 (e.g., through HA) can facilitate aggregation of CD44-integrin-kinase signaling components in lipid rafts. Src family kinases, such as Lck, associate with the cytoplasmic tail of CD44 and activate the PI3K/Akt signaling pathway. Alternatively, binding of either CD44 or VLA-4, which form a heterodimer at the cell surface, could activate PI3K through FAK. Activation of PI3K/Akt is associated with cell survival. Akt can inhibit Fas-mediated CD4 T-cell death by interfering with DISC assembly. In addition, the mTOR pathway may be engaged to support the survival and expansion of T cells.

Signal Transduction in T Cells via CD44

Ligation of CD44 can have an important role in signaling events that shape the immune response. However, CD44 lacks intrinsic signaling activity and the signaling pathways coupled to CD44 are not fully defined. Signaling can differ in different cell types and may depend on the proteins with which CD44 associates (e.g., VLA-4). Most studies have been performed with T-cell lines, and little is known regarding signaling events in primary T cells. CD44 engagement can facilitate aggregation of CD44-integrin-kinase signaling components in lipid rafts.44,45 Kinases that associate with the cytoplasmic tail of CD44 include the Src family kinases, Lck and Fyn,44,46,47 which can be activated through HA binding. Src family kinase activity is necessary for CD44-induced actin rearrangement, which is required for cell spreading.48 Lck appears to have a greater role than Fyn in CD44-mediated signaling in T cells and its function can be modulated by the transmembrane tyrosine phosphatase, CD45.49 Ligation of CD44 by HA can also activate the PI3K/Akt signaling pathway, which is associated with cell survival in various cell types, including T cells.40,43 We have recently shown that CD44-induced Akt activation is particularly important for Th1 cells.4 Activiation of PI3K/Akt can inhibit Fas-mediated CD4 T-cell death by interfering with DISC assembly.50 We hypothesize that this pathway is initiated by the binding of the intracellular domain of CD44 to Lck (Fig. 1B). Both calcium influx and PI3K activation are thought to depend on Lck activation after CD44 ligation.49,51 However, PI3K could also be activated through FAK since CD44 co-localizes with VLA-4, which in turn binds FAK. Thus, ligation of either CD44 or VLA-4 could activate PI3K through FAK.14,15,45,52 Activation of the PI3K/Akt pathway is also associated with various aspects of T-cell migration, including actin reorganization and cell motility.53 Thus, engagement of CD44 represents one means by which interactions with the environment and the ECM can be translated into a cellular response.

Pathways that mediate the effects of CD44 downstream of PI3K/Akt signaling have not been widely studied in T cells. However, we observe that PI3K/Akt activates p70 S6K downstream of the mammalian target of nutrient sensing rapamycin (mTOR) pathway (our unpublished results, Fig. 1B). mTOR, which can exist both in the TORC1 and TORC2 complexes, is activated both downstream and upstream of Akt. The TORC1
complex is essential for the differentiation of CD4 cells into Th1, Th2 and Th17 effector cells. The mTOR pathway may be engaged during the effector T-cell response to support the survival and expansion through engagement of inhibitors of apoptosis that include the X-linked inhibitor of apoptosis protein (XIAP) and survivin, which target both intrinsic and extrinsic apoptosis cascades by inhibiting caspases. Recently, activation of mTOR in the TORC2 complex has been associated with the differentiation of Th1 and Th2 cells but not Th17 cells. Furthermore, TORC2 regulates Th1 cell differentiation via Akt, but Th2 cell differentiation through PKC. Interestingly, TORC2 is necessary for the proliferation of T cells but not their survival. Dissecting the role of CD44 signaling in primary T cells will provide more information on other functions of CD44 and may provide potential molecular targets that can be exploited to modulate T-cell responses during an ongoing immune response.

Conclusions

Although CD44 is associated with multiple functions in various cell types, it is now evident that this surface receptor has unique roles in regulating the survival of Th1 cells and the function of Tregs. This is surprising because CD44 is upregulated during an ongoing immune response. However, Th1 cells may uniquely require additional survival signals through CD44 engagement of PI3K/Akt because of their elevated levels of Fas and inherent ability to rapidly assemble the DISC in response to Fas trimerization. Such a mechanism may not be necessary in Th2 cells, and possibly other subsets of T cells, because of a greater capacity to engage PI3K/Akt in response to activation in addition to overall lower levels of Fas expression. Low molecular weight fragments of HA, which are generated during an immune response, may regulate Th1 cells, whereas Tregs may be maintained by high molecular weight HA to maintain tolerance to self tissues. It is likely that differences in the engagement of signaling pathways in the various T-cell subsets after ligation of CD44 account for their differing responses that impact the outcomes of effector and memory T-cell generation. CD44 has previously been shown to regulate cell migration, but it is now apparent that CD44 plays previously unappreciated key functions in T-cell responses to regulate immunity and control autoimmunity.

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