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RESEARCH HIGHLIGHT

Sema 4D/CD100-plexin B is a multifunctional counter-receptor

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The discovery of Sema 4D can be dated to 1992, when Boumsell's team reported a novel 150-kDa glycoprotein dimer. It was expressed on T lymphocytes that had been activated with CD3 monoclonal antibody or phytohaemagglutinin.[1] Hence, this molecule has been designated CD100 by the International Workshop on Human Leukocyte Differentiation Antigen. In 1996, 3 years after the discovery of the semaphorin family,[2] the CD100 gene was cloned and identified as the first semaphorin with immune system functions.[3] Unlike the prototypical semaphorins, which are neuronal chemorepellents, Sema 4D/CD100 together with Sema 3A, Sema 4A, Sema 6D and Sema 7A have been described as 'immune semaphorins', because they are expressed on T cells, B cells, natural killer cells and dendritic cells, and exhibit a variety of immunological functions.[4]

The Sema 4D/CD100 molecule can bind to several receptors. CD72, a member of the C-type lectin family, is a low-affinity Sema 4D/CD100 receptor that is expressed on immune cells, such as B cells, dendritic cells, macrophages and mast cells (Figure 1a).[5] At least three Sema 4D/CD100 receptors are plexin family members. The high-affinity Sema 4D/CD100 receptor plexin B1 is mainly expressed on endothelial cells and epithelial cells (Figure 1b),[6] whereas plexin B2 and plexin C1 are low-affinity receptors for Sema 4D/CD100.[7]

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Recently, Witherden *et al.*[8] demonstrated that the interaction of Sema 4D/CD100 with plexin B2 plays a key role in activating skin-resident γδ T cells (DETCs) in mice to respond to tissue damage (Figure 1c). The morphological changes in DETCs that precede cutaneous wound healing appear to be associated with the activation of key actin regulators in response to Sema 4D/CD100's binding with its ligand. This is the first example indicating that Sema 4D/CD100 is not only a ligand for plexin B1 or CD72 but also a direct signaling receptor in mediating Sema 4D/CD100-plexin B's biological functions. It is not surprising to identify Sema 4D/CD100-plexin B as a counter-receptor, because many counter-receptors have already been well documented in the B7-CD28 family and TNF–TNFR superfamilies.

Another important point in Witherden's paper[8] is that the Sema 4D/CD100 molecule on γδ T cells mediates a function involved in innate immunity. Bonneville[9] pointed out that plexin B2 is broadly expressed on many epithelial tissues where resident CD100-expressing γδ T cells are located, suggesting that the Sema 4D/CD100–plexin B2 interaction may play a more general role in the immune control of the integrity of epithelial barriers.

It is thought that, similar to αβ T cells, complete activation of DETCs requires costimulatory signals. DETCs do not express many of the usual coreceptors that are important for αβ T-cell activation, such as CD4 or CD8, or the costimulatory molecule CD28. In 2010, Witherden *et al.*[10] identified a receptor–ligand pair, junctional adhesion molecule-like molecule and the cocksackie adenovirus receptor (CAR), which plays a crucial role in the DETC response. In addition, DETCs can recognize a stress- or damage-induced keratinocyte self-antigen through their γδ T-cell receptor (TCR), without the requirement for antigen presentation by MHC class I or class II molecules. More recently, Komori *et al.*[11] demonstrated the presence of an as yet-uncharacterized antigen that is expressed on the surface of damaged keratinocytes and is recognized by the canonical TCR expressed by DETCs. Furthermore, Witherden *et al.*[8] proposed that when keratinocytes are damaged, they express a self-antigen, plexin B2 and CAR, which can be recognized by the γδ TCR, Sema 4D/CD100 and junctional adhesion molecule-like molecule, respectively, on neighboring γδ T cells (Figure 1c). Therefore, these interactions may play a key role in regulating the ERK and cofilin signaling pathways of activated γδ T cells, leading to morphologic changes and the release of keratinocyte growth factor type 1 (KGF1) and KGF2. These growth factors can induce the proliferation and migration of keratinocytes and the restoration of epithelial integrity.

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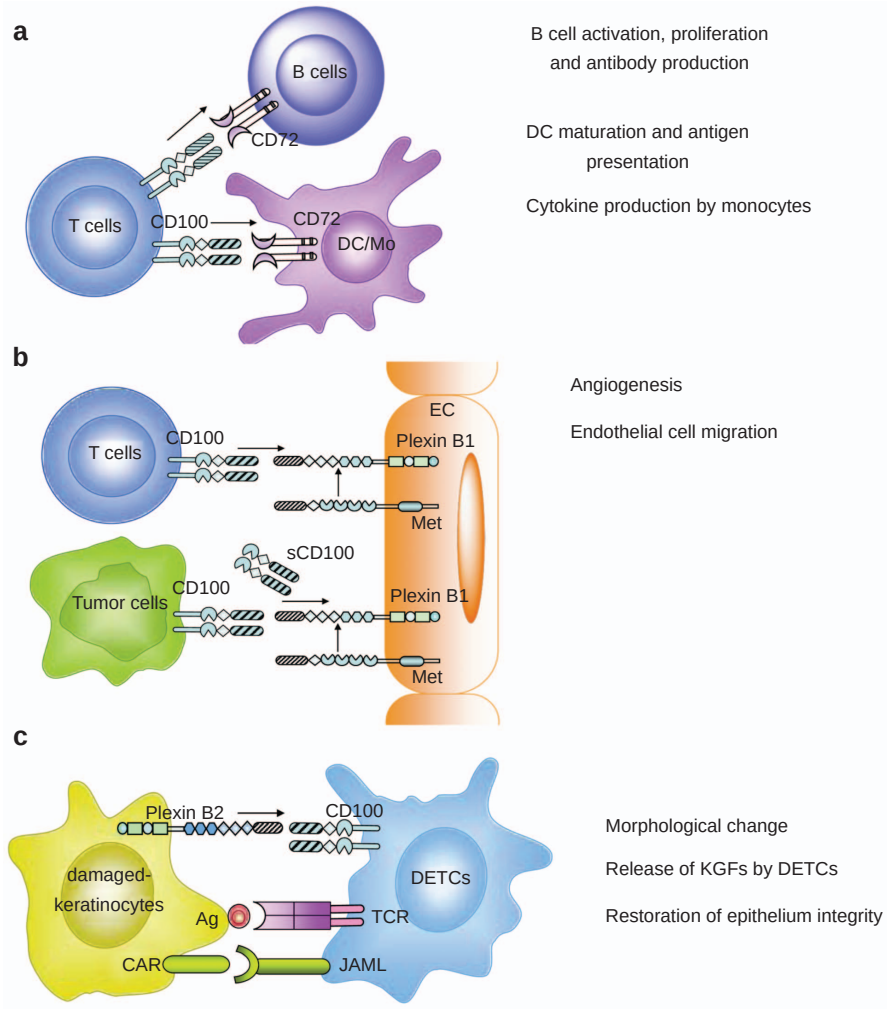

Figure 1 Multiple functions mediated by Sema 4D/CD100-plexin B counter-receptors. (**a**) As a ligand, the ligation of Sema 4D/CD100 with the low-affinity receptor CD72 stimulates the activation of, proliferation of and antibody production by B cells, promotes the maturation of and antigen presentation by dendritic cells (DCs), and induces the production of cytokines (IL-12, TNF-α, IL-6 and IL-8) by monocytes (Mo). (**b**) The binding of Sema 4D/CD100 molecules, which can be in both membrane-bound form (expressed on T cells or tumor cells) and soluble form (sCD100) (shed from activated T cells or tumor cells), to the high-affinity receptor plexin B1, which is expressed on endothelial and epithelial cells, induces angiogenesis and endothelial cell migration. (**c**) Damaged keratinocytes produce a self-antigen, plexin B2, and cocksackie adenovirus receptor (CAR), which can be recognized by the γδ T-cell receptor (TCR), Sema 4D/CD100, and the junctional adhesion molecule-like molecule (JAML), respectively, of dendritic epidermal γδ T cells (DETCs). These morphologically rounded DETCs release keratinocyte growth factor type 1 (KGF1) and KGF2, which may induce the proliferation and migration of keratinocytes and the restoration of epithelial integrity.

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