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Review

Endothelial-binding, proinflammatory T cells identified by MCAM (CD146) expression: Characterization and role in human autoimmune diseases

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ABSTRACT

A subset of T cells defined by the cell surface expression of MCAM (CD146) has been identified in the peripheral circulation of healthy individuals. These cells comprise approximately 3% of the pool of circulating T cells, have an effector memory phenotype, and are capable of producing several cytokines. Notably, the MCAM positive cells are enhanced for IL-17 production compared to MCAM negative effector memory T cells. These cells are committed to IL-17 production and do not require in vitro polarization with exogenous cytokines. MCAM positive T cells also demonstrate an increased ability to bind to endothelial monolayers. In numerous autoimmune diseases these cells are found at increased proportions in the peripheral circulation, and at the sites of active inflammation in patients with autoimmune disease, these cells appear in large numbers and are major contributors to IL-17 production. Studies to date have been performed with human subjects and it is uncertain if appropriate mouse models exist for this cell type. These cells could represent early components of the adaptive immune response and serve as targets of therapy in these diseases, although much work remains to be performed in order to discern the exact nature and function of these cells.

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Contents

1. Introduction

In the past decade, a population of T cells identified by cell surface expression of the melanoma cell adhesion molecule, MCAM (CD146), has been reported to be associated with a number of human autoimmune diseases. These cells have the ability to bind to endothelial

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monolayers, secrete cytokines, and have a pro-inflammatory phenotype and genotype; hence we have called these EPIC T Cells (**E**ndothelial-binding, **P**ro**I**nflammatory, with **C**ytokine secretion). MCAM is found on other cell types, notably on both endothelial cells and melanoma cells and was once thought to be specific for the former type of cells in healthy individuals. Endothelial MCAM has been well characterized and is expressed primarily at endothelial junctions, playing an important role in maintaining the integrity of endothelial monolayers. In this review we will discuss the discovery of EPIC T cells and subsequent studies alluding to their potential role in various autoimmune diseases, as well as some of the basic features and functions of CD146 in studies of this molecule on endothelial cells. Current data, such as higher levels of these cells in the blood of patients with autoimmune diseases and the enhanced secretion of IL-17A by these cells, strongly argue for a role of MCAM expressing T cells in the pathogenesis of numerous inflammatory autoimmune disease, although studies of EPIC T cells are hampered by the lack of a widely accepted mouse model.

2. Distribution and biological properties of CD146

MCAM (CD146) has an interesting history in that it has been the subject of intense investigation in two areas, melanomas and endothelial biology, but has received scant attention for its role in lymphocyte biology. In the study of melanoma, MCAM was first reported by Lehmann and colleagues [1] as a surface marker to discriminate between melanoma cells and benign melanocytes. Subsequently it was recognized to be an adhesion molecule with a potential role in tumor growth [2]. Nearly a decade after its first description in melanoma, Bardin and associates found expression of MCAM on endothelial cells, leading to its use as a marker for endothelial cells and circulating endothelial cells [3,4]. In endothelial cells CD146 is found primarily at the endothelial junctions and is thought to play a major role in tightly binding these cells together [5]. Much of the work concerning CD146 structure and expression on various tissues has been reviewed by several groups [6–8]. MCAM has also been recognized to be expressed on a number of cell types including mesenchymal stem cells (MSC) and dental pulp [9–12]. In the former expression of CD146 has been suggested to differentiate between perivascular and endosteal localization of non-hematopoietic bone marrow–MSC populations [13] and may be developmentally related [14].

3. Binding partners for MCAM

Initially CD146 was postulated to have a homotypic ligand–receptor interaction [15], a mechanism which has neither been proven nor discredited. However, several studies have provided data suggesting that CD146 has heterophilic ligands in addition to, or instead of, homophilic binding (Table 1). Recent reports suggest that a ligand for MCAM is laminin-411 (α4-chain, a β1-chain and a γ1 chain, also known as laminin-8) [16,17]. Schneider-Hohendorf et al. extended these findings by demonstrating that adhesion of MCAM positive cells was independent of very late antigen-4 (VLA-4) but may work in concert with p-selectin glycoprotein ligand-1 (PSGL-1)-mediated rolling of these cells [18]. In endothelial cells galectin-1, but not galectin-2, has been shown to bind to CD146 and may help to protect against apoptosis in these cells [19]. CD146 has also been demonstrated to be a coreceptor for VEGFR2 on endothelial cells, to interact directly with VEGFR2, and that this binding enhances VEGFR2 signaling [20]. Wnt5a has also been proposed as a binding partner for CD146 [21]. The reports of multiple ligands for CD146 create a degree of confusion regarding the mechanisms of adherence and migration of EPIC T cells. Unfortunately the reports describing these ligands for CD146 have not been widely confirmed by subsequent studies and it is unclear if these ligands are competitive or cooperative. More studies are needed to elucidate the binding ligands of MCAM and the precise mechanisms of migration and signaling in EPIC T cells.

Table 1
Ligands reported for CD146.

Ligand	Cell type	Reference
Galectin-1	CD146 transfected fibroblast	Jouve et al., 2013
Laminin-411	CD146 transfected Chinese hamster ovary (CHO) cells	Flanagan et al., 2012
Wnt5a	CD146 transfected human embryonic kidney cell line HEK293T cells	Ye et al., 2013
VEGFR2	CD146 transfected human embryonic kidney cell line HEK293T and endothelial cells for VEGFR-2	Jiang et al., 2012

4. CD146 engagement and signaling

Signaling resulting from MCAM engagement has been widely studied in a number of non-leukocytic cell types, however a comprehensive, coherent picture of CD146 has not been offered. In endothelial cells, engagement of CD146 was found to recruit $p59^{fyn}$ to CD146, triggering a calcium flux through phospholipase C-γ activation and initiate a protein tyrosine kinase (PTK)-dependent signaling pathway, with tyrosine phosphorylation of the focal adhesion kinase, $p125^{FAK}$ and paxillin [22,23]. Engagement of CD146 in endothelial cells also has been reported to cause actin redistribution to an activated form as well as translocation of NF-κB to the nucleus [24]. In human melanoma cell lines Li and colleagues [25] described a reciprocal regulation of MCAM and protein kinase B (PKB) (also known as Akt), leading to inactivation of the Bcl-2-associated death (BAD) promoter and increased survival of the melanoma cells.

There are several reports in the literature associating Wnt5a non-canonical signaling with CD146 expression and function. Witze et al. [26] demonstrated that brief treatment of melanoma cells with Wnt5a led to redistribution of MCAM from a uniformly distributed pattern to a highly polarized structure in concert with actin–myosin rearrangements. This mechanism could thereby control directional movement in response to chemokine gradients. Subsequent data using human umbilical cord endothelial cells as well as zebrafish embryos indicated that CD146 binds to Wnt5a with high affinity and is essential for endothelial cell migration and activity of c-jun amino-terminal kinase (JNK) via non-canonical signaling [21]. CD146 was reported to do this through phosphorylation of Dishevelled (Dvl). Insulin-like growth factor binding protein 4 (IGFBP4), an antagonist of the Wnt/β-catenin signaling, was found to activate Wnt/β-catenin signaling pathway and to induce the expression of MCAM in renal carcinoma cells [27]. To date, no studies have been performed in human T cells concerning the signaling pathways associated with CD146 engagement.

5. Early description on lymphocytes

The first description of MCAM expression on lymphocytes appeared in 1997 in a report by Pickl et al. [28]. Here, MCAM was described as an activation marker of T cells, 'not significantly' expressed on the leukocytes of healthy donors. It was, however, found on T cells in synovial fluid from patients with rheumatoid arthritis. Furthermore, skin specimens from contact dermatitis patients demonstrated that 50–80% of the CD3+ cells in tissue sections were MCAM+. These authors suggested, without any supporting data, that MCAM might facilitate extravasation or homing of these cells. This initial observation lay dormant for nearly a decade until a report identified MCAM+ T cells in the peripheral circulation of healthy donors [29]. The MCAM positive T cells could be found in both the CD4+ and CD8+ subpopulations and demonstrated no clonality in the peripheral blood of healthy donors based on TCRVβ analysis. CD146 is also expressed in a low percentage of B cells in the peripheral circulation of healthy donors but is only rarely expressed on the NK population. MCAM could be upregulated on B cells by mitogen stimulation and by activation with a combination of