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REVIEW

- 120 Type 2 diabetes and quality of life
Trikkalinou A, Papazafiropoulou AK, Melidonis A

MINIREVIEWS

- 130 Syndecan-1-coating of interleukin-17-producing natural killer T cells provides a specific method for their visualization and analysis
Jaiswal AK, Sadasivam M, Hamad ARA
- 135 Osteomyelitis in diabetic foot: A comprehensive overview
Giurato L, Meloni M, Izzo V, Uccioli L

ORIGINAL ARTICLE

Basic Study

- 143 Insulin-mimetic compound hexakis (benzylammonium) decavanadate is antilipolytic in human fat cells
Carpéné C, Garcia-Vicente S, Serrano M, Marti L, Belles C, Royo M, Galitzky J, Zorzano A, Testar X

Observational Study

- 154 Effects of intermittent fasting on health markers in those with type 2 diabetes: A pilot study
Arnason TG, Bowen MW, Mansell KD

SYSTEMATIC REVIEWS

- 165 KMAP-O framework for care management research of patients with type 2 diabetes
Wan TTH, Terry A, McKee B, Kattan W

ABOUT COVER

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Syndecan-1-coating of interleukin-17-producing natural killer T cells provides a specific method for their visualization and analysis

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Abstract

Natural killer T cells (NKT cells) are innate-like T cells

that acquire effector functions while developing in the thymus, polarize into three distinct functional subsets viz. NKT1, NKT2 and NKT17 cells that produce interferon (IFN)- γ , interleukin (IL)-4 and IL-17, respectively. However, there has been no unique surface markers that define each subsets, forcing investigators to use intracellular staining of transcription factors and cytokines in combination of surface markers to distinguish among these subsets. Intracellular staining, however, causes apoptosis and prevents subsequent utilization of NKT cells in functional *in vitro* and *in vivo* assays that require viable cells. This limitation has significantly impeded understanding the specific properties of each subset and their interactions with each other. Therefore, there has been fervent efforts to find a specific markers for each NKT cell subset. We have recently identified that syndecan-1 (SDC-1; CD138) as a specific surface marker of NKT17 cells. This discovery now allows visualization of NKT17 *in situ* and study of their peripheral tissue distribution, characteristics of their TCR and viable sorting for *in vitro* and *in vivo* analysis. In addition, it lays the ground working for investigating significance of SDC-1 expression on this particular subset in regulating their roles in host defense and glucose metabolism.

Key words: Natural killer T cell; NKT17; Syndecan-1 (CD138); Interleukin-17; Body fat

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Core tip: Discrete subsets of innate-like Natural killer T (NKT) cells differentially produce three of the most potent and polarizing cytokines, interferon- γ (NKT1), interleukin (IL)-4 (NKT2) and IL-17 (NKT17). But very little is known about how the relationship among the functional subsets of NKT cells is regulated. A major obstacle was the absence of specific single surface markers that reliably identify each subset. Here we

highlight our discovery of syndecan-1 as a specific marker of NKT17 subset and its significance for understanding the role of NKT17 in glucose metabolism and autoimmunity.

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INTRODUCTION

We have recently published that syndecan-1 (SDC-1; CD138) is specifically expressed on the interleukin (IL)-17-producing subset of natural killer cells (NKT17) cells^[1]. Briefly, we have previously shown that SDC-1 is expressed on double-negative T cells (DN T cells) that accumulate in *lpr* and *gld* mice^[2]. After that we sought to know if SDC-1 express in innate cells and detected SDC-1 in a subset of NKT cells. We sorted and analyzed NKT cells subsets by genome-wide gene profiling using microarrays and identified SDC-1 is specifically expressed on the IL-17-producing subset of NKT17 cells^[1]. Using SDC-1 expression on NKT17 cells, we visualized their development in the thymus, analyzed their tissue distribution. In addition, we sorted NKT17 cells, out distinguish them from interferon (IFN)- γ -producing NKT1 cells, we sorted each subset and study their characteristics *in vitro*. In this article, we briefly review SDC-1 expression on immune cells and highlight our results and speculate on the potential role of *sdcl* in regulating homeostasis of NKT cells and the implication for glucose homeostasis and body fat development.

SDC-1

SDC-1 is a heparan sulfate proteoglycans that is predominantly expressed on epithelial cells^[3,4]. It is composed of a short conserved cytoplasmic domain, a transmembrane domain, and a long variable ectodomain carrying heparan sulfate (HS) glycosaminoglycan chains^[5]. Sometimes, SDC-1 used chondroitin/dermatan sulfate beside or instead of HS chains^[6]. SDC-1 mediates its functions primarily by using HS chains to bind different ligands^[7,8]. These include various growth factors such as fibroblast growth factors, Wnt, vascular endothelial growth factor, hepatocyte growth factor, cell matrix proteins, growth factors, cytokines, and chemokines^[3,4] and their receptors^[9-12]. Ligand binding to HS is regulated at the cell surface by two sulfatases (SULF-1 and SULF-2) and heparanases^[13]. Number, position, and orientation of each sulfate group on HS chains play a role in dictating the ability of SDC-1 to bind ligands and initiate downstream signaling events^[14-19]. These regulatory sequences have been proposed to act with both autocrine and paracrine

mechanisms and represent potential novel targets for therapeutic interventions, particularly against cancer^[12]. In addition, recent discoveries indicate that SDC-1 core proteins also has biological functions and can modulate cell behavior independent of HS. In contrast, the transmembrane and cytoplasmic domains of SDC-1 do not have intrinsic kinase or catalytic activity, but yet play important roles in signal transduction pathway by multimerization and/or interaction with other intracellular components, like GTPases or kinases^[20]. This often happens in lipid rafts, which are enriched in glycosphingolipids and cholesterol^[21] and essential for receptor binding and signal transduction from the cell surface into the cell. In addition, the short cytoplasmic domain of SDC-1 interacts with a number of cytosolic proteins and plays a role in endocytosis.

Using these various mechanisms, SDC-1 regulates multiple cellular functions, including cell proliferation, differentiation, and survival of adherent cells and tumors. Expression of SDC-1 is dysregulated in a number of cancers, including head and neck, ovarian, breast, and colorectal carcinomas^[22]. In addition, SDC-1 has been implicated in regulating whole body energy metabolism in *Drosophila*^[23] and body fat in mice^[24]. Role of SDC-1 in cancers, infectious diseases, obesity, wound healing, and angiogenesis were reviewed recently^[9,22,25] and hence will not be discussed in depth here.

Expression of SDC-1 in immune cells is limited and discrete

While ubiquitously expressed on epithelia and other adherent cells, expression of SDC-1 by the immune cells is limited to few cells as discussed below.

Expression in plasma and B cells: SDC-1 is a well known marker of plasma cells^[3] and it has been reported on pre-B cells^[26]. Other than that, SDC-1 is not known to be widely expressed among various normal immune cell types. SDC-1, however, is commonly expressed by myeloma cells and lymphoid malignancies and it has been implicated in survival, proliferation and metastasis of tumors^[27]. But the exact roles of SDC-1 in the development and function of B cells and plasma cell remain poorly understood.

Specific expression of SDC-1 on NKT17 cells:

Invariant NKT cells are highly conserved innate-like T cells that, unlike conventional T cells, are restricted to CD1d molecules and recognize glycolipids as antigens^[28]. NKT cells acquire their effector functions while developing in the thymus^[29] and differentiate into three distinct subsets that produce IFN- γ , IL-4 or IL-17 cytokine. These subsets were labelled in a manner typical to that of T helper cells (Th)1, (Th)2, and (Th)17 cells^[29,30]. Hence, the IFN- γ -producing subset is referred to as NKT1, the IL-4 producing subset as NKT2, and the subset that produces IL-17 as the NKT17 subset. Due to their innate nature, NKT cells rapidly produce copious amounts of these cytokines upon stimulation,

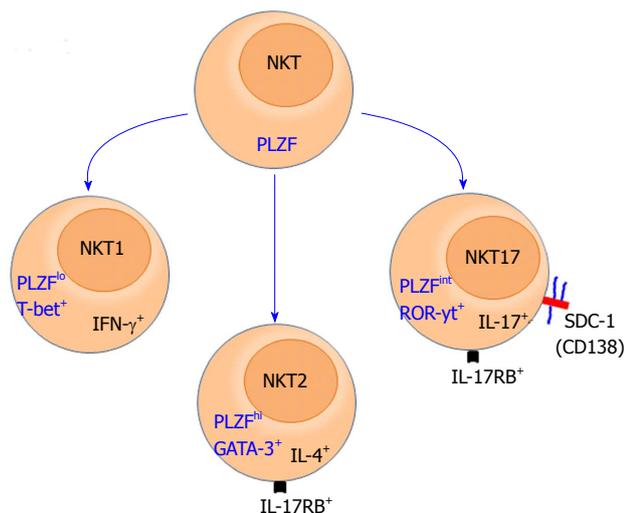


Figure 1 Surface expression of syndecan-1 specifically identifies Natural killer T 17 cells. The three functional subsets are currently distinguished from one another by intracellular staining for specific signature transcription factor or cytokine. Surface expression of SDC-1 can now be used for visualization and sorting of viable NKT17 cells. NKT: Natural killer T; SDC-1: Syndecan-1; IFN: Interferon; IL: Interleukin.

thereby playing critical roles in the initiation and shaping of adaptive immune responses^[29,31,32]. These cytokines are highly potent and capable of polarizing adaptive immune responses into Th1, Th2 or Th17 type. Furthermore, because of the ability of these cytokines to inhibit each other function, the overall physiological functions of NKT cells and how the opposing functions of the three subsets are reconciled under physiological and pathological condition remain a mystery. Lack of progress in solving this paradox is rooted in the absence of reliable surface markers that identify and distinguish subsets of NKT cells from one another.

Currently, distinguishing among the NKT subsets is made using intracellular staining for signature transcription factors that control production of IFN- γ (Tbet), IL-4 (PLZF and GATA3), and IL-17 [retinoic acid-related orphan receptor γ t (ROR γ t)]^[4,33]. Additionally, NKT subsets are identified based on intracellular staining for their signature cytokine, IFN- γ (NKT1), IL-4 (NKT2) and IL-17 (NKT17). Otherwise, It has been difficult to definitively distinguish among NKT cell subsets. Intracellular staining, however, requires fixation and permeabilization, which is a serious limitation that abrogates the ability of investigators to do *in vitro* functional analysis using purified individual subsets. It has also impeded *in vivo* tracking and characterization of individual NKT cell subsets and full appreciation of the pathophysiologic functions of each subset. To avoid this problem, a combination of surface markers are currently used for this purpose, but they have their own shortcomings. For example, NKT17 cells can be identified based on low expression of NK1.1 and CD4, and high expression of CCR6 and IL17RB^[34]. However, IL-17RB is also expressed by NKT2 cells and expression of NK1.1 is a strain-dependent and absent in most

mouse strains^[35]. Our recent identification of SDC-1 as a specific marker of NKT17 cells overcome this challenge at least for this subset^[1] (Figure 1). This finding has been confirmed by three independent studies^[36-38]. This discovery now allows visualization of NKT17 in the thymus and their peripheral tissue distribution, which is leading to novel insights into NKT cell biology.

Implication of SDC-1 expression on NKT17 cells on host defense and glucose metabolism

IL-17 is a potent proinflammatory cytokines that is required in host defense against infections^[39] and been implicated in pathogenesis of asthma^[40], and autoimmune diseases such as type 1 diabetes^[41-43] and regulation of body fat^[44]. In addition, IL-17 has been reported to modulate both adipogenesis and functions of adipocytes and glucose metabolism in mice^[44,45]. Both IL-17AKO and IL-17RAKO mice has been reported to gain in weight due to the accumulation of visceral fat^[44], suggesting involvement of IL-17 in maintaining body fat. NKT17 cells represent about 20% of NKT cells in the thymus^[1] and approximately 2%-10% of total NKT cells in secondary lymphoid organs. NKT17 can secrete large amounts of IL-17 in response to various stimuli, such as infections, allergens, tissue injury and metabolic disorders^[46,47].

Interestingly, NKT17 cells preferentially reside in visceral adipose tissue in mice^[1] and their local and systemic frequencies are reduced in obese patients, suggesting their involvement in inflammation during obesity^[48]. In addition, it has been reported that NKT17 could play a pathogenic role in the pathophysiology of diabetes^[41]. Therefore, we speculate that studies addressing the roles of SDC-1 expressing NKT17 cell may provide an alternative approach to understanding its role in fat metabolism and glucose homeostasis. Thus, the findings by our group and subsequently other groups that NKT17 cells are identifiable by surface expression SDC-1 is crucial for clear understanding of their biology and regulation and their physiologic role in this steady state and disease condition^[1,27,38]. For example, SDC-1 provides a unique opportunity for tracking and analysis of NKT17 cells *in vivo* and for sorting viable NKT17 for various *in vitro* functional studies and adoptive transfer experiments. In this regards, our findings of great responsiveness of NKT17 than do NKT1 cells is consistent with their preferential localization of NKT17 in white adipose tissue (WAT) and suggest special link to WAT.

CONCLUSION

The discovery of SDC-1 as specific marker for NKT17 cells laid the foundation for understanding the biology of NKT17 cells and their pathophysiologic functions. In addition, it will be helpful in uncovering specific markers for NKT1 and NKT2 by excluding NKT17 cells and sorting of pure NKT1 and NKT2 cells for gene expression profiling. Future studies are expected to develop into

understanding the significance of selective expression of SDC-1 by NKT17 cells and generating new information into the role of SDC-1 in the immune cells, which can lead to development of new strategies for manipulating individual subsets of NKT cells for therapeutic purposes.

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