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## Unexpected alliance between syndecan-1 and innate-like T cells to protect host from autoimmune effects of interleukin-17

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### Abstract

Innate-like T cells, namely natural killer T (NKT) and  $\gamma\delta$  T cells, play critical roles in linking innate and adaptive immune responses through rapid production of cytokines. Prominent among these cytokines is interleukin-17 (IL-17), which is a potent proinflammatory cytokine that plays a critical role in host defense against fungi and extracellular bacteria. However, excessive IL-17-production promotes autoimmune diseases, including psoriasis, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus. IL-17 has also been implicated in regulating body fat, which is highly relevant given rises in obesity and type 2 diabetes. NKT cells,  $\gamma\delta$  T cells and mucosal-associated invariant T cells (MAIT) are the major sources of IL-17 involved in protection of mucosal surfaces from opportunistic infections and causing autoimmunity when become dysregulated. Given the pathogenic effects of IL-17, efforts have been directed towards understanding mechanisms that guard against IL-17 overproduction. One novel potent mechanism is mediated by the heparan sulfate proteoglycan, syndecan-1 (sdc1), which is selectively expressed by IL-17-producing subsets of NKT and  $\gamma\delta$  T cells. This unexpected role for sdc1 is uncovered by analysis of NKT and  $\gamma\delta$  T cells in sdc1-deficient mice. In this mini-review, we discuss selective expression of sdc1 by these innate T cells and consequences of its absence on IL-17 homeostasis and pathological implications.

**Key words:** Natural killer T cell; Natural killer T 17 cells;  $T\gamma\delta$ 17 cells; Syndecan-1; Interleukin-17

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**Core tip:** Interleukin-17 (IL-17) is a potent proinflammatory cytokine that plays a critical role in host defense against fungi and extracellular bacteria. Excessive production of IL-17, however, has been implicated in pathogenesis of many autoimmune diseases. Our recent findings show that natural killer T (NKT) cells and  $\gamma\delta$  T cells employ syndecan-1 (sdc1), a heparan sulfate proteoglycan that is predominantly expressed by epithelia, to prevent out of control expansion of IL-17-producing subsets of NKT (NKT17) cell and  $\gamma\delta$  ( $T\gamma\delta 17$ ) cells. In this mini-review, we highlight these findings and briefly discuss their significance for developing new strategies to prevent IL-17-mediated autoimmune diseases.

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## INTRODUCTION

Recent data show that innate-like T cells utilize sdc1 to regulate interleukin (IL)-17 production. Significance of this alliance is uncovered by analysis of homeostasis of IL-17 production by natural killer T (NKT) and  $\gamma\delta$  T cells in sdc1-deficient mice. The results show significant increases in specific subsets of these innate-like T cells that specialized in production of IL-17 in the thymus and in peripheral organs in mice lacking sdc1 as illustrated (Figure 1). In this minireview, we briefly describe the three players forming this axis and how deficiency of sdc1 dysregulates homeostasis of IL-17 production by NKT and  $\gamma\delta$  T cells and the consequences in autoimmunity.

### Syndecan family

The syndecan (sdc) family is comprised of four transmembrane heparan sulfate proteoglycans (HSPGs)<sup>[1]</sup>. These four HSPGs are sdc1, 2, 3, and 4. The structures of these sdc1s are highly conserved with high sequence homology in vertebrates and invertebrates<sup>[2,3]</sup>. Sdc2 is primarily expressed on cells of mesenchymal cells<sup>[4]</sup>; sdc3 is primarily expressed by neuronal tissue and cartilage<sup>[5]</sup>, and sdc4 is ubiquitously expressed in most tissues<sup>[6]</sup>. On the other hand, sdc1 is a heparan sulfate that is ubiquitously expressed on epithelial cells, hepatocytes, endothelium. Sdc1 ectodomain interacts with various ligands (including growth factors, chemokines, cytokines and their receptors, and pathogens) to modulate various functions, including differentiation, migration, survival, and proliferation<sup>[7]</sup>. It is reported that sdc1 is a target of Blimp-1, the trans-

cription factor that regulates differentiation of B cells into plasma cells. Sdc1 is also involved in the growth and metastasis of multiple myeloma *in vivo*<sup>[8]</sup>. In contrast, there is very limited information on the role of sdc1 in the adaptive immune cells except as a marker for plasma and myeloma cells and regulators of their survival<sup>[9,10]</sup>. More recently, however, we have identified sdc1 as a marker of IL-17-producing subsets of NKT cells and  $\gamma\delta$  T cells, (NKT17 and  $T\gamma\delta 17$ ), respectively. The other members of sdc1 family, however, in the regulation of cytokines including IL-17 are not well documented.

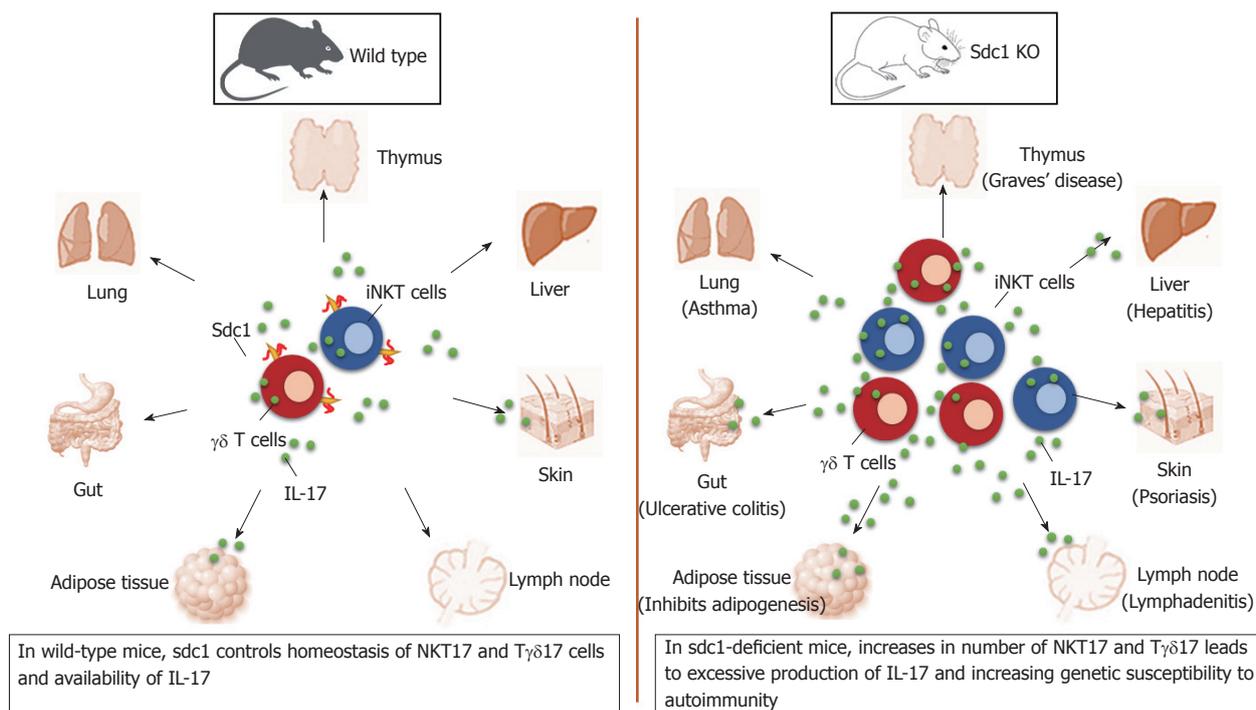
### IL-17

IL-17 (also called as IL-17A) is a member of the IL-17 family. The family of IL-17 consists of six members: namely IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. IL-17A is commonly known as IL-17<sup>[11]</sup>, is a potent proinflammatory cytokine that has been strongly associated with pathology, especially autoimmunity. IL-17-mediated recruitment of inflammatory cells in response to bacterial or fungal infections is vital for the clearance of infections and if not discontinued it leads to the initiation of chronic inflammation and autoimmunity. Indeed, increased production of IL-17 has been associated with a wide range of inflammatory diseases, including rheumatoid arthritis<sup>[12]</sup>, inflammatory bowel disease<sup>[13]</sup>, diabetes<sup>[14]</sup>, cancer<sup>[15]</sup>, and allergic asthma<sup>[16]</sup>. Although the Th17 subset of conventional T cells was the first to be identified<sup>[17]</sup>, subsequent studies identified several types of innate immune cells that are important sources of IL-17. Prominent among them are specialized subsets (NKT17 cell and  $T\gamma\delta 17$  cell) of NKT and  $\gamma\delta$  T cells. Mucosal associated invariant T cells (MAIT) cells is another innate like T cell that is a significant producer of IL-17. They comprise up to 5% of human peripheral T cells and they express a semi-invariant TCR alpha chain (V $\alpha$ 7.2) which recognizes antigens in the context of the nonpolymorphic major histocompatibility complex (MHC)-related protein 1 (MR1)<sup>[18]</sup>. Production of IL-17 by MAIT cells has been implicated in the pathogenesis of various diseases like multiple sclerosis<sup>[18,19]</sup>.

Here we will discuss the selective expression of sdc1 on innate-like T cells and its potential implications.

## SELECTIVE EXPRESSION OF SDC1 ON IL-17-PRODUCING NKT CELLS

NKT cells represent a distinct lineage of  $\alpha\beta$  T cells that expresses an invariant TCR and specializes in recognizing self and foreign glycolipids as antigens in the context of the CD1d MHC class1b molecule. They are experimentally stimulated using the synthetic glycolipid,  $\alpha$ GalCer ( $\alpha$ -Galactosylceramide)<sup>[20]</sup> and fluorochrome-conjugated  $\alpha$ GalCer/CD1d tetramers are routinely used to stain and identify NKT cells by flow cytometry. Thus, there are fundamental differences between NKT cells



**Figure 1 Innate-like T cells employ syndecan-1 to regulate interleukin-17 production.** Homeostasis of interleukin (IL)-17 production by natural killer T (NKT) and  $\gamma\delta$  T cells in wild type (left) and syndecan-1-deficient (right) mice. The diagram illustrated significant increases in numbers of NKT17 and  $T\gamma\delta 17$  subsets in the thymus and in peripheral organs thereby increasing genetic susceptibility to IL-17-driven autoimmune diseases. IL-17: Interleukin-17; NKT: Natural killer T cells; Sdc1: Syndecan-1; KO: Knockout; NKT17: Interleukin-17-producing subsets of natural killer T cells;  $T\gamma\delta 17$ : Interleukin-17-producing subsets of  $\gamma\delta$  T cells; iNKT: Invariant natural killer T cells.

and conventional T cells (which recognize peptides as antigens and express highly diverse TCR repertoire). NKT cells are considered innate-like T cells as they are selected through the agonist selection pathway that is favored by autoreactive T cell receptors (TCRs) and they acquire their effector functions while developing in the thymus by differentiating into three distinct subsets that produce interferon- $\gamma$  (IFN- $\gamma$ ) (NKT1), IL-4 (NKT2) or IL-17 (NKT17), respectively<sup>[21]</sup>. Upon stimulation, NKT cells produce massive amount of two of the most potent proinflammatory cytokines (IL-17 and IFN- $\gamma$ ). NKT cells are important early sources of these key cytokines that play central roles as first line of defense and in shaping adaptive immune responses, including differentiation of CD4 T cells into T helper (Th)1, Th2 and Th17 programs. These cells possess both protective and pathogenic roles in many microbial infections, autoimmune disease, allergic disease and cancer<sup>[22]</sup>. Moreover, other innate-like T cells in this regard are  $\gamma\delta$  T-cells. Both NKT cells,  $\gamma\delta$  T-cells develop in the thymus where a subpopulation specially  $T\gamma\delta 17$  cells, acquires the effector ability to produce IL-17 rapidly<sup>[9]</sup>.  $T\gamma\delta 17$  cells predominantly localize in peripheral lymph nodes and skin of the mice<sup>[23]</sup>.

## SDC1 DEFICIENCY LEADS TO EXPANSION OF NKT17 CELLS

We and others<sup>[24,25]</sup> have identified *sdc1* as a phenotypic

marker of NKT17 cells. Apart from being specific marker for NKT17 cell, *sdc1* is a regulator of NKT17 subset. Deletion of *sdc1* significantly increases the frequency of NKT17 at the expense of NKT1 cells, which was reflected in systemic increase in production of IL-17 in *sdc1*-knockout (KO) mice as compared to WT mice upon  $\alpha$ -Galcer stimulation<sup>[26]</sup>. These results uncover a critical role for *sdc1* expression in regulating homeostasis of NKT17 and consequently production of IL-17.

An intriguing aspect of NKT cells is their selective residence in metabolic organs with NKT1 residing mainly in liver and NKT17 cells in visceral adipose tissue<sup>[21,26]</sup>. Furthermore, whereas a great deal is known about specific roles of Th1, Th2 and Th17 subsets, the precise roles of NKT cells remain poorly undefined and the specific functions of its three distinct effector subsets and their relationships to one another remain unclear. The relationship between NKT17 cells and adipose tissue, however, has been difficult to dissect even though IL-17 inhibits adipogenesis and causes insulin resistance<sup>[27]</sup>. Moreover, attempts to understand overall metabolic role of NKT cells produced conflicting data that ranged from tolerogenic to pathogenic or no role<sup>[28]</sup>. A main likely reason, in our opinion, is the complex nature of NKT cells and studying them as one whole even though they are comprised of distinct subsets with clearly opposing functions. Therefore, our ability to sort NKT cells into viable NKT17 and NKT1 using *sdc1* expression present new opportunities to study their

specific properties, how they modulate one another, and to generate adoptive hosts bearing exclusively NKT17 or NKT1 cells to examine their specific effects on VAT separately. Sdc1 deficiency is associated with reduced body fat and insulin resistance in chow-fed mice. Kasza *et al.*<sup>[29]</sup> reported that sdc1KO Balb/c mice have reduced intradermal fat and that their VAT is also significantly reduced in 12-wk-old mice.

## SELECTIVE EXPRESSION OF SDC1 ON T $\gamma\delta$ 17 CELLS

T $\gamma\delta$  T cells are a population of lymphocytes expressing  $\gamma$  and  $\delta$  TCR chains and these innate immune T cells are considered as link between innate and adaptive immune responses. In the mouse, T $\gamma\delta$  T cells primarily develop in the thymus into completely functional subsets which further secrete high levels of pro-inflammatory cytokines, such as IFN- $\gamma$  or IL-17, upon activation in the periphery<sup>[30,31]</sup>. T $\gamma\delta$  T cells are abundant in the skin (dermis and epidermis), lymph node, respiratory mucosa such as nasal mucosa, bronchial mucosa, and lung<sup>[32]</sup>. Moreover, T $\gamma\delta$  T cell have been characterized in several epithelial tissues for the selective tissue homing and retention and involved in immune surveillance and immune defense. There is abundant evidence that T $\gamma\delta$  T cells are involved in allergic and inflammatory settings and suggest that they can both drive and regulate immune responses through different mechanisms. Here we will discuss the selective expression of sdc1 on innate T cells (NKT17 cell and Tgd17 cell) and its potential implications.

T $\gamma\delta$  T cells are the main source of early IL-17 in various murine models of infection, inflammation, and autoimmunity<sup>[33,34]</sup>. T $\gamma\delta$ 17 cells develop in the thymus where a subset acquires the innate effector ability of rapidly producing IL-17. In the periphery, T $\gamma\delta$ 17 cells localize to lymph nodes, mucosal tissues such as the intestine, skin and lung<sup>[35,36]</sup>. In human, T $\gamma\delta$ 17 cells have been found to increase in patients with tuberculosis, bacterial meningitis, ankylosing spondylitis, and psoriasis<sup>[32,37]</sup>. These findings provide a potential explanation that IL-17-producing T $\gamma\delta$  T cells are a key component in the pathogenesis of various inflammatory and autoimmune diseases. Recently, we have found that sdc1 is selectively expressed on IL-17-producing T $\gamma\delta$  T subset, including those in the thymus, lymph nodes and skin<sup>[23]</sup>. Given selective expression of sdc1 by NKT17 cells, its specific expression of on T $\gamma\delta$ 17 subset indicate a special relationship between sdc1 and innate-like T cells, which are major sources of IL-17 production. Therefore, sdc1 serves at least two roles on T $\gamma\delta$  T cells: (1) Acts as a surface marker for T $\gamma\delta$ 17; and (2) A negative regulator of T $\gamma\delta$ 17 cells.

## SDC1 NEGATIVELY REGULATES HOMEOSTASIS OF T $\gamma\delta$ 17 CELLS

T $\gamma\delta$ 17 cells play an important role in early host defense

against fungal and bacterial infections. Early reports suggested the functional involvement of T $\gamma\delta$ 17 cells as a critical source of IL-17 that drives autoimmune disease including psoriasis<sup>[38]</sup>. Thus, identifying the factors that control homeostasis of T $\gamma\delta$ 17 cells is important and could be useful for developing strategies to prevent pathogenic production of IL-17. Therefore, studies addressing the roles of sdc1 expressing T $\gamma\delta$ 17 cell may provide an alternative approach to understanding its role in autoimmune diseases. Sdc1 expression on T $\gamma\delta$ 17 might be useful for clear understanding of their biology and their physiologic role in steady state and disease condition.

In concordance and in light of our findings, that sdc1 is selectively expressed and negatively regulates homeostasis NKT17 cells<sup>[26]</sup>, we thought to determine whether sdc1 is also expressed controls homeostasis of T $\gamma\delta$ 17 cells. That turned out to be the case and as in NKT17, deletion of sdc1, significantly and selectively increased the numbers of T $\gamma\delta$ 17 cells in thymus, lymph nodes and skin, in steady state<sup>[23]</sup>. Sdc1 deficiency significantly exacerbated imiquimod (IMQ)-induced psoriasiform dermatitis and significantly increased T $\gamma\delta$ 17 cells, accompanied by increased skin inflammation in sdc1KO mice than wild type. Therefore, these findings suggest that targeting sdc1 could represent a novel strategy to control IL-17 production by NKT and T $\gamma\delta$  T cells.

## DOES SDC1 REGULATE PRODUCTION OF IL-17 BY OTHER INNATE-LIKE T CELLS OR INNATE CELLS?

As mentioned above, the other major innate-like T cells that produce IL-17 are MAIT cells. However, whether sdc1 is also involved in regulation of IL-17 by MAIT cells is currently unknown and worthy of future investigation. Furthermore, innate-like lymphocyte 3 are major producers of IL-17<sup>[39]</sup> and need to be investigated for expression of sdc1 in future studies.

## CONCLUSION

In summary, the discovery of selective expression of sdc1 on NKT17 and T $\gamma\delta$ 17 reveals a previously unexpected role for sdc1 in regulating IL-17 by innate-like T cells. The results provide an impetus for future experiments aimed at understanding specific mechanisms by which sdc1 regulates IL-17 production by innate-like T cells. In addition, sdc1-deficient mouse strains provide new model for of the role of innate-like T cells in IL-17-mediated autoimmune diseases. Such efforts may lead to new therapeutic strategies for autoimmune diseases where IL-17 plays a central role.

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