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Acta Dermatovenerol Croat 2019;27(3):159-162 REVIEW

The Role of CD8$^+$ T-Cells and their Cytokines in the Pathogenesis of Psoriasis

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ABSTRACT The important role of CD8$^+$ T-cells in the pathogenesis of psoriasis is well-determined. However, besides type 1 cytokines that were formerly known, it was recently found that these cells secrete type 17 and type 22 cytokines. The majority of IL-17A$^+$CD8$^+$ T-cells in the blood belong to a subset of innate T-cells named mucosa-associated invariant T-cells (MAIT). However, the majority of IL-17A$^+$CD8$^+$ T-cells in psoriatic epidermis are conventional T-cells and are up-regulated in psoriasis. In contrast to Th17 cells that secrete only IL-17, Tc17 cells secrete IFN-ϒ, TNF-α, CCL20, IL-22, and granzyme B as well. The key cytokine is IL-17A, which promotes keratinocyte hyperproliferation and stimulates them to produce other proinflammatory cytokines. These activities initiate and propagate the inflammation and architectural changes in the skin that clinically manifest as psoriatic lesions. However, a relatively novel cell subtype named Tc22 has been discovered in psoriasis that could secrete IL-22 in the absence of IL-17 and IFN-gamma. IL-22 stimulates proliferation and de-differentiation of keratinocytes, subsequently leading to epidermal acanthosis. As the understanding of the pathogenesis of psoriasis increases, the new selective therapies may offer an optimal balance between increased clinical benefit and reduced risk of side-effects.

KEY WORDS: cytokines, CD8$^+$ T-cells, IFN-gamma, TNF-alpha, IL-17, IL-22

INTRODUCTION

Psoriasis is a chronic, immunologically mediated skin disease that affects approximately 2-3% of the world's population (1). It may cause significant morbidity due to the possible co-existence with psoriatic arthritis and association with a large number of systemic diseases (1). The most common manifestation is chronic plaque psoriasis but other forms like guttate, pustular, or erythrodermic may also be present (1). The exact triggering agents are not fully recognized yet, but it is known that genetic, environmental, and immunological factors participate in psoriasis pathogenesis (2,3).

Despite the obvious involvement of innate immunity in psoriasis pathogenesis, it is commonly believed that T-cells and cytokines play a central role (4). While CD8+ T-cells are predominantly found in the epidermis, CD4+ T-cells are located in the upper dermis of psoriatic skin lesions (5,6).

For a long time, psoriasis was considered a Th1-mediated skin disease (7). However, an important advancement in understanding the pathogenesis of this complex disease was discovery of T-helper type 17 (Th17) cells and very recently of T-helper type 22 or Th22 cells (7). Despite CD4+ T-lymphocytes, cytotoxic CD8$^+$ T-cells are also capable of producing cytokines such as IL-2, IFN-gamma, TNF-alpha, IL-17, and the IL-22 cytokine family (8). They are consecutively named Tc1, Tc17, and Tc22 cells, and the knowledge of their involvement in psoriasis has been growing recently (Figure 1) (8).

Acta Dermatovenerol Croat
2019;27(3):159-162

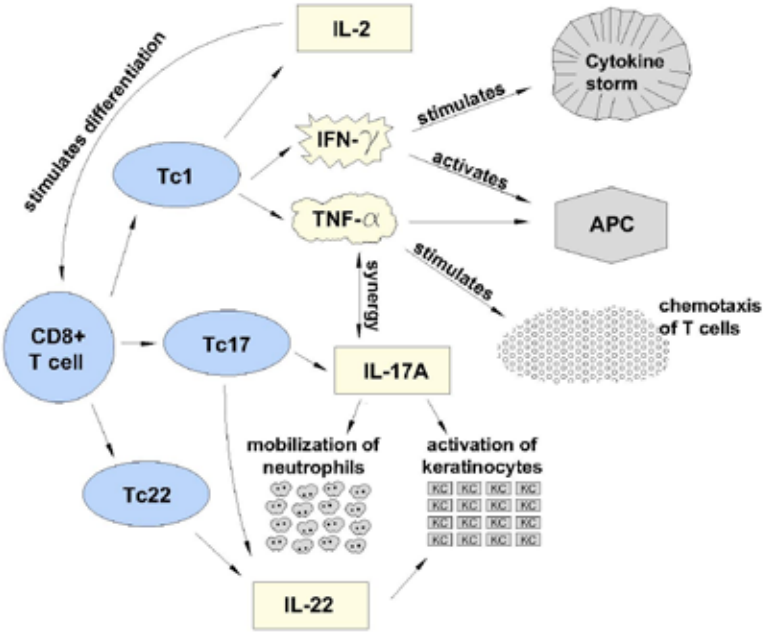

Figure 1. Roles of Tc1, Tc17, and Tc22 cells in the pathogenesis of psoriasis.

Legend: Tc1: cytotoxic lymphocyte type 1; Tc17: cytotoxic lymphocyte type 17; Tc22: cytotoxic lymphocyte type 22; IL: interleukin; IFN: interferon; TNF: tumor necrosis factor; APC: antigen presenting cell; Kc: keratinocyte

Tc1 LYMPHOCYTE POPULATION IN PSORIASIS

Generally, there are subsets of $CD8^+$ T-cells that are similar to their $CD4^+$ counterparts (8,9). Analogous to the Th1/Th2 terminology and depending on the cytokines they produce, these two subsets were termed Tc1 and Tc2 (8,9). In psoriasis, Tc1 cells are activated, produce cytokines such as IFN-gamma, IL-2, and TNF-alpha, and play an important role in the inflammatory process (9). For a long time Tc1 cells were thought to be main CD8+ subset in CD8 cytokine production (9,10).

Most of Tc1 cells isolated from psoriatic lesions produce IFN-γ (11). Serum levels of CD8+IFN-γ+ T-cells in the blood of patients correlate with psoriasis disease severity (12). The main effects of IFN-γ are activating keratinocytes and antigen-presenting cells early in the psoriatic cascade to produce IL-1β and IL-22, thus promoting the cytokine storm in psoriasis (12). However, because of the failure of an IFN-γ targeted therapy and discovery of other cytokines, the role of IFN-γ in the pathogenesis of psoriasis is not crucial as previously believed (12).

The main function of TNF-α in psoriasis is regulation of antigen-presenting cells (13). It also stimulates the secretion of other cytokines such as IL-23 from dendritic cells (14). TNF-α alone does not lead to significant response of cultured keratinocytes, but it forms strong synergies with other cytokines such as IL-17A and subsequently amplifies the immunologic cascade (12). TNF-α is also capable of stimulating proliferation and chemotaxis of T-cells to the site of the lesion, with the mediation of CXCL-10 through regulation of the adhesion molecules in the endothelial cells (13).

Tc17 LYMPHOCYTE POPULATION IN PSORIASIS

The oligoclonal Tc17 cells infiltrate the lesional epidermis (15). They may be activated by Th17 cells or may infiltrate after recognition of autoantigens in the context of MHC class I (15). The influx of Tc17 T cells significantly correlates with the disease severity (15).

The predominant IL-17A-producing $CD8^+$ T-cells in psoriatic lesions are conventional $CD8^+$ T-cells that generally predominate in psoriatic skin (15). However, it has been reported that the vast majority of Tc17 cells in peripheral blood are mucosa-associated invariant T-cells (MAIT cells) (15,16). MAIT cells belong to the innate immune system and express an invariant TCR α-chain for recognition of bacterial ligands in the context of MR1, a MHC class I-like antigen-presenting molecule (15,16). They secrete IL-17, but not exclusively (15,16). IL-17A-producing CD8+ MAIT cells

Acta Dermatovenerol Croat
2019;27(3):159-162

were found in psoriatic skin as well (15,16). Contrary to Th17 cells that secrete only IL-17, Tc17 cells secrete IFN-γ, TNF-α, CCL20, and granzyme B as well (17). Furthermore, Tc17 cells express CCR6, the ligand for CCL20, and it seems to be crucial for epidermal homing of all CD8+ cells (17).

The IL-17 family consists of 6 members, namely IL-17A to IL-17F (18). They bind five different types of receptor subunits, IL-17RA to IL-17RE (18). The most active IL-17 cytokines in psoriasis are IL-17A and IL-17F (7). IL-17A is about 10-30 times more potent than IL-17F, and so plays a key role in the pathogenesis of psoriasis (19). Elevated levels of IL-17A have been measured in psoriatic lesions compared with nonlesional tissue (20). IL-17A activates keratinocytes, activates and recruits neutrophils, and promotes the release of other inflammatory cytokines (18). It also stimulates the expression of keratinocyte chemokines such as CCL20 that subsequently mediate recruitment of Th17 cells and dendritic cells to skin, and CXCL 1, 3, 5, 6, and 8 that drive neutrophil recruitment (19). It also increases expression of antimicrobial peptides in psoriatic epidermis, including β-defensins and S100A family members (21). Effects of IL-17A depend on the local cytokine milieu, and overlap with other cytokines present in psoriatic lesions (19).

Despite cytokine production, CD8+IL-17+ cells could produce cytotoxic molecules in psoriatic plaques such as granzyme B and kill target cells in a TCR/CD3-dependent manner (17). These mechanisms require the coordinated expression of NKG2C and NKG2D on CD8+ T-cells, which are not detected in psoriatic CD8+ T-cells (17). Therefore, the precise mechanism of cytotoxic target cell killing in psoriasis is still to be elucidated.

Besides IL-17, Tc17 cells could secrete IL-22 that has keratinocyte proliferation-promotion capacity and is consequently responsible for the induction of acanthosis as well as production of antimicrobial peptides by keratinocytes (22). IL-22mRNA expression is up-regulated in psoriatic skin lesions compared with healthy skin (22). Whereas Th17 cells do not expand in the lesional skin, Tc17 cells that could secrete IL-17A alone or in combination with IL-22 are the key IL-17-producing cells in psoriatic skin (22).

Tc22 LYMPHOCYTE POPULATION IN PSORIASIS

Another CD8+ cell population recently determined in psoriasis are Tc22 cells (23). They are found in the epidermis of psoriatic skin in much higher numbers than in the adjacent dermis (22). Together with Tc17, they are a main source of IL-22 (23). Th22 from lesional psoriatic skin secrete IL-22 in the absence of IL-17 and IFN-gamma, therefore producing only IL-22 (22). A concrete explanation for this phenomenon is still lacking. However, it is presumed that those cells derived from Th17 and Tc17 cells that lose their capacity to express IL-17A and develop into IL-22 single-producing T-cells (22). As we already mentioned IL-22 stimulates proliferation and de-differentiation of keratinocytes through the activation of the STAT3 signaling pathway that subsequently leads to epidermal acanthosis (23). It also promotes keratinocytes to produce chemokines such as CXCL8 and CXCL1 (23).

CONCLUSION

Psoriasis is a complex immune-mediated skin disease that clinically presents with inflammatory plaques on the skin. Today, there is considerable experimental and clinical evidence supporting a role of T-cells in the pathogenesis of psoriasis. Although there is much evidence that supports the theory that psoriasis is a Th17-mediated disease, recent studies have demonstrated the important role of Tc1, Tc17, and Tc22 cells. These cells produce an array of cytokines that results in keratinocyte and vascular response changes. It is a relatively unexplored research avenue in psoriasis but offers considerable promise as a possible approach to efficient and safe treatment of psoriasis. Further research should reveal new targets in the pathogenesis of psoriasis, so the new therapy with the least possible side-effects can be explored.

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