

## The status of Regulatory Cells/Molecules in Psoriatic Skin

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In normal non-inflamed skin, the balance between the expression of pro-inflammatory cells/cytokines and regulatory/protective functions are extremely important for the maintenance of healthy skin. Normal skin T cells (mostly Th1 memory effector cells) have a remarkably diverse TCR repertoire and express high levels of CCR4, CCR6 and CCR8. In addition, the normal composition of skin resident T cells contains also Th2 and functional T regulatory cells (Tregs), namely FoxP3 and IL-10 positive [1]. Tregs were assessed in normal human skin and found to have an activated memory phenotype (mTregs). Conventional memory T helper cells and mTregs in the skin have almost no homology between them, suggesting that they recognize different antigens. In normal skin, mTregs are relatively unresponsive compared to their status in inflamed skin from psoriatic patients. In this case, mTregs are highly proliferative but functionally defective [2]. The role of increased expression of Th1, Th17 and pro-inflammatory cytokines such as TNF- $\alpha$ , IL-12, IL-21, IL-23 and IFN- $\gamma$  in the pathogenesis of psoriasis and their association with disease severity is well established. The histological features of psoriatic lesioned skin (a proliferation of keratinocytes, epidermal and vascular hyperplasia) are a consequence of inflammatory crosstalk between T cells, dendritic cells, and epidermal keratinocytes. In this case, myeloid dendritic cells secrete IL-13 and IL-12, thereby inducing the activation of IL-17-producing T cells, Th22 and Th1 cells and the enhanced production of IL-17, TNF and IL-21 [3-5]. The balance between pro-inflammatory cells and T regulatory cells (Tregs) was widely reported to be disturbed in psoriatic patients. However, the mechanisms by which regulatory cells and anti-inflammatory cytokines in psoriatic skin fail to maintain immune tolerance and immune surveillance are complex and as a result are continuously investigated. When regulatory T cell functions fail, pro-inflammatory cytokines are increased and inflammatory skin diseases such as atopic dermatitis and psoriasis develop.

### T and B Regulatory/Th17 cells in Psoriasis

In peripheral blood of patients with psoriasis, decreased CD4+CD25+ Tregs were shown to be in correlation with increased Th17 and T cytotoxic17 (Tc17) cells. This finding agrees with the idea that increased pro-inflammatory cells in psoriatic skin are a result of Tregs failure in their function. In another study, Tregs from peripheral blood of psoriatic patients were found to have altered suppressive function as a result of increased STAT3 phosphorylation. The ability of these cells to secrete TNF- $\alpha$  and IL-17, as well as their impaired function was restored when a STAT3-inhibitor was added to their co-culture with effector T cells. Under pro-inflammatory conditions, Tregs may differentiate into inflammation-associated Th17 cells (a paradigm shift), a process that is still poorly defined in human immune-mediated skin diseases [6,7]. In a previous study, Tregs from patients with severe psoriasis were shown to have an enhanced ability to differentiate into IL-17A-producing cells when properly stimulated. This was linked to a high expression of the transcription factor retinoic acid-related orphan receptor  $\gamma$ t (ROR $\gamma$ t) and a significant loss of FoxP3. Interestingly, IL-17A+/Foxp3+/CD4+ triple-positive cells were expressed in skin lesions of psoriatic patients, thereby stressing the pathogenic role of Tregs differentiation during the development of chronic inflammatory skin diseases [8]. In another study, Treg/Th1 cell ratios from the center and margin of the lesion, perilesional skin and distant uninvolved skin were analyzed regarding their association with certain stages of the inflammatory process. The ratio of Treg vs CD4+ T cells was significantly higher in the distant uninvolved skin than in the perilesional and lesional skin. The relatively high Foxp3/CD4 ratio in symptomless skin of patients with psoriasis suggests an active immune-controlling mechanism distant from the psoriatic plaque. In the margin and center of the plaque, the ratio appears skewed towards effector cells associated

with inflammation [9]. CD19+CD24<sup>high</sup>CD38<sup>high</sup> transitional and IL-10+ B regulatory cells (Bregs) are important in maintaining self-tolerance and suppressing immune-mediated inflammation and inhibiting Th1 and Th17 cells in psoriatic arthritis (PsA) and psoriasis (Ps). Peripheral blood Bregs were therefore assessed in patients with PsA and Ps. Bregs were decreased in PsA and Ps and found to be inversely correlated with the severity of psoriasis (PASI score) and with IL-17A+CD3+ and IFN- $\gamma$ +CD3+ T cells [10].

### Protective Cytokines in Psoriasis

Suppressive/anti-inflammatory cytokines are important players in the pathogenesis of immune-mediated skin diseases and specifically in preventing the development of psoriatic skin plaques. The most studied regulatory cytokines are IL-10, IL-35 and TGF- $\beta$ , all of which have been reported by many studies to be altered in the serum and inflamed skin of psoriatic patients. In one of our earlier studies IL-10 expression in biopsies from lesional psoriatic skin was demonstrated to be significantly lower when compared to that in normal skin biopsies [10]. In a recent study, inhibitory cytokines such as IL-10, TGF- $\beta$  and IL-35 were assessed in the serum and skin of psoriatic patients. The serum levels of IL-35, IL-10 and TGF- $\beta$  were higher in psoriatic patients than in controls but without any statistically significant relationship with disease severity. The level of IL-35 was the lowest in psoriatic lesions compared to perilesional skin and to controls. CD4, IL-10 and TGF- $\beta$  expression were higher in perilesional skin than in lesional, and TGF- $\beta$  expression was decreased in psoriatic lesions compared to the controls. In addition, Foxp3 expression was enhanced in psoriatic skin, as compared to healthy and perilesional skin. The increase of these cytokines in perilesional areas of the skin reflects the protective role of these cytokines in the process of skin inflammation [11]. In another recent study, anti-inflammatory cytokine profiles were assessed in patients with psoriasis. Of the many analyzed cytokines, TGF- $\beta$  and adiponectin were significantly lower in psoriasis as compared to that in healthy individuals. The most important single biomarker of psoriasis was found to be adiponectin, believed to be crucial in modulating the chronic inflammatory response in psoriasis and therefore is suggested to become a therapeutic target in active psoriasis [12]. In previous studies, IL-27 (a novel member of the IL-6/IL-12 family) was shown to be a promoter of inflammatory processes through the enhancement the differentiation of Th1 cells. When IL-27 was assessed in the serum and skin lesions of psoriatic patients, serum levels and skin expression of IL-27 were significantly lower, as compared to those of healthy control subjects. The subcutaneous administration of IL-27 recombinant protein decreased the severity of the imiquimod-induced psoriasis-like mouse model. In addition, the administration of IL-27

to these mice suppressed IL-17 secretion from CD4+ T lymphocytes. These results suggest that IL-27 is a protective cytokine in the pathogenesis of psoriasis through its suppressive effect on Th17 differentiation. Thus, future studies should focus on using IL-27 in treating psoriasis [13]. The potential therapeutic effect of recombinant IL-35 in psoriasis was also assessed. The induction of recombinant IL-35 reversed inflammation in animal models of psoriasis and slowed down the pathological skin process by promoting the secretion of IL-10 and inhibiting the expression of pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  [14]. Another protective cytokine in psoriasis is IL-33 which protectively was found to be highly expressed in lesional skin of patients with moderate-to-severe plaque psoriasis. In this respect, the subcutaneous injection of IL-33 into an animal model of psoriasis reduced the proportion of Th17 cells in the skin-draining lymph nodes. Similar protective results were reported following the administration of low dose IL-10 to psoriatic patients. Disease severity was decreased as compared to baseline status and patients who had received a placebo [15,16].

### Sema3A/NP-1 and Psoriasis

Semaphorins, are a large family of guidance molecules for axonal/dendritic projections and are composed of both secreted and membrane-bound proteins sharing a Sema domain [17,18].

Semaphorin3A (Sema3A), is a secreted molecule known to have a variety of biological functions, among which are anti-angiogenesis, and the inhibition of tumor progression in a variety of solid tumors [19,20]. Sema3A was also characterized as a modulator of immune responses. Thus, it was found to inhibit primary human T-cell proliferation and pro-inflammatory cytokines [21,22]. These early studies suggested that Sema3A may have beneficial effects in a variety of auto-immune diseases. Indeed, the concentration of Sema3A is decreased in the circulation of systemic lupus erythematosus (SLE) patients as well as in the circulation of systemic sclerosis patients [23], suggesting that Sema3A may play an inhibitory role in these diseases. Moreover, we have found that the administration of Sema3A had a beneficiary effect on the development of kidney failure in the NZB/W mouse model of lupus nephritis [24].

Likewise, the administration of recombinant Sema3A reduced the severity of asthma in a mouse model of the disease [25]. These beneficiary effects were likely due to Sema3A stimulation of FoxP3 and IL-10 expression in Treg cells [25,26]. Neuropilin-1 (Nrp1) binds to Sema3A with high affinity and is necessary for Sema3A-mediated biological effects [27]. Several reports demonstrated that Nrp1 is a pivotal player in the formation of the immune synapse between dendritic cells (DCs) and T cells, leading

to the activation of T cells, which are dependent on the expression of Nrp1 on the membrane of both cells [28]. This interaction leads to the formation of T regulatory cells, and Nrp1 expression is directly related to the expression of Foxp3 and the suppressive abilities of Tregs. It was also found that Nrp1 serves as a transforming growth factor- $\beta$  (TGF- $\beta$ ) receptor [29]. In this study, when Nrp1 was added to T cells in culture it could bind to LAP-TGF $\beta$  or active TGF $\beta$ . Importantly, this interaction leads to increased suppressive capacity of Treg cells. Lately, it was published that circulating sNRP-1 was significantly higher in psoriatic patients in comparison to the controls, and this increment was in correlation with the psoriatic disease severity score (PASI). NRP-1 and sNRP-1 act in the opposite way to one another in angiogenesis and in the immune response; sNRP-1 is a decoy receptor able to bind its ligand and prevent long-term interactions between Tregs and immature DCs, thereby promoting immunity, specifically- psoriasis [30].

As a result, we designed a study in order to explore the involvement of Sema3A and Nrp1 in psoriatic skin lesions. Skin is home to a large proportion of the body's Treg cells; however, their suppressive function is not well defined. Under steady-state conditions, memory regulatory T cells reside in human skin as mostly unresponsive cells. However, it was found that in psoriatic inflamed skin, Treg cells are highly proliferative but defective in their suppressive abilities in inflammatory skin [2,31,33]. In our study, we showed that Sema3A and NP-1 expressing Treg cells are significantly altered as compared to that in normal skin. Our finding of decreased IL-10 expression in inflamed skin, being well expressed in normal skin, emphasizes the importance of regulatory cells and molecules in the skin lesions of psoriasis and the need to be therapeutically targeted.

## Conclusion

Psoriasis is a chronic immune-mediated skin disease characterized by increased expression of pro-inflammatory T cells namely, Th1 and Th17 and their relevant cytokines such as IL-17, TNF- and IL-6. Recent attention is directed to a better understanding of the pathogenic role of regulatory cells/molecules. Once better defined and characterized, regulatory pathways could be targeted as a potential therapeutic strategy in psoriasis.

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