ImmunoTools IT-Box-Cy55M-Award 2013

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The role of the innate immune system in a mouse model of psoriasis

Psoriasis is a frequent, chronic, debilitating autoinflammatory disease of the skin. In this condition, the skin is affected by disorganization of the epidermis, resulting in loss of stratification as well as thickening and dedifferentiation of the corneal layer. Based on these observations an intrinsic defect of the keratinocyte layer has been proposed to be the primary event in disease initiation. However, the sequence of events that ultimately leads to psoriasis onset has not yet been clarified. Several different subtypes of dendritic cells (DC) are present in the psoriatic inflammatory infiltrate, however, their role in psoriatic skin is not known. The epidermis constitutively contains a DC subset called Langerhans cells (LC). LC are myeloid DC that populate the epidermis during embryonic age and that have a broad repertoire of immune functions depending on the inflammatory situation. In psoriatic lesions, LC numbers are often reduced compared to noninvolved skin (NS), however, in skin surrounding psoriatic lesions, LC are more abundant compared to NS. Plasmacytoid dendritic cells (pDC) are not found in healthy skin, but are present in psoriatic skin and are crucial for disease development by production of IFN-α in response to the tissue damage accompanying skin barrier breach. Recently, it was reported that mice harboring an inducible deletion of the AP-1 transcription factors c-jun and junB in the basal layer of the epidermis (Psor mice) develop a psoriasis-like phenotype resembling human disease. We found that in early stages of psoriatic disease, the number of LC was increased, however, within active lesions, LC were reduced compared to less involved sites. In order to study LC function in psoriasis in vivo, we crossed Psor mice to Langerin-DTR mice, in which LC can be selectively ablated by application of diphtheria toxin (DT). With this technique, we were able to deplete Langerin$^+$ cells efficiently and consistently over an extended time period. Additionally, we were able to selectively deplete LC and Langerin$^+$ dermal DC, respectively, by using bone marrow chimeric mice. LC have been reported to originate from two distinct progenitor pathways. In healthy skin, LC that die or emigrate are replaced by

skin-resident progenitors. However, in the presence of an ongoing inflammation, LC can be recruited by a second pathway, leading over bone-marrow borne precursor cells. A recent study demonstrated that hair follicles produced CCL-2 and CCL-20 in response to external stress, which attracts pre-committed LC-progenitors to the epidermis. We have identified these progenitors in psoriatic skin of Psor mice. We would like to investigate whether application of a cocktail of these chemokines is sufficient to facilitate recruitment of bone-marrow derived LC and furthermore, whether an intraauricular injection of these cytokines attracts LC to the epidermis and has an influence on the psoriatic phenotype. To date, it is not possible to generate murine LC in culture. Cytokines from the *IT-Box-Cy55M* could be therefore helpful for us to investigate whether factors that are present in psoriatic skin can facilitate LC differentiation from the bone marrow. The advent of another DT-based depletion strategy using BDCA2-DTR mice enables us to furthermore study pDC function in psoriatic mice. We have found that pDC infiltrate the skin of psoriatic mice. Murine pDC can be easily generated by cultivating bone marrow in the presence of Flt3L. Thereby, we plan to study interactions between keratinocytes and pDC Using psoriatic Langerin-DTR and BDCA2-DTR mice, we will investigate, whether LC and pDC are involved in the development of psoriatic disease, or whether the disease phenotype is altered upon ablation of these cell types during active disease. These experiments will provide insight not only on the role of DC subsets in the initiation of psoriasis, but also, whether it is therapeutically useful to target DC in psoriasis.