Compartmentalisation of the Immune Response in Human Skin: Cross-talk between Dendritic Cells and T Cells in Healthy Conditions and in Psoriasis

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Elisa Martini defended her thesis in Karolinska University Hospital, Solna on May 4, 2018. Opponent was Clare Bennett, Department of Hematology, University College London, UK. Principal supervisor was Associate Professor Liv Eidsmo, and co-supervisors were Anna Smed Sörensen, Professor Mona Ståhle, Department of Medicine, Karolinska Insitutet, Solna and Professor Francis R. Carbone, Department of Microbiology and Immunology, University of Melbourne, Australia. The thesis is available here: https://openarchive.ki.se/xmlui/handle/10616/46267

The skin is a highly compartmentalised barrier in which epidermis and dermis form distinct microanatomical niches. These two skin niches host different subsets of dendritic cells (DCs) and T cells, immune cells that form the first line of antimicrobial defence. In psoriasis, an inflammatory skin disease associated with overexpression of IL-17, both DCs and T cells are altered. The thesis "Compartmentalisation of the immune response in human skin: cross-talk between dendritic cells and T cells in healthy conditions and in psoriasis" explores compartmentalised differences in DCs and T cells functionality in different phases of psoriasis compared to healthy skin. My analysis focused on inflammatory mediators or cytokines that were produced by DCs and T cells in homeostasis and inflammation. Moreover, after defining the cytokines present in the skin environment in psoriasis, we investigated how these cytokines affected the development and function of T cells residing in the skin.

In study I we observed that the total number of DCs in the epidermis in active psoriasis dramatically increased compared to healthy skin, due to the infiltration of a population of inflammatory DCs. These cells displayed high expression of pro-inflammatory genes and were capable of producing the disease-driving cytokine IL-23 after stimulation. In accordance with other studies, the number of DCs normalised in the epidermis of resolved psoriatic skin after successful treatment, but the remaining cells retained high expression of pro-inflammatory genes and were poised to produce IL-23, indicating that epidermal DCs may activate T cells in resolved psoriatic skin.

In study II we showed that Granzyme A, a cytotoxic protein normally produced in combination with perforin, was pro-

Fig. 1. Elisa Martini during her presentation.

Fig. 2. Elisa Martini with the opponent Clare Bennett, Department of Hematology, University College London, UK.

duced by epidermal T cells from active psoriasis. Taken that perforin was not expressed, we next tested pro-inflammatory features of Granzyme A. Primary human keratinocytes were stimulated with Granzyme A in combination with the psoriasis-associated cytokine IL-17. Granzyme A together with IL-17 activated keratinocytes to release mediators involved in inducing inflammation and attracting other immune cells into the skin. This study revealed a new pathway of T cell-mediated recruitment of immune cells in psoriasis.

Study III focused on the dermal compartment in resolved psoriasis. Here we identified an enrichment in the expression of the tolerogenic markers *FOXP3, CTLA4, PD1* (T cells), and *IDO* (DCs). DCs from the dermis of resolved skin were also characterised by their enhanced ability to produce the anti-inflammatory molecule IL-10. Analysis conducted by confocal microscopy revealed the presence of clusters of Foxp3+ regulatory T cells in close proximity to DCs, indicating a possible interaction between regulatory T cells and DCs in resolved skin to maintain a tolerogenic state within the dermis, despite the constant presence of IL-17-producing T cells and IL-23-producing DCs.

Study IV focused on the phenotypic and functional plasticity of skin T cells. The Eidsmo laboratory previously showed that skin T cells in homeostasis are divided in distinct functional subsets based on their expression of the markers CD69, CD103 and CD49a. In this final study, we showed that skin T cells residing in the dermis, mainly $CD69^{+}CD103^{-}CD49^{-}$, upregulated CD103 or both CD103 and CD49a after stimulation with cytokines present in the skin environment in homeostatic conditions. In stark contrast with the dermal skin T cells, the epidermal skin T cells did not change their phenotype after the exposure to the same conditions. However, when epidermal skin T cells were stimulated with pro-inflammatory cytokines, their functionality was affected despite maintained expression of CD69, CD103 and CD49a, which indicates functional plasticity in these cells.

In conclusion, the results from my PhD project provided an insight in the distinct inflammatory potential of DCs and T cells located in different skin compartments in different phases of psoriasis. Moreover, I showed that the phenotype and functionality of skin T cells is affected by their surrounding environment. Collectively, the results indicated that the compartmental differences of immune cells residing in the two skin layers should be taken into consideration when designing targeted therapies.

List of publications

I. Martini E, Wikén M, Cheuk S, Gallais Zérézal I, Baharom F, Ståhle M, et al. Dynamic changes in resident and infiltrating epidermal dendritic cells in active and resolved psoriasis. J Invest Dermatol 2017; 137: 865–873.
II. Cheuk S, Martini E, Bergh K, Chang D, Rethi B, Ståhle M, et al. Granzyme A potentiates chemokine production in IL-17 stimulated keratinocytes. Exp Dermatol 2017; 26: 824–827.
III. Martini E, Cheuk S, Hoffer E, Wikén M, Gallais Sérézal I, Eidsmo L. Anti-inflammatory features of T cells and dendritic cells residing in the dermis of psoriasis-treated patients. In manuscript.
IV. Martini E, Kärner J, Cheuk S, Detlofsson E, Bryceson Y, Eidsmo L. Development and plasticity of human skin resident T cells. In manuscript.
V. Eidsmo L, Martini E, Human Langerhans cells with pro-inflammatory features relocate within psoriasis lesions. Front Immunol 2018; 22: 300.