Skin resident T cells

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Discovery of skin lymphocytes was a game changer in experimental dermatology

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ABSTRACT

A substantial part of ongoing research in experimental dermatology focuses on skin T cells – for that reason we find important to highlight the pioneering work of Jan D. Bos et al. from 1987 (The skin immune system (SIS): Distribution and immunophenotype of lymphocyte subpopulations in normal skin). This key article set the record straight, once and for all, about the presence of lymphocytes in healthy skin; characterized the immunophenotypes of subpopulations, quantified these cells, and studied their location. It was perhaps the critical discoveries made by Bos et al. that fueled the scientific community’s interest in skin lymphocytes, contributing to a new generation of cutaneous immunology research. We briefly describe additional scientific breakthroughs made since 1987. Nonetheless, the study of cutaneous lymphocytes remains essential to understand the relationship of these cells to human diseases, and to develop therapies that can be leveraged to selectively mobilize, enhance or deplete these cells.
The skin is no longer viewed merely as a physical barrier tissue; rather, it is considered to be a novel and active immune organ. The successful control of pathogens by the skin’s immune surveillance and its’ effector functions are likely mediated by a variety of migratory and resident cells that include keratinocytes, dendritic cells, macrophages, Langerhans cells and T cells. Currently, significant ongoing research in experimental dermatology focuses on skin T cells – for that reason we find important to highlight the pioneering work of Jan D. Bos and colleagues, who characterized the immunophenotypes of lymphocyte subpopulations, quantified these cells, and studied their location in healthy human skin.\(^1\) The presence of intraepidermal lymphocytes was probably first described in 1922 by Kondo\(^2\), but subsequent reports on the absence of T cells in healthy human skin shed doubt on the existence of these cells.

The article by Bos et al. from 1987 (*The skin immune system (SIS): Distribution and immunophenotype of lymphocyte subpopulations in normal skin*) set the record straight, once and for all, about the presence of T cells;\(^1\) these authors showed that all lymphocytes present in healthy skin are T cells, and that the vast majority are clustered around vessel; also that these perivascular cells are either CD4\(^+\) or CD8\(^+\), and are generally activated. Only fewer than 10% of lymphocytes are intraepidermal, directly subepidermal, or not perivascular, and these are mostly CD8\(^+\). Bos et al. also proposed and emphasized the concept of a skin immune system (SIS): together with their findings, this conceptual breakthrough contributed to a new generation of lymphocyte-focused dermatology research. Since then, it has been found that healthy human skin contains nearly 20 billion T cells, almost twice as many as are found circulating in the blood.\(^3,4\) These skin T cells can currently be studied via numerous methods, such as immunohistochemistry, high-throughput T cell receptor sequencing or retrieved from the skin by crawl-out culture method and consequently analyzed by flow cytometry.\(^3,5\) A recent developed technology allows to study early signaling events in skin T cells by multiplex immunoprecipitation flow cytometry, even if only few T cells are available from skin biopsy samples.\(^6,7\)

Skin T cells are mostly CD45RO\(^+\) memory T cells that co-express the skin-homing addressins CLA and CCR4.\(^3\) More recently Watanabe et al. (2015) reported that, depending on migration territories and functional activity, these human skin cells are of 4 types: (1) dermal resident memory T cells (T\(_{RM}\)), which are mostly CD4\(^+\), and co-express CD69 and CD103. (2) Epidermal T\(_{RM}\) cells, which are CD103\(^+\), and are either CD4\(^+\) or CD8\(^+\). These epidermal cells have a limited proliferative ability compared to dermal cells, but a higher effector capacity. Nevertheless, T\(_{RM}\) are stronger effector cells than re-circulating T cells. (3) Re-circulating Central Memory T cells (T\(_{CM}\)), which are CCR7\(^+\)/L-selectin\(^+\). And (4), re-circulating Migratory Memory T cells (T\(_{MM}\)) that are CCR7\(^+\)/L-selectin\(^−\). T\(_{CM}\) produce
more cytokines and re-circulate faster than do $T_{MM}$. Only 2% of skin-tropic memory T cells are in circulation; the rest all persist in the skin.3

The nature of the relationship between lymphocytes and the skin has been debated over many years, including the conjectured existence of skin-associated lymphoid tissue (SALT) in 1978.9 However, these cumulative observations were crucial in overcoming the prior paradigm that T cells are only recruited to tissue sites in case of infection or inflammation, and that tissues otherwise have very few resident T cells. In fact, $T_{RM}$ are highly functional and persist in the skin long after the resolution of skin infections. Interestingly, the deposition of $T_{RM}$ in epithelial tissue is antigen-independent, and $T_{RM}$ can protect against re-infection, even in the absence of circulating T cells and antibodies. In addition, a portion of the $T_{RM}$ generated by skin infections migrates to lymph nodes, and drains distant epithelial tissues like the gut and lung, protecting these tissues.10

On the other hand, dysregulation of skin T cells can lead to human autoimmune and inflammatory diseases. A prototypic $T_{RM}$ disease presents as recurrent inflammation in the same anatomical locations, with well-demarcated borders. The inflammation usually has a rapid onset (24 to 48 hours), which may resolve with anti-inflammatory therapy; but when treatment is interrupted, the lesions often recur in the same sites. Psoriasis, mycosis fungoides, and fixed drug eruption have been directly linked to pathologic $T_{RM}$, although the clinical characteristics of many other human inflammatory diseases also suggest a role for $T_{RM}$.11 In contrast, pathologic $T_{CM}$ recirculate between the blood, lymph nodes and skin, and lead to a diffuse erythema of the skin, as seen in leukemic cutaneous T cell lymphoma.10

Bos et al. also noted that of the CD4+ cells in healthy skin, less than 5% can be classified as suppressor inducer T cells.3 Regulatory T cells (Tregs) are now one of the most studied suppressor cells, because of their relevance in maintaining self-tolerance. Bos did not study FoxP3+ Tregs, because the FoxP3 gene, essential for Tregs, was only discovered later, in the beginning of the twenty-first century. Clark and Kupper (2007) demonstrated that between 5-10% of $T_{RM}$ in healthy human skin are FoxP3+ Tregs.12 The presence of Tregs in the skin, and not only in the skin draining lymph nodes, is now considered to be vital for controlling inflammation even in under normal, non-challenged conditions. Tregs dysfunction is correlated with several auto-immune diseases such as psoriasis, SLE and MS. For example, ultraviolet irradiation is an effective treatment for many auto-immune skin diseases, in part because it upregulates FoxP3+ Tregs.13-16 Additionally, cancers such as squamous cell carcinoma, basal cell carcinoma, Merkel cell carcinoma, and primary and metastatic melanoma are known to contain expanded Tregs to escape immune detection.17
In summary, we highlight the work of Bos et al., which might be unfamiliar to the majority of junior investigators in dermatology. Bos’s critical discoveries fueled the scientific community’s interest in skin lymphocytes, and contributed to the development of the field of cutaneous immunology. Despite all scientific breakthroughs made since 1987, the study of cutaneous lymphocytes, their biology, and repertoire remains essential for fully understanding the relationship of these cells to human diseases, and for developing therapies that can be leveraged to selectively mobilize, enhance or deplete these cells.

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REFERENCES