Immunology Letters 190 (2017) 125–129

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Mini-Review

Human T cell immune surveillance: Phenotypic, functional and migratory heterogeneity for tailored immune responses

Christina E. Zielinski[a,b,*]

[a] Institute for Medical Microbiology, Immunology and Hygiene, Technical University of Munich, Germany
[b] German Center for Infection Research (DZIF), Munich, Germany

ARTICLE INFO

Keywords:
T cell
Immunosurveillance
Migration
Chemokine receptor
Tissue residency

ABSTRACT

The human immune system constantly provides a balance between pathogen clearance as well as tolerance for autoantigens and the commensal microbiota. This is achieved by immune responses, which are highly specialized and diversified in terms of their phenotype, function, regulation and location. Despite the complexity that is inherent to human immunity, our current knowledge is primarily shaped by very reductionist insights gained from peripheral blood T cells. Since only 2% of human T cells recirculate in the blood, the vast majority remains undetected by common sampling strategies and therefore unexplored. This review highlights and discusses recent developments in human T cell immune surveillance with a particular focus on functional and migratory T cell heterogeneity and provides a critical framework for new conceptual ideas, which could serve as a starting point in the quest for novel targeted therapies for chronic tissue restricted inflammatory diseases.

1. Dissecting human immunity – challenge and chance

T cells have critical roles in the defence against a great variety of pathogens as well as in the tolerance of autoantigens and of the commensal microbiota. This is achieved by diverse T cell fates and identities that are shaped by distinct qualitative and quantitative cues from the microenvironment and from direct cellular interaction partners [1]. T cell receptor signal strength and duration, costimulation and cytokines represent the classic signals for the instruction of divergent T cell differentiation [2]. Recently, novel signals have entered the stage as potent immunomodulators. Sodium chloride has been shown to promote naïve T cell polarization into Th17 cells [3,4]. The impact of tonicity as a novel immunomodulatory signal seems highly relevant considering the enrichment of sodium chloride in peripheral tissues such as the skin and of potassium in the tumour microenvironment [5,6]. It can be expected that more microenvironmental signals will emerge in the near future, which shape immune responses in a tissue specific manner.

A major research limiting factor is human tissue availability. Most fundamental findings in human immunology are currently based on blood as a surrogate of systemic immune surveillance. But only 2% of all human T cells are present in the blood [7]. The vast majority, instead, resides in peripheral tissues where they adapt to their local microenvironments in terms of their phenotype, function and regulation. The classic strategy so far has been to extrapolate tissue specific functionalities from sampling blood T cells, which, by their differential expression pattern of chemokine receptor surface markers, denote specific tissue destinies [8,9]. Cutaneous lymphocyte antigen (CLA) expression, for example, marks skin-homing T cells, whereas CCR9 has been shown to endow T cells with gut-tropic properties [10,11]. But this strategy is highly biased, since it only identifies the recirculating T cell fraction while resident T cells are not represented in the blood (Fig. 1). In addition, the function and regulation of T cells changes upon arrival in the target tissues due to their adaptation to local microenvironmental cues. Most human T cells have therefore escaped detection and remain unexplored on a quantitative as well as qualitative basis.

The complexity of human T cell fates is generated over a lifetime on a constantly evolving antigen experienced background. Not only is the generation of an immunological memory response shaped by the pre-existing memory T cell repertoire but also by age specific factors that translate into distinct organ related microenvironments. Recent elegant work, made possible by a unique infrastructure for procurement of individual organs from dead donors, allowed the longitudinal analysis of human organ-wide immune cell subsets [12,13]. It revealed profound changes in the immune cell composition in various organs at different time points in life [14]. This cannot be recapitulated with laboratory mice, which rather mimic the human neonatal immune system and therefore are of limited translational value. Only profound changes in microbial expose, which would not be in accordance with general standards of mouse husbandry, have recently been shown to mimic

* Corresponding author at: Institute of Medical Microbiology, Immunology and Hygiene, Technical University of Munich, Trogerstrasse 30, D-81675 Munich, Germany.
E-mail address: christina.zielinski@tum.de.

http://dx.doi.org/10.1016/j.imlet.2017.08.001
Received 19 June 2017; Received in revised form 30 July 2017; Accepted 2 August 2017
Available online 04 August 2017

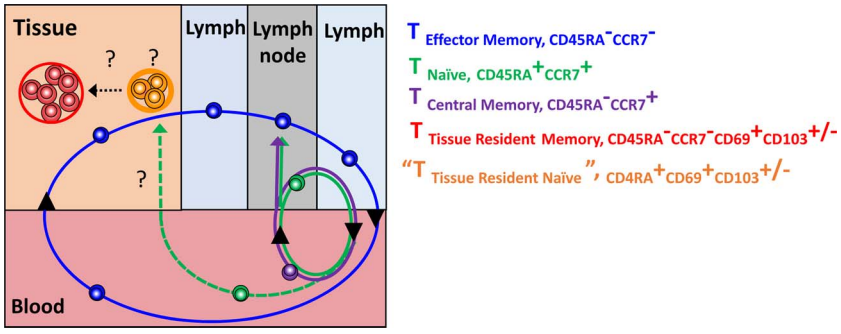

Fig. 1. Compartmentalized immune surveillance.
T cell subsets differ in their migration patterns based on their differential expression of the chemokine receptor CCR7 and based on tissue retention markers such as CD69 and CD103. T cell migration and function are co-regulated and jointly participate in immune surveillance.

human immune traits [15].

Taken together, dissecting human immune surveillance represents an extraordinary challenge for scientists. Its complexity is almost impossible to recapitulate in mouse models. It is, however, a crucial endeavour to embrace those challenges in order to advance our understanding of physiological and pathophysiological processes in humans.

2. Cell migration and differentiation – tailored programs for pathogen control

The last 10 years have witnessed an unprecedented quest for novel T helper cell subsets. They differ in their master transcriptional regulators, which translate into distinct cytokine repertoires as well as migration properties. Their programs are well tailored towards their respective cognate antigens and have been shaped by integrating stimulatory as well as cytokine signals during the differentiation process [1]. For more than 20 years these principles have been exclusively applied to the Th1 and Th2 cell programs, which cover the clearance of intracellular pathogens and parasites, respectively [16]. The identification of Th17 cells as a distinct T helper cell subset has shaken this dichotomous view on the division of labour between T cells and has heralded the discovery of a so far unappreciated heterogeneity of T cell identities and fates. Even divergent functional specializations can be assumed within the same T helper cell subset [8]. Recently, it has been demonstrated that Th17 cells can be generated by two distinct differentiation pathways depending on their antigen specificity. *C. albicans* specific naïve T cells differentiate into pro-inflammatory Th17 cells that co-express IFN-γ, whereas *S. aureus* specific naïve T cells differentiate into anti-inflammatory Th17 cells that instead co-express IL-10 [17–20]. This dichotomous outcome in the Th17 polarization process is due to differential requirements for IL-1β during human Th17 cell polarization, a property, which is determined by the antigen specificity and the associated cytokine microenvironment induced upon pathogen interactions with the antigen presenting cells [17]. This is also associated with differential migration properties since IL-1β dependent pro-inflammatory Th17 cells co-express CXCR3 with CCR6, whereas anti-inflammatory Th17 express CCR6 in the absence of CXCR3 [21]. Whether this indeed translates into a local segregation of pro- and anti-inflammatory Th17 cell subsets in the peripheral tissues remains to be determined. Analogous insights have been generated in mouse models, where most of the functions exerted by IL-1β in humans are adopted by IL-23 to instruct a pathogenic program in Th17 cells [22,23].

GM-CSF has also been shown to exert Th17 cell pathogenicity. In mouse models, it is co-regulated with IL-17 and, accordingly, induced by IL-1β, IL-23 and ROR-γt [24,25]. In humans, GM-CSF has been demonstrated to be regulated independently of the Th17 cell program. Instead, its expression is controlled by Th1 permissive regulatory pathways such as the IL-12-Tbet-IFN-γ axis [26,27]. In addition, T cells that produce GM-CSF independently of other signature cytokines and which are also regulated independently of any so far identified master transcriptional regulator have been described recently. This suggests the existence of a distinct T cell identity, a putative Th-GMCSF subset [26]. They are also characterized by a specific chemokine receptor profile. $CCR10^+CCR4^+CXCR3^-CCR6^-$ cell surface expression identifies GM-CSF-only producing T helper cells *in vivo*. GM-CSF producing T cells have been detected in highly increased frequencies in the cerebrospinal fluid of patients with multiple sclerosis, which suggests an association of this T cell functionality with multiple sclerosis and possibly also with other autoimmune diseases [26,28].

Likewise, several other T cell differentiation programs have been demonstrated, which translate into specialized functions and migratory preferences, i.e. Th22 cells, which display the skin homing surface marker CCR10 and are associated with chronic inflammatory skin diseases such as psoriasis [29,30]. Novel technologies and computational developments that allow an in-depth dissection of T cell heterogeneity on the single-cell level such as time of flight mass cytometry (CyTOF) and single-cell transcriptomics are expected to unravel even more T cell specializations, fates, developmental programs and functional states that translate into precisely tailored immune responses [31–34].

Together, the diversification of human T helper cell subsets and the co-regulation of their migration properties exemplify the division of labour of human immune surveillance on the effector T cell level. Still, almost all insights have been derived from studies of peripheral blood T cells that might display different functions and regulation patterns from their counterparts in the peripheral tissues.

3. Tissue immune surveillance

Phenotypic heterogeneity based on the differential expression of lymph node homing markers such as CCR7 and CD62L in T cells from the peripheral blood led to the conceptualization that memory T cells are categorized two main subsets, the central ($CCR7^+$) and effector ($CCR7^-$) memory T cells. This distinct homing receptor expression profile in both CD4 and CD8 T cells translates into unique functional specialization programs [35]. Central memory T cells (T_{CM}) patrol secondary lymphoid organs and undergo robust proliferation and differentiation into effector T cells, which can then enter peripheral tissues. Effector memory T cells (T_{EM}) lack lymph node homing receptors and instead recirculate between the blood and peripheral tissues. They are poised for rapid effector functions such as cytokine production and cytotoxicity and have a poor proliferative potential. Consistent with this model, T_{EM} cells could be harvested in the bloodstream in order to make extrapolations about their identity in the tissues, which they pass as part of their immune surveillance trajectories (Fig. 1).

Despite the elegance of this model, several issues remain unexplained and also inconsistent, i.e. the exit strategy of T_{EM} from the peripheral tissues into the draining lymph nodes. Since absence of CCR7 expression is a defining feature of this subset, it remains elusive how they could exert their recirculation pattern. In addition, the mismatch of T cell phenotypes in peripheral tissues and blood suggests distinct T cell identities in the tissues that are sequestered from recirculation.

Over the past several years, the existence of a novel T cell population has been established, the tissue-resident memory T cells (T_{RM}) [36]. The absence of T cell recirculation via the blood, as assessed by