Emerging Skin T-Cell Functions in Response to Environmental Insults

Jutamas Suwanpradid[1], Zachary E. Holcomb[1,2] and Amanda S. MacLeod[1,3,4]

Skin is the primary barrier between the body and the outside world, functioning not only as a physical barrier, but also as an immunologic first line of defense. A large number of T cells populate the skin. This review highlights the ability of these cutaneous T cells to regulate skin-specific environmental threats, including microbes, injuries, solar UV radiation, and allergens. Since much of this knowledge has been advanced from murine studies, we focus our review on how the mouse state has informed the human state, emphasizing the key parallels and differences.

Journal of Investigative Dermatology (2016) ■, ■–■; doi:10.1016/j.jid.2016.08.013

INTRODUCTION

Mouse models have been instrumental in furthering our understanding of cutaneous T-cell biology and function. Importantly, despite the differences of T-cell types and TCR usage between murine and human skin T cells, many of their roles are shared between these two species. The heterogeneity of cutaneous-resident T cells in murine and human skin is highlighted in Table 1.

T CELLS IN MURINE SKIN

In a steady state, murine T cells reside predominantly at the epidermal-dermal junction (Figure 1). The epidermis contains a unique population of γδ T cells, called dendritic epidermal T cells (DETCs) (Havran et al., 1989; Tamaki et al., 2001). DETCs reside within the skin near the interface with the skin and the external environment, indicating their role in barrier function and immunity (Girardi et al., 2002, 2006; Jameson et al., 2002; MacLeod et al., 2013; Sharp et al., 2005). DETCs develop in the embryonic thymus and express an invariant Vγ3Vδ1TCR, yet the antigen of the DETC remains elusive. In addition, DETCs also express natural killer group receptor 2D (NKG2D) and can receive signals from NKG2D ligands, expressed by stressed keratinocytes (Nielsen et al., 2015; Strid et al., 2008). In a steady state, DETCs form polarized immunologic synapses that anchor to keratinocyte tight junctions and likely provide TCR-mediated signals for maintenance in the skin (Chodaczek et al., 2012). Despite detailed experimental analyses, a DETC population has not been identified in human skin. The dermis of healthy mice contains both γδ and αβ T cells. Murine dermal γδ T cells are self-renewing and are largely maintained independently of circulating precursors (Sumaria et al., 2011). Similar to DETCs, dermal γδ T cells display an activated memory-like $CD44^+CD69^+CD103^+$ phenotype; however, they express variant γδ TCR chains, with some preference for Vγ4 (Sumaria et al., 2011). DETCs require TCR (co-)stimulation, dermal γδ T cells are highly "innate" and sensitive to cytokine and pathogen-associated molecular pattern recognition (MacLeod et al., 2013; Nielsen et al., 2014, 2015; Strid et al., 2008; Witherden et al., 2010, 2012). Whereas DETCs are dependent on both IL-7 and IL-15 for survival and maintenance, $V\gamma4^+$ dermal γδ T cells are largely dependent on IL-7 but not IL-15. A small subset of $V\gamma4^-$ dermal γδ T cells is IL-7 independent (Sumaria et al., 2011; Ye et al., 2001).

Under homeostatic conditions, αβ TCR^+ T cells comprise approximately 40–50% of all dermal T cells (Cai et al., 2011; Sumaria et al., 2011). Both $CD8^+$ and $CD4^+$ T cells, the latter comprising regulatory T cells (T_{REG}) and nonregulatory T cells, exhibit strong tropism for the hair follicle region (Figure 1), suggesting that the hair follicle is critical in regulating skin residence of these tissue-resident memory T cells (T_{RM}) (Chow et al., 2013; Collins et al., 2016; Gratz et al., 2013). Studies demonstrate that hair follicle epithelial cells produce IL-7 and IL-15, the former cytokine required for both $CD4^+$ and $CD8^+$ T_{RM} persistence, whereas the latter is required for $CD8^+$ T_{RM} epidermotropism (Adachi et al., 2015; Gratz et al., 2013; Lawson et al., 2015). Epidermal T_{RM} are comprised predominantly of CD8+ T cells, and similar to DETCs, these cells typically bear the α-chain of the integrin αEβ7 and CD103, and express the activation marker CD69 (Adachi et al., 2015; Mackay et al., 2013). CD103-mediated retention of T cells in the skin likely occurs via adhesion to E-cadherin. Integrins expressed by the interfollicular and isthmus keratinocytes of the hair follicle activate latent transforming growth factor-β production in the skin, which enhances CD103 expression (Adachi et al., 2015; Casey et al., 2012; El-Asady et al., 2005; Mackay et al., 2013; Masopust et al., 2010; Mohammed et al., 2016).

The murine skin also contains $CD103^-CD8^+$ T_{RM} cells (Mackay et al., 2013), but the underlying mechanisms of their

[1]Department of Dermatology, Duke University Medical Center, Durham, North Carolina, USA; [2]Duke University School of Medicine, Durham, North Carolina, USA; [3]Department of Immunology, Duke University Medical Center, Durham, North Carolina, USA; and [4]Pinnell Center for Investigative Dermatology and Skin Disease Research Center, Duke University Medical Center, Durham, North Carolina, USA

Correspondence: Amanda S. (Büchau) MacLeod, Laboratory for Cutaneous Immunobiology, Department of Dermatology, Duke University Medical Center, Purple Zone, DUMC 3135, 40 Duke Medicine Circle, Durham, North Carolina 27710, USA. E-mail: Amanda.MacLeod@duke.edu

Abbreviations: APC, antigen-presenting cell; CHS, contact hypersensitivity; CLA, cutaneous lymphocyte-associated antigen; DETC, dendritic epidermal T cell; FDE, fixed drug eruption; T_{CM}, central memory T cell; T_{EFF}, effector T cell; Th, T helper; T_{REG}, regulatory T cell; T_{RM}, tissue-resident memory T cell

Received 27 April 2016; revised 12 August 2016; accepted 18 August 2016; corrected proof published online XXX XXXX

© 2016 The Authors. Published by Elsevier, Inc. on behalf of the Society for Investigative Dermatology.

Table 1. Heterogeneity of human and murine skin resident T cells

Location	T-cell subset	Mouse	Human
Epidermis	γδ T cells	DETC ($V\gamma3^+V\delta1^+$)	$V\delta1^+$ enriched
Epidermis	$CD4^+$ T cell	$CD103^+ > CD103^-$ T_{RM}	$CD103^+ > CD103^-$ T_{RM}
Epidermis	$CD4^+$ T_{REG}	$FoxP3^+$ T_{REG}	$FoxP3^+$ T_{REG}
Epidermis	$CD8^+$ T cell	$CD103^+ > CD103^-$ T_{RM}	$CD103^+ > CD103^-$ T_{RM}
Dermis	γδ T cells	$V\gamma4^{-/+}$	$V\delta1^+$ enriched
Dermis	$CD4^+$ T cell	$FoxP3^-$ T_{RM}	$CD103^- > CD103^+$ T_{RM}
Dermis	$CD4^+$ T_{REG}	$FoxP3^+$ mT_{REG}	$FoxP3^+$ T_{REG}
Dermis	$CD8^+$ T cell	$CD103^- > CD103^+$ T_{RM}	$CD103^- > CD103^+$ T_{RM}

Abbreviations: DETC, dendritic epidermal T cell; T_{REG}, regulatory T cell; T_{RM}, tissue-resident memory T cell.

maintenance in the skin are not well understood. CD69 suppresses sphingosine-1-phosphate receptor 1, a molecule known to prevent T cells from emigrating from lymphoid organs or other tissues into the skin (Skon et al., 2013). Furthermore, CCR4 and CD103 expressed by dermal T_{REG} cells are critical to T_{REG} migratory behavior and maintenance in the skin, respectively (Chow et al., 2013; Suffia et al., 2005). Disruption of the skin barrier induces αβ T-cell migration to and from the lymph node, including effector T_{EFF}, regulatory, and central memory T cells (T_{CM}) (Bromley et al., 2013; Mackay et al., 2013; Tomura et al., 2010), and many of them become long-lived antigen-specific skin-resident memory T cells, termed T_{RM}. The critical roles of αβ and γδ T cells in the contexts of defense against skin infections, host-microbiome interactions, and skin damage will be discussed in this review article.

THE CUTANEOUS T-CELL REPERTOIRE IN HUMAN SKIN

Both epidermal and dermal γδ and αβ T cells are present in noninflamed human skin; however, cutaneous γδ T cells are approximately 300 times less abundant than αβ T cells (Clark et al., 2006; Streilein, 1983; Toulon et al., 2009; Watanabe et al., 2015). Cutaneous γδ T cells express predominantly the Vδ1 TCR chain and the skin-homing cutaneous lymphocyte antigen (CLA) (Toulon et al., 2009). T_{RM} participate in immunosurveillance because of their robust and long-lasting memory responses and derive from a surviving effector T cells (T_{EFF}) pool. Human skin T_{RM} comprise $CD103^+$ and $CD103^-$ subsets; $CD103^+$ T cells are enriched in the epidermis, whereas $CD103^-$ T_{RM} are more frequent in the dermis (Watanabe et al., 2015). Recent studies demonstrate that in addition to T_{RM}, there are two subsets of $CCR7^+$ T_{CM} that can also migrate to the skin. One subset coexpresses L-selectin (CD62L), whereas the other subset does not; the latter subset has been termed migratory memory T cells (Park and Kupper, 2015). In addition, healthy human skin also harbors $Foxp3^+$ memory regulatory T cells, termed mT_{REG} cells, residing around hair follicles where they contribute to immune homeostasis, or if dysregulated can mediate immunopathology (Chow et al., 2013; Sanchez Rodriguez et al., 2014; Seneschal et al., 2012). The composition and function of cutaneous T cells can change dramatically on environmental insults and may be driven by both antigen exposure and innate immune signals derived from surrounding keratinocytes, dendritic cells, macrophages, and other cells (Iwasaki and Medzhitov, 2015; Schroder et al., 2006). This review article focuses on the effects of cutaneous T-cell activation in the context of environmental insults and the factors that maintain T cells in the skin to provide long-lived protective functions.

CONTROL OF COMMENSAL AND PATHOGENIC MICROBIOTA BY SKIN T CELLS

The cutaneous microbiome is highly diverse and consists of trillions of bacteria, fungi, viruses, archaea, and small arthropods (Byrd and Segre, 2015; Costello et al., 2009; Grice et al., 2009; Human Microbiome Project Consortium, 2012;

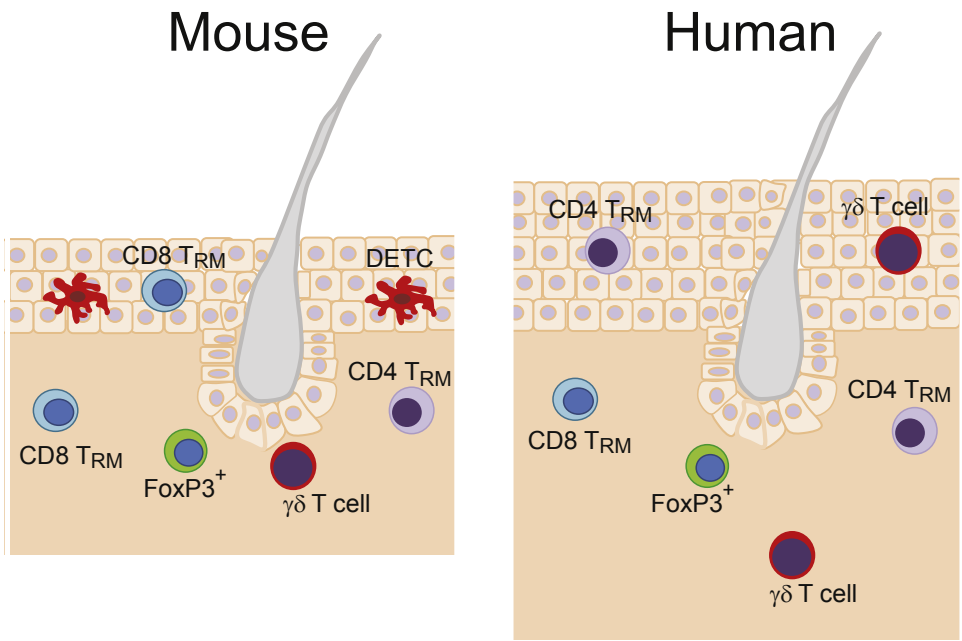

Figure 1. Murine and human skin harbors T cells. The illustration of diverse cutaneous T cell populations in the human and mouse. DETC, dendritic epidermal T cell; T_{RM}, tissue-resident memory T cell.

Download English Version:

https://daneshyari.com/en/article/5649776

Download Persian Version:

https://daneshyari.com/article/5649776

Daneshyari.com