SnapShot: Resident Memory T Cells

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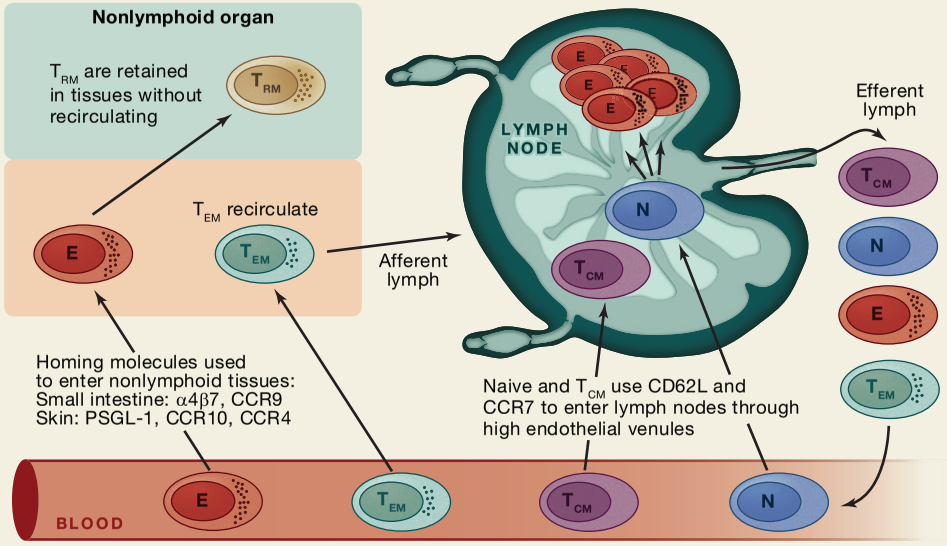
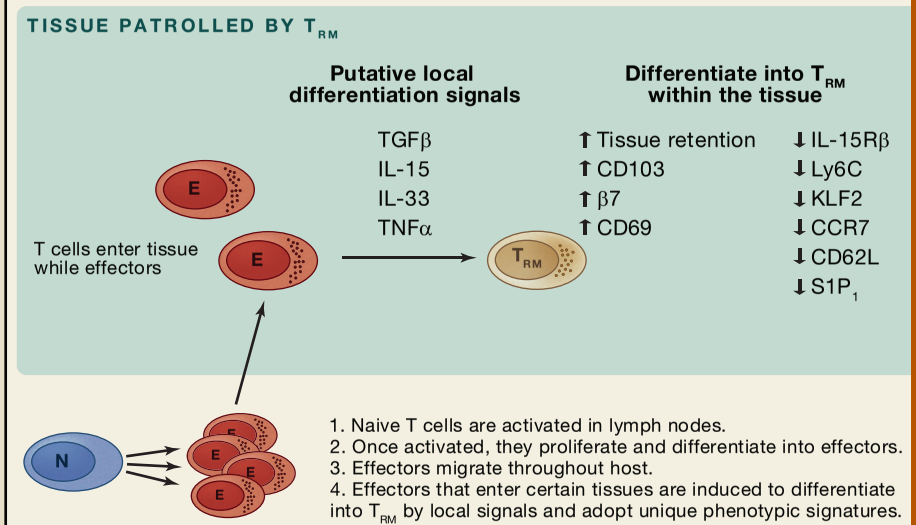
Cell

T CELL RECIRCULATION PATTERNS

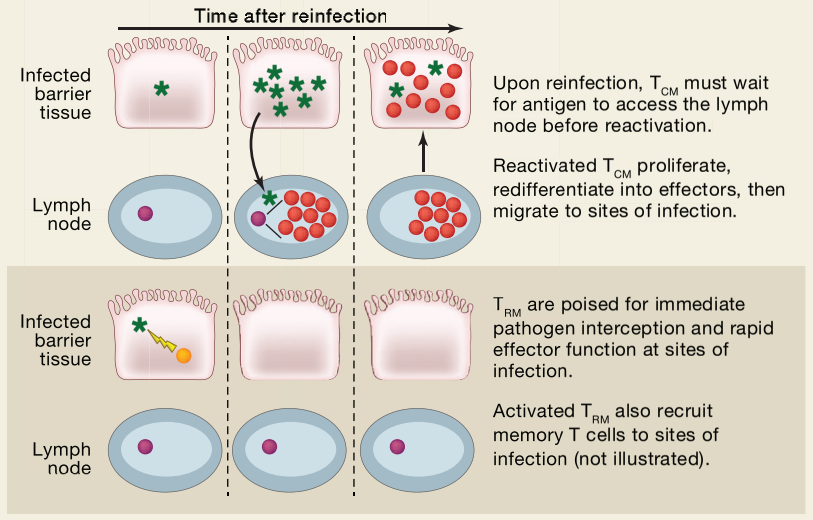


THE TISSUE MILLIEU INDUCES T_{RM} DIFFERENTIATION AND MAINTENANCE

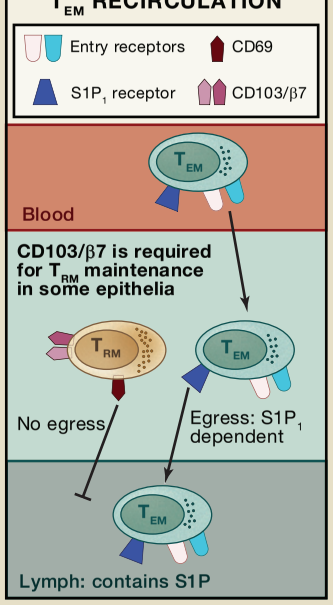


1. Naive T cells are activated in lymph nodes.
2. Once activated, they proliferate and differentiate into effectors.
3. Effectors migrate throughout host.
4. Effectors that enter certain tissues are induced to differentiate into T_{RM} by local signals and adopt unique phenotypic signatures.

T_{RM} MAY INTERCEPT PATHOGENS AT SITES OF EXPOSURE



T_{RM} MAINTENANCE VS T_{EM} RECIRCULATION



	Markers	N	E	T_{CM}	T_{EM}	T_{RM}
Effector differentiation	Granzyme B	–	+++	–	+	++*
	Eomes	–	+	++	++	+
	Ly6C	±	++	++	++	–
Migration/ retention	L-selectin	++	–	++	–	–
	CCR7	++	–	++	±	–
	CD44	–	+++	+++	+++	++
	CD69	–	–**	–	–	++
	CD103	+	–	–	–	+++*
	$S1P_1$	++	++	++	++	–
	KLF2	++	++	++	++	–
Cytokine receptors	IL-15Rβ	++	+	+++	++	±
	IL-7Rα	++	–	+++	+	++
	Location	SLO, blood, lymph	SLO, blood, non-lymphoid tissues	SLO, blood, lymph	Blood, spleen, red pulp, some nonlymphoid tissues	Barrie tissue

* Varies among different tissues **Effectors transiently express CD69 after stimulation

See online version for legend and references.

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Resident memory T cells (T_{RM}) comprise a subset of non-recirculating memory T cells that remain positioned at common portals of re-infection. These include barrier tissues such as the mucosae and skin. T_{RM} orchestrate the initial response to pathogens re-encountered at these locales, thereby accelerating protective immune responses.

Defining T_{RM}

When naive T cells are stimulated by pathogens within secondary lymphoid organs, they proliferate and differentiate into effector T cells, many of which home to nonlymphoid tissues. Following clearance of the infection, a fraction of pathogen-specific T cells differentiate into long-lived memory T cells. Memory T cells can be divided into three operationally distinct subsets based on trafficking properties (upper-left). Central memory T cells (T_{CM}) recirculate between lymph nodes, lymph, and blood. Effector memory T cells (T_{EM}) recirculate between certain nonlymphoid tissues, lymph (transiently passing through lymph nodes), and blood. However, some tissues, including many epithelial surfaces, are excluded from routine immune surveillance by recirculating T_{CM} and T_{EM}. Instead, these tissues are populated by a distinct lineage of memory T cells recently termed T_{RM}. T_{RM} are constitutively poised for rapid effector function and have been identified within many barrier tissues (Cauley and Lefrançois, 2013).

The defining signature of T_{RM} is their persistence within a single anatomic compartment without recirculating. T_{RM} do not exit tissues, enter circulation, and then reenter tissues. Rather, they remain stationed within one locale. One definitive experimental approach that informs whether a population of memory T cells is resident versus recirculating utilizes parabiosis (conjoining two animals so that they develop a shared circulatory system) and monitoring memory T cell movement between host tissues (Klonowski et al., 2004). Due to the challenges associated with performing this assay, T cell phenotype is typically used as a surrogate for identifying T_{RM} (right), although characterization and validation of a lineage-defining T_{RM} phenotype remains an area of active inquiry.

T_{RM} Ontogeny and Differentiation

Effector T cells express combinations of chemokine receptors, selectins, and/or integrins in order to extravasate from blood and enter nonlymphoid tissues. Different nonlymphoid tissues have distinct entry requirements. For example, T cells express $\alpha4\beta7$ and CCR9 to enter small intestine and PSGL-1 and CCR10 or CCR4 to enter skin (upper-left). Following infection clearance, some effectors differentiate into long-lived memory T cells. Importantly, the location where memory development occurs directly shapes their differentiation program. T_{RM} adopt signatures that distinguish them from T_{CM} and T_{EM} (right). These developmental cues are encountered within the tissues patrolled by T_{RM}, may contribute to T_{RM} survival and site-specific retention, and may include TGFβ, IL-15, IL-33, and TNFα (Casey et al., 2012; Mackay et al., 2013). T_{RM} signatures include expression of CD69 and reduced expression of the transcription factors KLF2 and Eomes as well as the lymph node homing molecule CD62L. A subset of CD8+ T_{RM}, particularly those resident within epithelial surfaces of the intestinal mucosa and skin, also express $\alpha_E\beta_7$ integrin (often referred to as CD103, an alternative term for α_E), which is induced by local TGFβ. Many T_{RM} constitutively express granzyme B and remain poised for rapid antipathogen function.

It should be noted that T_{RM} are not terminally differentiated. In mice, they arise from KLRG1^{lo} effector T cells, a subset of effectors that still exhibits developmental plasticity (Mackay et al., 2013). Moreover, if T_{RM} are experimentally removed from the anatomic compartment in which they reside, they can be reprogrammed to differentiate into T_{CM} and T_{EM} (Masopust et al., 2006).

Mechanisms of T_{RM} Survival and Stasis

Most T_{RM} characterized thus far express CD69. CD69 expression indicates that cells are refractory to sphingosphine-1 phosphate (S1P) signals, which attract lymphocytes to leave tissues via the lymph. T_{RM} also downregulate a critical S1P receptor, $S1P_1$. Reports indicate that either downregulation of $S1P_1$ or upregulation of CD69 is required to establish or maintain T_{RM} in barrier tissues (lower-middle) (Mackay et al., 2013; Skon et al., 2013).

$\alpha_E\beta_7$ integrin binds to E-cadherin expressed by epithelial cells. Induction of $\alpha_E\beta_7$ integrin expression is required for the maintenance of T_{RM} in the small intestine epithelium, where epithelial cells are replaced every 4–5 days, as well as many other compartments (Casey et al., 2012; Mackay et al., 2013; Lee et al., 2011). $\alpha_E\beta_7$ integrin can also be expressed by T cells in some locations where it appears dispensable for maintenance (e.g., the small intestinal lamina propria) yet is not expressed by T_{RM} in many locations (Casey et al., 2012). To make matters more complicated, recirculating naive and regulatory T cells also express $\alpha_E\beta_7$ integrin. Thus, $\alpha_E\beta_7$ integrin expression is a useful, but not unequivocal, marker of T_{RM}.

The cytokine IL-15 is important for the survival and continued basal "homeostatic" (not pathogen-driven) proliferation of T_{CM}. IL-15 has also been shown to be important for the establishment of long-lived T_{RM} within the epidermis (Mackay et al., 2013). Paradoxically, T_{RM} in many locations express unusually low levels of the IL-15 receptor and fail to undergo homeostatic proliferation (Masopust et al., 2006; Gebhardt et al., 2009). So, the precise role of IL-15 in the formation and maintenance of T_{RM} in many locations remains to be elucidated.

Function of T_{RM}

T cells must contact host cells to recognize infection and execute functions. T_{RM} in barrier tissues can accelerate infection control when pathogens are re-encountered at these body surfaces (Gebhardt et al., 2009; Jiang et al., 2012; Teijaro et al., 2011). T_{RM} are positioned for immediate pathogen interception, which precedes the lengthy process of reactivation of T_{CM} within downstream secondary lymphoid organs followed by proliferation, redifferentiation, and migration of T_{CM} progeny to the site of infection (lower-left). T_{RM} contribution to protective immunity may be mediated by direct cytotoxicity of infected host cells by effector cytokine production or by contributing to the recruitment of recirculating memory T cells to the site of infection.

It should be noted that the range of T_{RM} functions within tissues has not been thoroughly characterized and remains a critical area for further inquiry. Additionally, the longevity of T_{RM} within tissues is unknown, though evidence from mice and rhesus macaques indicates that they may persist for at least 1–2 years. Identification of strategies that optimize T_{RM} establishment after vaccination could potentially pay dividends for protecting against pathogens encountered at body surfaces, including HIV and *Mycobacterium tuberculosis*.

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