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Tissue-resident memory T cells in mice and humans – towards a quantitative ecology

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Abstract

In recent years, tissue-resident memory T cells (T_{RM}) have emerged as essential components of immunological memory. Following antigenic challenge, T_{RM} remain in nonlymphoid tissues and defend against re-exposure. Although accumulating evidence suggests important roles for T_{RM} in mediating protective immunity, fundamental aspects of the population biology of T_{RM} remain poorly understood. Here we discuss how results from different systems shed light on the ecological dynamics of T_{RM} in mice and humans. We highlight the importance of dissecting processes contributing to T_{RM} maintenance, and how these might vary across phenotypically and spatially heterogeneous subsets. We also discuss how the diversity of T_{RM} communities within specific tissues may evolve under competition and in response to antigenic perturbation. Throughout, we illustrate how mathematical models can clarify inferences obtained from experimental data, and help elucidate the homeostatic mechanisms underpinning the ecology of T_{RM} populations.

Introduction

Following primary infection and resolution of the associated cellular immune response, memory T cells are generated to protect against secondary exposures. It is well established that memory T cells comprise heterogeneous subsets. While central memory T cells (T_{CM}) and effector memory T cells (T_{EM}) circulate between the blood and secondary lymphoid organs (SLOs) or peripheral tissues, respectively, tissue-resident memory T cells (T_{RM}) are found in diverse tissue sites and provide crucial defenses against previously encountered pathogens (1–13). T_{RM} are widely dispersed throughout the body and have been associated with protection against viral and bacterial infections, anti-tumor immunity, and the pathology of allergic and autoimmune diseases (3, 7, 14–21).

T_{RM} are phenotypically and transcriptionally distinct from T_{EM} and T_{CM}, and the factors involved in their differentiation and maintenance have been studied extensively (reviewed in

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refs. (22–28)). As shown in parabiosis experiments involving the conjoining of two mice, T_{RM} persist within a wide variety of nonlymphoid tissues (NLT) (17, 29, 30). T_{RM} have also been identified in draining SLOs following local infection in the female reproductive tract (FRT) and skin (31). Evidence that T_{RM} persist in the presence of agents which deplete circulating peripheral T cells (e.g. FTY720 or anti-T cell antibodies) further indicates that T_{RM} are non-circulating and largely maintained independently of circulating populations (14, 32, 33). While T_{RM} are phenotypically heterogeneous, and there are no perfect markers of tissue residency, the most commonly associated marker in mice is CD69. Although CD69 is often attributed to recent antigenic stimulation, it may also function to retain T_{RM} within NLT (22), and parabiosis experiments have confirmed its utility in distinguishing tissue-resident from circulating cells (11, 17, 25). Another frequently used marker is CD103, which is predominantly associated with $CD8^+$ T_{RM} (34), although $CD103^+$ $CD4^+$ T_{RM} are found in skin and FRT (3, 34–37). Other markers, such as CD11a and CXCR3, are associated with the T_{RM} phenotype in certain tissues (11, 32, 34, 38–40).

Despite this extensive characterization, many fundamental aspects of T_{RM} biology remain poorly understood. For example, what determines the longevity of memory encoded by T_{RM}? How does the presence of T_{RM} impact the recruitment of new antigen-specific T cells upon exposure to related or unrelated pathogens? Is there competition between pre-existing and newly generated T_{RM}, and if so what factors mediate this competition? To address these questions requires formulating a quantitative ecology of tissue-resident memory, so that we may understand how continual exposure to environmental and infectious antigens impacts the distribution, diversity and persistence of T_{RM} at different sites across the body.

By pairing quantitative models with experimental observations one can test different hypotheses regarding cellular turnover and interactions, estimate quantities that may not be directly measured, and generate quantitative, testable predictions. Notably, mathematical models have elucidated mechanisms underlying the generation and resolution of effector T cell responses, and the maintenance of naive and circulating memory T cell populations (reviewed in ref. (41); see also, for example, refs. (42–52)). Further afield, there is a rich literature employing models to understand the ecological processes sustaining communities of plants, animals, and infectious agents (see, for example, refs. (53–56)). In this article we collate information regarding the ecological dynamics of T_{RM}, including current quantitative estimates of growth and loss rates in different tissues. We first consider studies performed in mice, as these comprise the bulk of the work to date, and then discuss our understanding of T_{RM} ecology in humans. Throughout this review we illustrate how mathematical tools can be harnessed to refine and enhance current experimental insights, and highlight open questions and areas for future work.

Identifying ontogenic pathways

The ontogeny of T_{RM} across different tissues has not been fully characterized. Although, in general, it seems that T_{RM} are enriched for relatively long-lived, quiescent cells in an early-differentiated state (57, 58), a definitive differentiation pathway remains elusive. One barrier to consensus in this area is that T cell responses are heterogeneous, and move through high-dimensional phenotypic trajectories, of which any given experiment only views a projection.

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However, by allowing us to frame mechanistic descriptions of the dynamics of proliferation, loss and differentiation, mathematical models can be used to explore competing hypotheses regarding patterns of T cell differentiation (45, 47, 59–61).

In addition to identifying precursor populations, quantifying the rate of T_{RM} generation from these populations, and whether this rate changes over both short timescales (such as during the contraction phase of an immune response) and throughout life is important for understanding how T_{RM} populations are established and maintained. Recent work suggests that host age modulates the rate of T_{RM} generation, as activated T cells in infants show reduced capacity to differentiate into lung T_{RM} compared to cells in adults (62). Such hypotheses can be explored using models that test the impact of host and/or cell age on population kinetics (49, 52, 63). For instance, a comparison of models describing different mechanisms of naive T cell homeostasis identified increasing cell survival with post-thymic age as the most likely determinant of population stability throughout life (49). Such methods could be used to dissect the roles of host and cell age in modulating T_{RM} formation.

Discriminating between models of T cell responses *in vivo*, and of T_{RM} ontogeny in particular, requires frequent sampling of the phenotypic profile of T cells during the acute, resolution and memory phases, both in the tissue and draining lymph nodes. Such data are typically cross-sectional, but even data from single cell fate-mapping experiments leave uncertainty regarding lineage relationships (45, 59, 64, 65). Nevertheless, if candidate mechanisms or pathways can be expressed as mathematical models, there exist statistical methods to compare the support for each (see, for example, ref. (66)). Such methods assess the ability of different models to describe observations while penalizing those which are too complex and tend to 'over-fit' – that is, those models which are overly tailored to the particulars of a given (inevitably noisy) dataset, and do not generalize well to data from other experiments. The most parsimonious models can thus be identified from a set of candidates, and used to infer biological parameters and underlying mechanisms. Additional data may then be used to test the predictions of models, and further assess their biological relevance.

Quantifying and dissecting contributions to T_{RM} longevity

Perhaps the key motivation for understanding mechanisms of T_{RM} development and maintenance is to optimize immunization protocols and maximize the longevity of tissue-resident immunity. Important questions include: does the longevity of T_{RM} clones depend on antigen-specificity and/or tissue location? Does longevity map directly to the phenotypic heterogeneity of T_{RM}? And to what extent does competition between T_{RM}, either at the level of the whole population or among antigen-specific populations, influence longevity? To tackle these questions quantitatively, we first note that the longevity of a T_{RM} population is determined by the balance between self-renewal, loss, and recruitment from circulating precursor populations (Box 1). In particular, if there is proliferative self-renewal of T_{RM}, the lifetime of individual T_{RM} cells may be shorter than the lifetime of the population as a whole. In what follows, then, we use the term 'longevity' to define the persistence of a population, combining the net effects of influx, division, and loss.

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Measuring longevity is hampered by the censoring of experimental information – estimates can be dependent on the duration of sampling. Nevertheless, broad patterns have emerged that indicate potential tissue-specificity in T_{RM} longevity: populations in the lungs and liver persist for weeks to months (7, 11, 32, 67–70), whereas those in tissues such as the brain and skin may persist for months to years (Table 1) (4–6, 8, 12, 17, 35). While the longevity of T_{RM} may also be phenotype-specific, as it is in circulating memory subsets (41), little is known in this regard. Despite evidence that $CD8^+$ memory cell populations persist longer than $CD4^+$ memory cells in tissues such as the skin and FRT (5, 35, 71, 72), there have been no direct comparisons of the longevity of $CD4^+$ and $CD8^+$ T_{RM}. Similarly, although some evidence suggests regulatory $CD4^+$ T cells, another distinct subset of resident memory, can persist for over 50 days in the skin and lungs, their population dynamics are, in general, more poorly defined than those of conventional $CD4^+$ and $CD8^+$ T_{RM} (73, 74).

Although experimental studies have provided valuable insights into longevity in different tissues, the majority measure T_{RM} abundance over time and cannot untangle the contributions of recruitment, self-renewal, and loss. For instance, the rapid loss of influenza-specific T_{RM} in the lung has been attributed to all three components of population longevity: high levels of apoptosis-driven loss, low levels of proliferation, and decreasing recruitment of circulating precursors over time (67, 69, 75). However, direct quantitative comparisons of the relative roles of each are currently lacking. Ultimately, to develop a mechanistic understanding of T_{RM} homeostasis, we need to quantify the relative contributions of proliferation, recruitment, and loss. These factors are discussed in detail below.

The extent of T_{RM} recruitment at steady state (in the absence of infection) varies across NLT, cell phenotypes, and possibly infections. Recently-generated $CD4^+$ T_{RM} in the lung, and $CD8^+$ T_{RM} in the brain and skin, remain stable in numbers in the absence of input from the circulation (32, 35, 76). In contrast, $CD8^+$ T_{RM} in the lung are at least partly replenished by circulating memory precursors (69, 77), and there may also be low level seeding in the FRT (17). Given the sensitivity of the above analyses to sampling times, and the potential for changes in the rate of recruitment from precursors over time (69), further work is needed to measure the long-term contribution of recruitment to T_{RM} maintenance.

Although T_{RM} populations expand efficiently in response to antigenic restimulation (12, 58, 78), the extent to which they self-renew at steady state is unclear. BrdU-labeling experiments have indicated that low-level proliferation occurs in the lung, skin, and brain, with 0–5% BrdU uptake over seven days (3, 69, 76). However, it has also been shown that a more substantial fraction (around 9%) of established T_{RM} in the brain express Ki67, a marker of recent division (12). Evidence that these $Ki67^{hi}$ cells are established T_{RM}, rather than recently-divided immigrants, implies a more important role for self-renewal in certain tissues (12, 76).

Finally, loss of T_{RM} can result from cell death (turnover) or tissue egress. In some systems, such as the lungs, T_{RM} express lower levels of the anti-apoptotic protein Bcl-2, and increased levels of the pro-apoptotic caspase 3/7, than their circulating counterparts, suggesting impaired cell survival (69). However, this impairment is not apparent for T_{RM} in the skin, illustrating that loss rates likely vary across different tissues and cell phenotypes.

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Combining these experimental observations with quantitative models will enable (i) characterization of homeostatic dynamics as cells die, divide, and/or differentiate; and (ii) rates of recruitment, self-renewal, and loss to be inferred (41, 46, 48). Although some quantitative methods have been employed to infer population half-lives in the liver and lungs (Table 1; see refs. (11, 70, 79)), these may be overestimates as cell recruitment was not taken into account (Box 1). To discriminate self-renewal of existing T_{RM} from the recruitment of new cells, one can use fate-mapping systems, or adoptive transfer of congenically labeled T cells prior to secondary challenge. As an example, the former has been employed to track the differentiation of congenically labeled cells that develop normally in the thymus and are released into a lymphoreplete periphery (47). In combination with BrdU-labeling, models were used to quantify heterogeneity in the dynamics of effector and memory $CD4^+$ T cells, and the rate of naive cell recruitment into these populations. Applying similar approaches to T_{RM} could disentangle the processes of recruitment and renewal, and identify heterogeneity in population dynamics. In particular, heterogeneity is suggestive of T_{RM} subpopulations with distinct homeostatic niches (Box 2), and the combination of modeling and fate-mapping may reveal whether these coexist independently or whether there is interconversion between them. These methods also allow projection of T_{RM} population dynamics beyond typical experimental timecourses, to develop a more complete picture of T_{RM} homeostasis and persistence (Box 3).

T_{RM} competition and community composition

Community composition refers to the diversity and spatial distribution of cells coexisting within a tissue. This composition may be altered if T_{RM} compete with other cells (including other T_{RM} subsets) within their local niche. In the following section we consider competition and its subsequent impact on cell diversity within NLT, first by focusing on competition arising during homeostasis, or following a single inflammatory response, and then by considering how populations change across multiple exposures.

First, it is important to understand the extent to which T_{RM} compete with one another for homeostatic resources. In particular, competition implies the existence of a ‘carrying capacity’ that may limit the amount of T_{RM} a tissue can support. Such a restriction on population size may be important in the skin following HSV challenge, where T_{RM} numbers eventually plateau with increasing numbers of transferred effector cells, despite a continued increase in numbers in the spleen (58). Although saturation in T_{RM} formation must be carefully distinguished from saturation of other upstream immune responses (80), identifying potential carrying capacities is important as the density of antigen-specific T_{RM} within a tissue can influence the efficacy of protection (11, 58). Models can provide further insights into these systems by exploring the density of T_{RM} required to provide effective protection and predicting when populations will drop below this threshold (79, 81).

One mechanism that may drive cell competition is cytokine-mediated signaling. For example, T_{RM} maintenance and homeostatic division in the skin, salivary glands, liver, and kidney may be IL-15 dependent, with IL-15 deficiency leading to significant reductions in cell numbers (34, 70, 82–84). However, these data do not address whether IL-15 is limiting at steady state and thus are not direct evidence for cytokine-mediated competition under

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normal conditions. Another mechanism through which T_{RM} may compete is antigen availability. If T_{RM} formation is antigen-dependent, immunodominance hierarchies can arise amongst the newly generated population: more abundant epitopes stimulate greater numbers of the corresponding clone. Such hierarchies have been observed in the lungs, skin, and FRT (3, 8, 68, 85, 86). The clonal composition of T_{RM} at a tissue site may be further shaped by influx from memory precursors (17, 69) and subsequent antigen exposure (78).

One caveat to the above discussion is that most studies of T_{RM} maintenance use specific pathogen-free (SPF) or germ-free mice, which are typically isolated from exposure to environmental antigens. As such, the density and diversity of T_{RM} in tissues may be relatively low. In contrast, greater insights may be gained from so-called 'dirty mice' which are exposed to more diverse environmental antigens than those in traditional SPF facilities, and in which T_{RM} are typically found at greater densities (31). The populated tissues of these mice may more closely reflect normal conditions, and thus provide a better system to study competition between cells.

With respect to sequential exposures, multiple antigenic stimuli may change the diversity of the T_{RM} community as newly recruited and pre-existing cells compete for resources within a particular niche (87). In the skin, proliferation of pre-existing T_{RM} following HSV rechallenge is accompanied by increased apoptosis, suggesting prior population expansion may be controlled during recall responses (58). Despite this, a stable population of original cells can coexist with new recruits following either homologous or heterologous infection (58). In the FRT, T_{RM} numbers increase following consecutive homologous challenge, primarily due to *in situ* proliferation of pre-existing cells (78). Finally in the liver, pre-existing and newly established T_{RM} coexist following consecutive transfers of three heterologous populations (70). Together these results suggest heterogeneous T_{RM} populations can persist in a number of NLT following multiple exposure events. However, the extent to which this applies over longer timescales, across other sites, and against more biologically relevant exposure histories (e.g. SPF vs dirty mice) has yet to be determined.

An additional challenge in understanding community composition is to identify the specific rules of replacement – is T_{RM} homeostasis democratic, in the sense that all specificities or phenotypes compete equally for space and/or homeostatic resources in the absence of antigen? Do pre-existing T_{RM} tend to exclude new immigrants, or do newer cells have a competitive advantage? Does competition take place on a global level (independent of antigen specificity), or are there antigen-specific niches, created either by persistent antigen, or cell congregation at previous sites of infection? These questions can be addressed by further measuring the persistence of epitope-specific T_{RM} after multiple exposures to related and heterologous pathogens (70). Such insights will be of critical importance in understanding how host immunity changes in response to sequential infections.

The ecology of tissue-resident memory in humans

T_{RM} in humans are less well studied, primarily due to difficulties in sampling NLT. Although *in vivo* challenge experiments have been carried out with healthy volunteers (10, 88), such studies are generally rare. Nonetheless, recent insights have been gained from a variety of valuable sources, including tissues sampled from organ donors and patients

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undergoing surgical procedures (86, 89–94). These snapshots in time reveal the diversity of T_{RM} populations that accumulate throughout life in response to multiple pathogen exposures. In addition, they complement studies of germ-free and SPF mice that do not consider dynamics in the context of pre-existing immune landscapes.

In general, the phenotypes of human T_{RM} are relatively well-characterized. Despite differences in the transcription factors regulating their differentiation (95–99), human T_{RM} share core transcriptional and phenotypic profiles with their murine counterparts, including high expression of CD69 and enrichment for CD103 in $CD8^+$ populations (86, 90, 96, 100–104). Additional surface markers, including CD49a, CXCR6, and CD101, are also enriched at multiple sites (96, 105). Another notable finding from human studies is that T_{RM} are more widely distributed than in laboratory mice: T_{RM} have been identified in human lymphoid tissues (e.g. spleen, lymph nodes, and tonsils) in addition to NLT, and are the most abundant T cell subset at these sites (90, 96). This greater dissemination may reflect increased exposure to environmental antigens (103), and is consistent with recent findings that T_{RM} accumulate in the draining lymph nodes of mice following repeated antigenic stimulation (31). Overall, these studies highlight the importance of considering environment and host ecology when developing a conceptual framework of T_{RM} dynamics.

Determining the dynamics of T_{RM} maintenance in human tissues is particularly challenging given the difficulty of tracking cell populations over time. Nevertheless, cross-sectional analyses of mucosal and lymphoid tissues has revealed that T_{RM} are maintained at remarkably stable frequencies from childhood well into old age, at levels that are tissue-specific (106, 107). Important insights have also been gained from longitudinal studies. Firstly, T_{RM} clones specific for the allergen diphenylcyclopropenone (DPCP) persist in healthy human skin for at least four months (10). Secondly, donor T_{RM} persist in lung and intestine transplant recipients for over one year following transplantation (93, 94). Collectively, these findings suggest stable maintenance of human T_{RM}, although quantitative estimates from other tissues and antigens will be required before broad conclusions can be drawn.

The relative contributions of recruitment, self-renewal, and loss to overall population maintenance are also not well known. However, the gradual formation of recipient T_{RM} following lung transplantation suggests continual recruitment can occur (94). In addition, cross-sectional data from donor tissues indicate homeostatic proliferation of resident $CD8^+$ and $CD4^+$ cells is detectible, but low, across mucosal sites (91). In particular, few resident skin and intestine cells express Ki67 (93, 108), and expression levels in the lung are less than 8% (96). Although these observations suggest relatively low average rates of homeostatic self-renewal, recent partitioning of T_{RM} based on their ability to efflux fluorescent dye has revealed underlying differences in Ki67 expression: cells capable of efflux ($efflux^+$) show reduced rates of proliferation compared to $efflux^-$ cells (106). Moreover, the $efflux^+$ subset exhibited increased CD127 expression and enhanced IL-7 signaling following *ex vivo* stimulation, suggesting greater survival capacity. Together, these findings suggest important heterogeneity in cell quiescence and survival that modulates T_{RM} longevity at the population level.

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Finally, with respect to competition and community composition, humans are exposed to a greater number and diversity of environmental antigens than germ-free or SPF mice. Thus, one important question is how the accumulation and composition of different T_{RM} communities is impacted by these more frequent and multifaceted challenges. Recent sampling of donor tissue suggests a diverse range of influenza-specific T_{RM} clonotypes can be maintained in the adult human lung (86). A high degree of TCR diversity has also been observed in healthy human skin, and is largely maintained *in vitro* during IL-2 and IL-15 induced expansion (89). These findings hint that human NLT can support an array of coexisting T_{RM} communities. Mapping the dynamics of such communities, in the face of differential individual exposure history and genetic background, will be a key challenge for the future. In the absence of longitudinal sampling, one approach may be to use quantitative imaging of human tissue sections, including markers of proliferation and apoptosis, to establish the spatial organization of T_{RM} in different organs and how self-renewal and turnover reflect tissue location and local T_{RM} densities.

Concluding remarks

T_{RM} are a crucial component of the adaptive immune system and provide frontline defenses against invading pathogens. Understanding the mechanisms underlying population persistence and community composition is therefore crucial to enhancing immune memory and improving vaccine-mediated protection. Although recent experimental studies have provided many insights into the molecular factors governing cell differentiation and maintenance, a broader picture of T_{RM} ecology is still lacking. Mathematical modeling can help bridge this gap by providing a quantitative framework for exploring multiple different aspects of T_{RM} ecology. In particular, integrating models with data will allow us to disentangle the contributions of recruitment, proliferation, and loss to T_{RM} longevity, and project population dynamics beyond current experimental limits. Success in this endeavor will require longitudinal data from NLT and SLOs – a particularly challenging prospect for human studies.

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Box 1:

Modeling T_{RM} homeostasis

Consider a single homogeneous population of T_{RM}, T. A simple model of homeostasis assumes that newly recruited T_{RM} cells enter the population from a precursor subset at a constant rate, r. They then divide *in situ* at rate p and are lost at some rate d, which reflects both cell death and egress from the tissue (Fig. 1). The average residence time of an individual cell in the tissue is $1/d$. These processes can be expressed mathematically as

$$\begin{aligned} \frac{dT}{dt} &= r + pT - dT \\ &= r - (d - p)T, \end{aligned} \tag{1}$$

where $d - p$ is the net loss rate from the population, which is the balance of loss and self-renewal through division.

If there is no recruitment from precursor populations, then $r = 0$ and Eq. 1 can be solved to give

$$T = T(0)e^{-(d - p)t}, \tag{2}$$

where $T(0)$ is the initial number of T_{RM}. Thus, assuming cells are lost at a faster rate than they divide (*i.e.* $d > p$), the population will decline exponentially at net loss rate $(d - p)$. This quantity, rather than the residence time of any particular cell, is most relevant for quantifying the duration of immunity (*i.e.* the persistence of a T cell population that undergoes both loss and self-renewal). It follows that the average time for this population to halve in size is $\ln(2)/(d - p)$. One can use this net loss rate to estimate, for example, the time taken for the population size to fall below a defined threshold of protection.

Finally, if r 6= 0, then some cell loss will be masked by recruitment of new T_{RM}. Models that fail to account for this recruitment will underestimate the net loss rate, $(d - p)$, and thus overestimate the corresponding population halflife. If r is constant and $d > p$, the population will eventually reach an equilibrium, T^*, where influx and renewal are balanced by loss. This steady-state population size can be found be setting $dT/dt = 0$, giving $T^* = r/(d - p)$.

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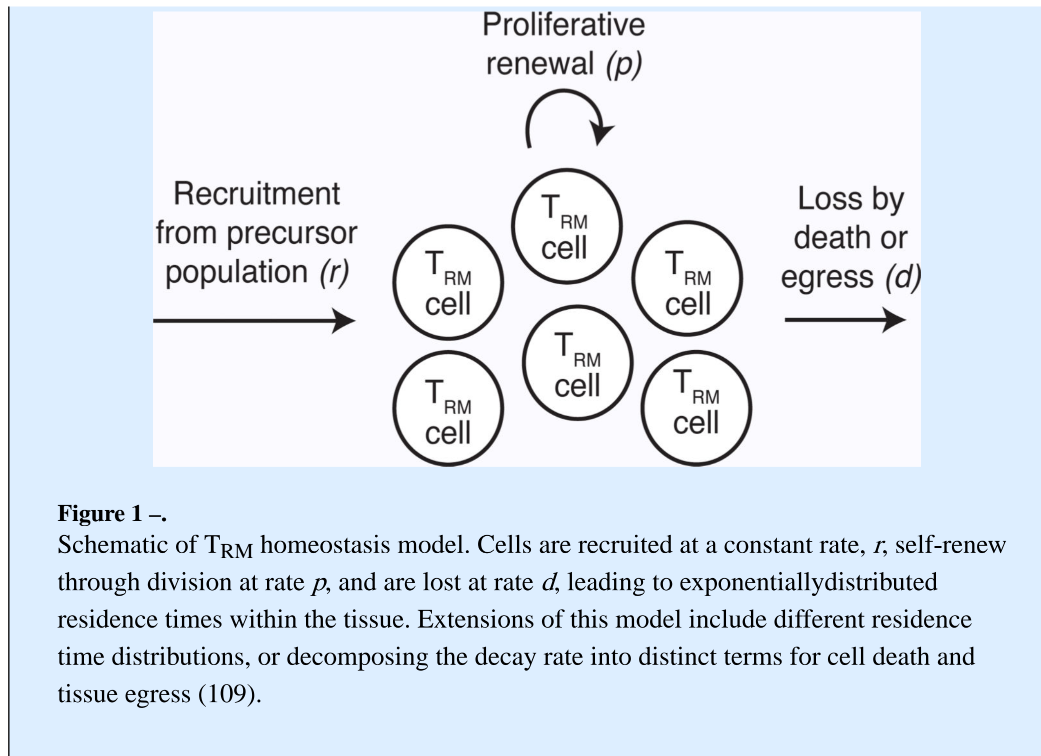

Figure 1 –.
Schematic of T_{RM} homeostasis model. Cells are recruited at a constant rate, *r*, self-renew through division at rate *p*, and are lost at rate *d*, leading to exponentiallydistributed residence times within the tissue. Extensions of this model include different residence time distributions, or decomposing the decay rate into distinct terms for cell death and tissue egress (109).

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Box 2.

Heterogeneity in T_{RM} populations

The homogeneous model of T_{RM} homeostasis (Eq. 1) assumes the rates of input, loss, and division are constant over time, and across all cells in the population. However, these assumptions may not always hold. For instance, input rates may wane over time, as has been found in the lung (69), and phenotypic heterogeneity may lead to different rates of division and/or loss, as has been found in other T cell subsets (43, 47). Such mechanisms can lead to heterogeneous population dynamics. For example, differences in net loss rates among phenotypic subsets can manifest as multiple phases of exponential decline, rather than the single phase of a homogeneous population (Fig. 2) (46). By modifying Eq. 1 to reflect these scenarios, heterogeneity in T_{RM} ontogeny and homeostasis can be identified and compared (although the ability to detect such heterogeneity requires sufficient data, such as detailed timecourses from fate-mapping and DNA labeling) (47, 110, 111).

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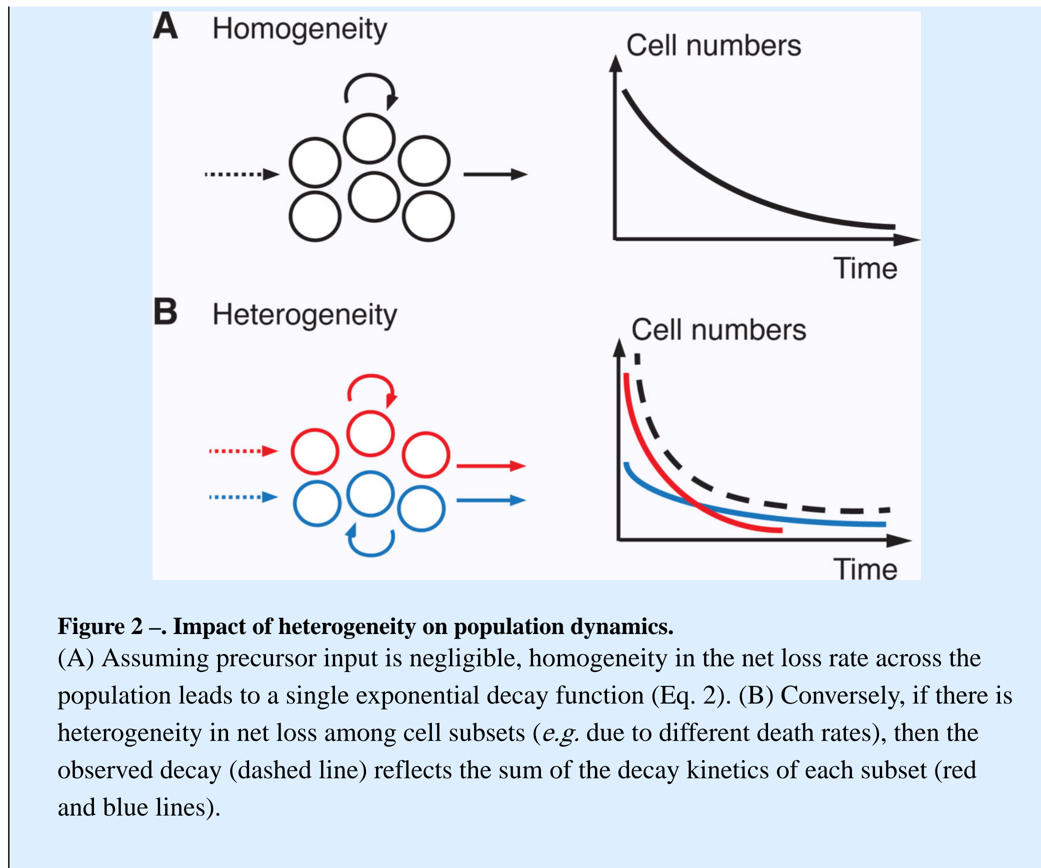

Figure 2 –. Impact of heterogeneity on population dynamics.

(A) Assuming precursor input is negligible, homogeneity in the net loss rate across the population leads to a single exponential decay function (Eq. 2). (B) Conversely, if there is heterogeneity in net loss among cell subsets (*e.g.* due to different death rates), then the observed decay (dashed line) reflects the sum of the decay kinetics of each subset (red and blue lines).

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Box 3:

Mathematical analysis of published data

To illustrate the insights that can be gained from mathematical modeling, we collated data from two independent studies of $CD8^+$ T_{RM} persistence in mice. One describes the number of OT-I T_{RM} in the lungs and nasal tissues (NT) from 20–120 days following infection with the recombinant X31-OVA strain of influenza virus (68). The other follows the number of P14 T_{RM} in the skin and lungs 20–200 days after infection with either Vaccinia-GP33 (skin) or PR8-GP33 (lungs) (69). The latter study also follows the endogenous T_{RM} response to the NP366 protein following infection with the PR8 strain of influenza.

Due to sparse information on the extent of T_{RM} recruitment in each tissue, we make the simplifying assumption that $r = 0$; i.e. influx is negligible over the experimental time frame. Although this assumption may be applicable to the NT and skin, it is unlikely to hold strongly in the lung (35, 68, 69). We also assume cells within each population are homogeneous with respect to their rates of division (p) and loss (d). T_{RM} decline can then be modeled using Eq. 2 to estimate the half-life of the population (Fig. 3). If *in situ* proliferation is minimal, then $p \approx 0$ and the net loss rate of the population ($d - p$) is equivalent to the loss rate of individual cells (d); this may be the case for lung and NT T_{RM} (68, 69). More generally, however, p 0 (12), and distinguishing the contributions of p and d to the net loss rate requires further data regarding T_{RM} self-renewal (e.g. Ki67 expression), death, or egress. Note also that the net loss rate will be underestimated if there is significant T_{RM} recruitment (Box 1).

Importantly, mathematical models can be used to project population dynamics beyond experimental time frames. For example, our model predicts that OT-I (Fig. 3A) and NP_{366} (Fig. 3B) T_{RM} cells will become undetectable in 230 and 210 days, respectively. These estimates are in agreement with the observation that lung T_{RM} are undetectable seven months (approximately 210 days) after infection (7).

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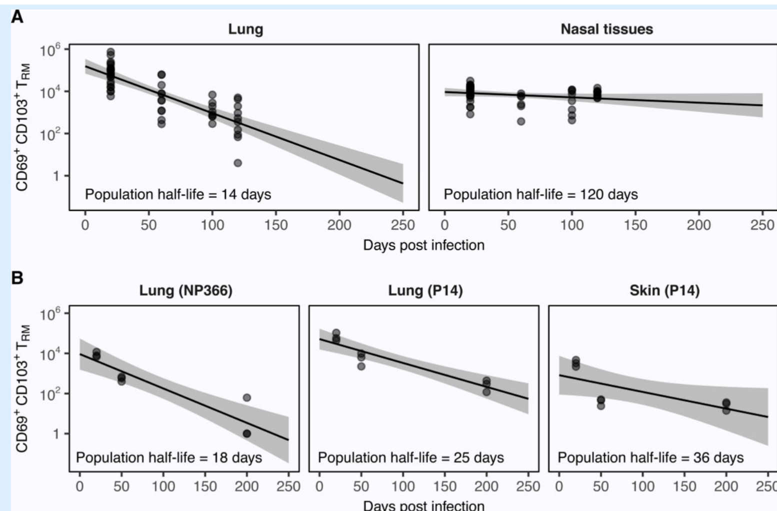

Figure 3 –. Mathematical analysis of published T_{RM} data.

Eq. 2 fitted to data from refs. (68) (A) and (69) (B). Solid lines are the model predictions, points are the data, and grey shaded regions are prediction envelopes obtained by sampling parameters from their 95% confidence intervals. Least-squares optimization was performed on the log-scale and residuals were normally-distributed (using the Shapiro-Wilk test), except those for the NT. The NT fits are thus included for approximate comparison only. Note that we use the above approach to illustrate how a simple model can be applied to experimental data. In a more thorough analysis, these predictions would then be compared with those from alternative models to identify the most parsimonious description of the data. Code for the above analysis can be found at https://github.com/SineadMorris/TRMecology.

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Table 1 –

Experimental estimates of CD8+ T_{RM} population parameters in different murine tissues and infection settings.

Time detectable represents the maximum observed duration of T_{RM} persistence; tissues are approximately arranged in order of increasing estimates.

Tissue	System	Time detectable	Population half-life*	Self renewal	References
Lungs	Influenza	< 210d	5–7d	No BrdU uptake detected	(7, 69, 79)
Liver	Malaria	> 100d	28–36d		(11, 70)
	LCMV	> 120d			(17)
FRT	HSV	> 80d			(5, 35)
	LCMV	> 120d			(17)
Intestine	YPTB	> 120d			(16)
	LCMV	> 120d			(17)
Brain	VACV	> 120d		<1% $BrdU^{+}$ in 1 wk	(76)
	LCMV	> 240d		9% $Ki67^{+}$	(12)
Skin	VACV	> 160d			(6)
	LCMV	> 200d			(69)
	HSV	> 540d		<5% $BrdU^{+}$ in 1wk	(3, 4, 58, 83)

FRT = female reproductive tract; HSV = herpes simplex virus; LCMV = Lymphocytic choriomeningitis; VACV = vaccinia virus; YPTB = Yersinia pseudotuberculosis.

*Half-life estimates do not account for any ongoing recruitment from circulating subsets.