Peripheral selection rather than thymic involution explains sudden contraction in naive CD4 T-cell diversity with age

Philip L. F. Johnson^{a,1}, Andrew J. Yates^b, Jörg J. Goronzy^{c,d}, and Rustom Antia^{a,1}

^aDepartment of Biology, Emory University, Atlanta, GA 30322; ^bDepartment of Systems and Computational Biology and Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461; ^cDepartment of Medicine, Stanford University School of Medicine, Stanford, CA 94305; and ^dDepartment of Medicine, Palo Alto Department of Veterans Affairs Health Care System, Palo Alto, CA 94304

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A diverse array of T cells is required for defense against pathogens. The naive CD4 T-cell repertoire reaches its peak diversity by early human adulthood and is maintained until older age. Surprisingly, around age 70, this diversity appears to plummet abruptly. A similar qualitative pattern holds for the CD4 T memory-cell population. We used mathematical models to explore different hypotheses for how such a loss of diversity might occur. The prevailing hypotheses suggest that the loss of diversity is due to a decline in emigration of cells from the thymus or a contraction in total number of cells. Our models reject these mechanisms because they yield only a gradual and minimal decline in the repertoire instead of the observed sudden and profound decrease later in life. We propose that an abrupt decline in the repertoire could be caused by the accumulation of mutations (defined here as any cell-intrinsic heritable event) that provide a short-term fitness advantage to a small number of T-cell clones (e.g., by an increased division rate or decreased death rate), with the person as a whole incurring the long-term cost of a decreased ability to fight infections.

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The adaptive immune system depends crucially on the ability to recognize antigens produced by any pathogen. Though individual T cells bind and recognize one or at most a few epitopes via their T-cell receptor (TCR), the entire population of T cells encompasses a diverse repertoire of TCRs that, ideally, allows recognition of the epitopes on essentially any pathogen. The diversity of this repertoire declines over time, as demonstrated by experimental work in aged mice (1–3), rhesus macaques (4), and humans (5). This decline in diversity has implications for susceptibility to disease, yet, as we explore in this paper, the driving forces underlying this decline remain unclear.

The diversity of the repertoire arises from how the TCR is constructed. Each TCR consists of one α - and one β -chain. Each chain is generated through somatic recombination of V, D (only for the β -chain), and J segments during T-cell ontogeny in the thymus. In principle, the total combinatorial diversity from the within-chain recombination, together with the $\alpha\beta$ pairing, could amount to 10^{15} distinct TCRs (6). In reality, the number is lower due to limited physical space in the body and preferential recombination and pairing. Early experimental evidence suggested humans have a minimum of 10^6 and possibly as many as 10^7 distinct α - and β -chains, which pair together to form even more distinct $\alpha\beta$ TCRs (7–9). Recent deep sequencing of the TCR β -chain locus has directly identified 1 million unique sequences; however, the total diversity is likely much higher because this analysis used only a small number of cells and found relatively few shared sequences in two independent samples from the same individual (10). Though sequencing studies allow direct measurement of the number of distinct α - and β -chains in a population of cells, lack of knowledge of $\alpha\beta$ pairing limits our ability to measure repertoire diversity on an absolute scale. In practice, most experimental studies apply measures of the repertoire

designed to detect changes in the repertoire on a relative scale—such as during aging—rather than making absolute estimates of its magnitude.

Aging affects the naive and effector/memory (i.e., antigen-exposed) T-cell repertoires differently. The naive population acquires new T-cell lineages only by emigration from the thymus. The effector/memory population acquires new lineages by recruitment from the naive population following exposure to novel antigens throughout life. Further, in the antigen-exposed CD8 T-cell population, oligoclonal T cells steadily accumulate that are specific for latent viruses, such as cytomegalovirus (11–13), although such oligoclonality is infrequent in the corresponding CD4 population in healthy individuals.

A cross-sectional study in humans provided evidence for a surprising nonlinear loss in repertoire diversity with age. Naylor et al. (5) found that the CD4 β -chain repertoire changes little from adulthood until age 65, and then a dramatic loss in diversity occurs after age 65; they observed a similar pattern of loss in older age in both the naive and memory cell compartments (data for naive compartment reproduced in Fig. 1). The measurements of diversity in a given person were obtained by sampling 50 β -chains and measuring the frequencies using a limiting dilution assay. Naylor et al. (5) focused exclusively on the β -locus, which, as noted above, provides a lower bound on the overall $\alpha\beta$ diversity but should give a robust picture of the relative change in the repertoire with age.

The conventional view is that the loss of diversity arises as a consequence of (i) involution of the thymus and the related decline in the production of new naive T cells (14–17); (ii) stochastic extinction resulting from drift in the number of cells in different lineages during homeostatic turnover (2, 18) or, equivalently, from the perspective of the naive population, conversion of naive cells into memory cells (18); and (iii) a decline in the total number of naive T cells with age (18, 19). Recent work showed elegantly that the thymus, though critical to sustaining the naive T-cell population size in adult mice, plays a minor role in sustaining this population in adult humans (20). However, the relative importance of these factors for maintaining diversity remains unclear, as is whether these factors are even sufficient to produce the observed pattern of loss.

Because diversity is inherently a population-level question, we probe this puzzle using mathematical models that build on ideas

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¹To whom correspondence may be addressed. E-mail: plfjohnson@emory.edu or rantia@emory.edu.

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Fig. 2. The conventional (neutral) model does not generate a sudden loss of diversity. The conventional view holds that the loss of the repertoire in older age is due to a decline in thymic emigration, decrease in the number of naive cells, and stochastic turnover. We plot two measures of diversity for representative simulations: the number of unique TCRs (A) and Simpson's diversity index (B). Even a dramatic decrease in thymic emigration and the loss of 95% of the total population of cells results in only a very gradual loss in the number of unique TCRs, and a negligible decrease in Simpson's index. Under the aging thymus conditions, thymic emigrants decrease at a rate of 3% per year. The reduction in total population size occurs linearly with age such that the final population size at age 100 is reduced by 0%, 50%, or 95%. We start the simulations at age 20 at the equilibrium TCR distribution, as detailed in *Materials and Methods* with the following parameters: carrying capacity $k_0 = 5 \times 10^5$ cells, relative division rate $\lambda_0 = 1$ per cell per day, death rate $\delta = 0.001$ per cell per day, initial thymic influx $\tau = 0.0017$ lineages per day, initial clone size $s = 500$ cells, thymic recombination bias $\phi = 10^{-3}$, and $T = 10^4$ possible TCR identities.

age (Figs. S1 and S2). Similarly, we see little effect if division rates inherently vary between TCR lineages starting from when they leave the thymus (Fig. S3).

In summary, this model in which diversity is lost by the conventional explanations of thymic involution, stochastic extinction, and decreasing population size does not fit the empirical observation that diversity plummets suddenly in older age.

Alternative (Selection) Model. Given that the conventional explanations were insufficient to reproduce the data, we revised our model to test an alternative hypothesis: What would happen if one or a few TCR lineages gained rare selective advantages over time? Such a selective advantage could arise from an increase in the division rate of cells.

Under this hypothesis, we assume that, at the time of emigration from the thymus, all lineages have the same division rate, but that during homeostatic replication, clones can undergo transformations that affect their homeostatic division rate as well as

that of their daughter cells. These heritable changes could be either genetic or epigenetic; for simplicity of terminology, we refer to all such changes as mutations. Though we model mutations as affecting the division rate, similar qualitative results would arise if mutations affected the death rate or sensitivity to the carrying capacity.

We assume the simplest possible relationship between mutations and division rate by making all mutations exchangeable and using either a model in which mutations act additively to increase the division rate until a maximum rate is reached (additive model) or a model in which a fixed number of mutations are required before the division rate jumps directly to a maximum rate (jackpot model).

These selection models incorporate all of the components of the previous conventional model, with the addition of allowing mutations with rate μ and tracking the number of accumulated mutations in each cell along with its TCR identity and division history. As with the conventional model, we defer a formal description of these models to *Materials and Methods*.

In contrast to the previous conventional model, these models with mutation and selection can lead to a steep decrease in diversity, as seen in Fig. 3. Here we see that the additive model is sufficient to produce a steep decline later in life in the number of unique TCRs; its effect on Simpson's index is less severe, but still profound compared with the conventional model. The jackpot model, however, exhibits a sudden and precipitous decline in both the number of unique TCRs and Simpson's index. Note that the stochastic generation of mutants results in variation in the time of the decline in different simulations. For instance, in the jackpot model, each mutation occurs after an exponential waiting time, so the time to four mutations in a single lineage will be the minimum of N γ -distributed random variables with shape parameter 4 and scale parameter μ , where N is the number of cells in the population. In Fig. 3, we shade the region covering 90% of simulations as a means of illustrating this variation. Almost identical results hold if we model zero thymic output after age 20 instead of exponentially declining output (Fig. S4).

As in the conventional model, we use biologically reasonable parameters scaled for the population size of our simulations. In particular, the small simulated population size ($\sim 10^5$) relative to the actual T-cell population ($\sim 10^{11}$) requires scaling the mutation rate parameter (μ) upward. We address the issue of parameter scaling in more detail in *Materials and Methods*.

Thymic Rejuvenation. Immunologists have long hoped to slow immune senescence by rejuvenating the thymus by manipulating hormones or cytokines (18, 42, 43). If the loss in TCR diversity over time was primarily due to stochastic extinction after thymic involution, then thymic rejuvenation would certainly counter this loss. However, if the change in diversity was due to mutation and selection, then an increase (or lack of decrease) in thymic emigration would have little effect, as seen from representative simulations in Fig. 4. In fact, even rejuvenating the thymus to a level well above the baseline would have relatively little effect, because a clone that had acquired a selective advantage would still dominate over the less-fit new thymic emigrants.

Discussion

The human naive T-cell repertoire appears to decline abruptly and dramatically in older age (5) (Fig. 1). Our models allow us to reject the conventional view that this loss arises as a result of thymic involution; homeostatic turnover or conversion to memory; and decline in total cell numbers (Fig. 2). Instead, we propose alternative models with mutation and selection that qualitatively replicate the late onset of repertoire thinning (Fig. 3). These selection models have similarities to multistage models of cancer development, with the additive model similar to that of Moolgavkar and Knudson (44), and the jackpot model similar to that

Fig. 3. Models with mutation and selection generate a dramatic decrease in the repertoire in aging individuals. Because the heritable events (mutations) leading to changes in division rate are stochastic, the timing of the sharp decrease varies considerably from simulation to simulation. Dashed lines show median across replicate simulations when diversity is measured by the number of unique TCRs (A) and Simpson's diversity index (B). Shaded regions illustrate where 90% of simulated trajectories fall. Note the y-axis scale for B is much larger than for Fig. 2B. The additive model in which the selective advantage increases linearly for one, two, and three mutations shows a more gentle decrease in the diversity than the jackpot model in which the selective advantage only arises after a clone acquires four mutations. The times at which the relevant mutations first appeared in a representative simulation are indicated by numbers adjacent to lines. Simpson's index (B) crashes earlier than the number of unique TCRs (A) because the former is also sensitive to the unevenness in TCR frequencies that arises before a lineage goes extinct. We show the results of simulations for the model with an aging thymus and a 50% decline in population size; Fig. S4 shows similar results for a model with no thymus after age 20. Initial conditions and nonmutation/selection parameters are the same as in Fig. 2. For the additive model, $\mu = 5 \times 10^{-4}$ per cell division and $c_1 = 0.6$. For the jackpot model, $\mu = 7 \times 10^{-3}$ per cell division and $c_2 = 5$. The value of μ in the simulations scales inversely with the size of the simulated population as described in *Materials and Methods* (e.g., the physiological mutation rate would be $\approx \mu k_0 / 10^{11}$).

of Armitage and Doll (45). In contrast to these models of cancer in which cell lineages grow without limit, our models only allow T cells to compete for growth factors with other lineages of T cells, such that the total number of T cells stays roughly constant.

Our rejection of the conventional (neutral) models and support for the alternative (selection) models is robust to both changes in parameters and the form of selection. Under the conventional models, we see little reduction in diversity even under a maximal-loss scenario with no thymus and a 95% reduction in the total naive T-cell population size. In contrast, under the selection models, we see a dramatic decline in diversity even under a minimal-loss scenario with a noninvoluting thymus and no reduction in the total population size. As detailed in [SI](#)

Text, these results are unaffected by changing the degree of bias in TCR recombination in the thymus, incorporating variance in division rates under the conventional model, and different combinations of positive and negative mutations.

Though our models are robust, technical limitations prohibit a quantitative comparison between model and experiment because, as mentioned in the Introduction, current experimental measures of diversity are only qualitative. Further, the dynamic range within which empirical TCR β -frequencies were determined by Naylor et al. (5) places upper and lower bounds on the experimental frequency spectrum, whereas we have no such constraints in our model. That said, the experiment of Naylor et al. (5) covered a 400-fold range of frequency, making the central observation of an abrupt loss in diversity unlikely to have arisen as a consequence of a threshold in the measurement technique. Though our qualitative results are robust, without better quantitative measures, we cannot assign specific values to parameters such as the degree of bias in TCR production in thymus. Rapid advances in technology will likely surmount these limitations in the near future (e.g., ref. 10) and allow quantitative fitting of our models to data.

Though we have focused on the dynamics of the naive CD4 repertoire, future studies could extend these models to consider

Fig. 4. Thymic rejuvenation does not prevent the abrupt contraction in repertoire diversity found under the selection models, even with an unchanging total population size. Though a constant rate of thymic emigration will reduce the loss due to neutral drift (i.e., in the representative simulated trajectories, until ~60 y), new thymic emigrants cannot compete with the selective advantage of clone(s) with elevated division rates already in the periphery. This pattern holds for both the number of unique TCRs (A) and Simpson's index (B), although the maintenance of diversity through age 60 is more apparent in the former. Parameters same as Fig. 3, except that thymic involution does not occur ($\nu[t] = \tau = 0.0017$).

memory and CD8 populations. In addition to the forces of mutation and selection examined in this paper, these populations are affected by factors such as the shorter telomere lengths of memory cells (46), the increased frequency of cells specific for persistent latent herpes virus infections (11, 12, 18), and interconversion between naive and memory cells. Of particular note, phenotypic interconversion has been recently suggested by experimental work using high-throughput sequencing that found a surprising amount of overlap between the naive and memory repertoires (37, 38).

Regardless of the cause of selection, our conclusion has an important implication for possible therapeutic interventions to counter the decline of the immune system in old age. Previous effort has focused on rejuvenating the thymus (15). Though this approach will be valuable under extreme forms of lymphocyte depletion, such as after chemotherapy or HIV infection (47), it may have little effect on age-associated contraction in diversity. Instead, our model suggests that treatment would require an intervention that targets the specific cells growing abnormally and pushing other TCR lineages toward stochastic extinction. Alternatively, if a common mechanism underlies the heritable genetic or epigenetic changes leading to this selective advantage, then early therapy could potentially preempt the decline in diversity.

Materials and Methods

Model Description. We follow a population of $N[t]$ naive T cells that may change over time, t . We use an agent-based model that tracks each cell's TCR specificity and number of accumulated mutations. In this section, all cells with a given TCR and number of mutations are referred to as a lineage. Homeostasis maintains the population at a target level (i.e., a carrying capacity) of $K[t]$, which may decrease linearly over time corresponding to a loss of 0%, 50%, or 95% over 80 years, $K[t] = k_0(1 - \gamma t/80)$, where $\gamma \in \{0, 0.5, 0.95\}$. For computational efficiency, we simulate from a reduced population with $k_0 = 5 \times 10^5$ instead of the actual human size of $\approx 10^{11}$.

Four types of stochastic events affect the population: (i) cell division, with rate $\lambda(1 - N[t]/K[t])$, which may vary as a function of the cell's properties; (ii) cell death or conversion to memory, with rate δ ; (iii) thymic emigration, with rate $\nu[t]$; (iv) mutation, with rate μ . We describe each event in more detail below.

- i) The cell-specific relative division rate, λ , is constant under the conventional models ($\lambda = \lambda_0$) but increases under the selection models as a function of the number of accumulated mutations, m , in a particular cell. With the additive selection model, $\lambda = \lambda_0(1 + c_1 \min[m, 3])$, where c_1 is a parameter. With the jackpot selection model, $\lambda = \lambda_0$ for $m < 4$, and $\lambda = \lambda_0 c_2$ otherwise, where c_2 is a parameter.
- ii) In all simulations, we set the homeostatic death (or conversion to memory) rate to be $\delta = 0.001$ per cell per day as suggested by labeling studies of

naive T cells (40). This rate has corresponding implications for the baseline level of thymic emigration, as noted below.

- iii) We use three patterns of thymic emigration: constant ($\nu[t] = \tau$), negligible ($\nu[t] = 0$), and involuting at a rate of 3% per year ($\nu[t] = \tau e^{-0.03t}$) (14). When thymic emigration occurs, a new lineage of naive cells with a potentially novel TCR enters the population with clone size s , corresponding to the net effect of intra- and postthymus divisions after TCR rearrangement. For adult humans, $s \approx 500$ (34). The TCR identity index, j , is drawn from a truncated geometric distribution with bias parameter ϕ and total unique TCRs T such that $\Pr(j) = (1 - \phi)^j \phi / (1 - (1 - \phi)^T)$. See *SI Text* for further discussion of this bias. The constant level parameter, τ , is set such that the expected number of distinct clones in the population (e.g., without biased rearrangement, $k_0/s = 10^3$, for our simulations) remains stable given the death rate δ . Note that because we simulate a reduced population size, the emigration τ is correspondingly reduced from its physiological level.
- iv) Mutations that potentially affect a cell's relative division rate (λ) occur at a rate μ per cell per division. These mutations could be either genetic or epigenetic but do not change the TCR specificity. The overall rate at which mutations occur, $\mu N[t]/\delta$, must be quite low. However, because our simulated population size ($k_0 = 5 \times 10^5$) is much smaller than the physiological population size ($\approx 10^{11}$), our per-cell, per-division mutation rate μ is correspondingly higher than physiological.

Initial Conditions. We consider the initial conditions for the model to be a fully developed but still young immune system. We assume that at $t = 0$ (≈ 20 y old) the immune system is at equilibrium. In particular, all simulations start with a distribution of TCR clone sizes (i.e., frequency spectrum) drawn from the approximate equilibrium distribution that arises from neutral drift within a population of constant size and a constant rate of influx of new TCRs from the thymus. Consider: each TCR clone enters the population with a clone size of s . Over time, the number of cells having this particular TCR will drift up and down in a diffusion process similar to that studied in the context of allele frequencies in population genetics (48). We approximate this equilibrium distribution using a geometric distribution with mean equal to s .

Implementation. We simulate trajectories from our stochastic model using an implementation in C called from the R statistical environment (49) (C source code available upon request). To generate simulated trajectories in a reasonable amount of computer time, we follow the model in intervals of dynamically chosen time-steps. Specifically, we pick the size of the time step to correspond to a 10% chance that any particular cell will divide or die. Though this step size hides some fine-scale variance, it still captures the key dynamics of the TCR repertoire.

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