Challenging the assumption of exponential decay. A review on the life expectancy of T-cells.

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Abstract

Mathematical models are a common tool used to describe and understand the kinetics of immune cells. However, these models often make certain assumptions in order to describe a simplified view of reality. In this review we take a closer look at the assumption of exponential cell loss. Exponential cell loss assumes that the loss rate of a cell is defined by a single, fixed, parameter. However, this results in a random, fixed, chance for a cell to die irrespective of its life history. In this review we aim to challenge this assumption, and give an overview of how T-cell loss rates have been observed to dynamically change throughout a cell's lifespan. Additionally, we will discuss several model implementations that avoid the assumption of exponential cell loss, and show how these models use mechanisms of individual cell based adaptation or population based selection to give a better description of T-cell kinetics.

Plain language summary

Mathematical models, such as ordinary differential equations, are a common tool used to describe and understand the birth and death rates of immune cells. However, these models often make certain assumptions in order to describe a simplified view of reality. In this review we take a closer look at the assumption of exponential cell loss. Exponential cell loss means that the death rate of a cell is defined as a single value that is fixed throughout the entire lifespan of a cell. However, this results in a situation where newborn, mature, and elderly cells all have exactly the same random chance to die at any given moment. This assumption feels unintuitive as we would expect that older cells die at a different rate compared to newly produced cells. In this review we aim to challenge this assumption of exponential cell loss, and give an overview of how T-cell loss rates have been observed to dynamically change throughout a cell's lifespan. Additionally, we will discuss several possible model implementations that do not assume an exponential cell loss. These models show us that a form of non-exponential cell loss is required to properly describe experimental data. However, it remains unclear which model implementation is the best choice to use. Models of individual cell based adaptation describe cells that are able to adapt and dynamically decrease their death rate as they age. Alternatively, models of population based selection describe a situation where there is a natural variation of cell lifespans within a population, and over time the cells with a long lifespan remain while the short lifespan cells die out. Over time, both of these mechanisms result in an accumulation of old, long lived cells. However, the end goal is reached through different means. The mechanisms of adaptation and selection can help us to better understand the behaviour of immune cells, and give us a better description of their dynamics.

Introduction

In the field of immunology, mathematical models are commonly used as a tool to describe and understand the kinetics of immune cells. Models often make certain assumptions in order to describe a simplified view of reality. An interesting assumption that is commonly made is that of exponential cell loss. Exponential cell loss assumes that the loss rate of a cell is defined by a single parameter value that is fixed throughout the entire lifetime of a cell (Figure 1, blue line). This implies that newborn, mature, and elderly cells within a population all have exactly the same chance to die at any given moment. This implementation of cell loss feels unintuitive and overly simplified. It describes a situation where cells are randomly chosen to die without any regard for their life history. This review aims to challenge the assumption of exponential cell loss, and give an overview of how T-cell loss rates have been observed to dynamically change according to cell- and host age. Additionally, we will discuss several model implementations that do not assume exponential cell loss, and how these models can be used to give a better representation of T-cell kinetics.

Cell labeling methods using deuterium or BrdU are often used to measure the kinetics of cell populations by measuring the rate of label uptake, or the decay rate of the fraction of labeled cells over time. In these cases, mathematical models can be fitted to experimental data to get a quantitative description of the cell kinetics. Despite their unintuitive behavior, models that assume exponential cell loss are often used, likely due to their simplicity, and are able to give an acceptable fit to experimental data [ref 1-5] (Figure 2). At the stages of label uptake, and the early stage of down labeling, these models are able to give a good fit to the data. However, in the later stages of down labeling, it can be seen that these models assuming exponential decay tend to undershoot the later data points (Figure 2). This could be due to the assumption of exponential decay being incorrect, and that there is some form of kinetic heterogeneity in the death rates of T-cells within a population. As a result of this heterogeneity the population will be enriched with long lived cells over time. Given this new assumption, the question still remains which form of kinetic heterogeneity is the correct choice to use. There are two main perspectives that will be discussed here: individual cell based adaptation, and population based selection. With cell based adaptation we refer to a situation where individual cells change their loss rate throughout their lifetime, and as a result dynamically alter their lifespan over time. This leads to a heterogeneous population where the loss rate of each individual cell is dynamically determined by its life history. Alternatively, with population based heterogeneity we refer to a heterogenous population where each cell has their own, fixed, loss rate which is determined at birth, and pulled from a given distribution. Such population based models are able to describe the heterogeneity of an entire population, while still assuming exponential decay for each individual cell. Both of these perspectives will be discussed in the light of experimental observations, and implementations of mathematical models.

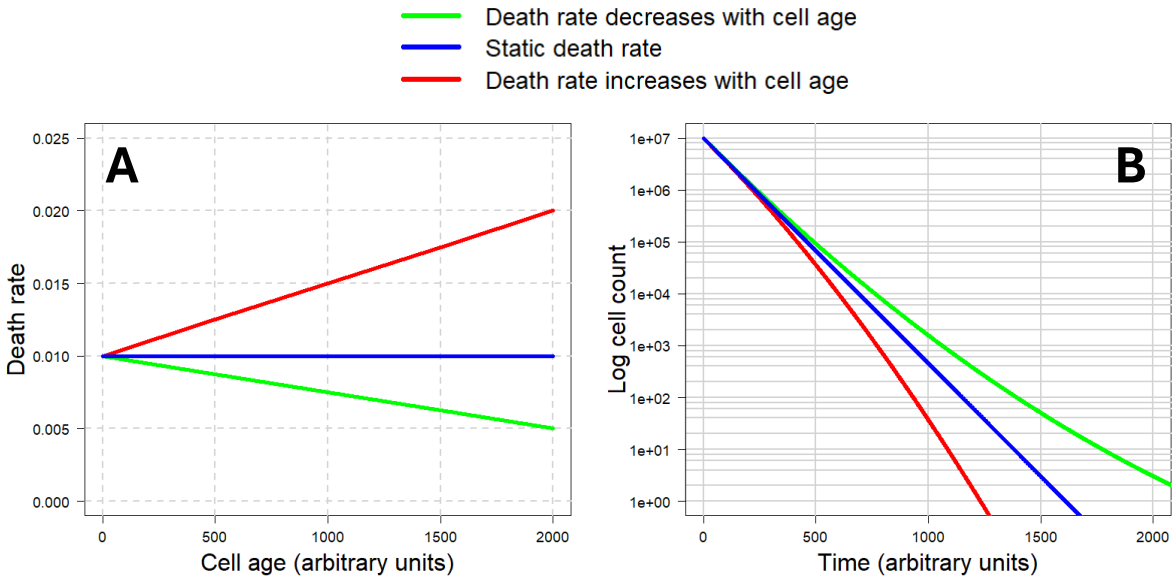

Figure 1.

A toy example showing the behaviour of exponential and non-exponetial cell loss in a decaying cell population. Cell dynamics are described as $\frac{dN}{dt} = -\delta(t)N$ where the entire cell population starts out at age zero and death rate $\delta(t)$ changes linearly with cell age. For simplicity we assume no self-renewal of cells. A) An overview of three possible death rate developments: death rate linearly decreases with cell age (green line), death rate is fixed and does not change throughout a cell's lifespan (blue line; exponential decay), death rate linearly increases with cell age (red line). B) Log cell counts of simulated decaying cell populations with death rates either decreasing (green line), remaining fixed (blue line), or increasing (red line) with age.

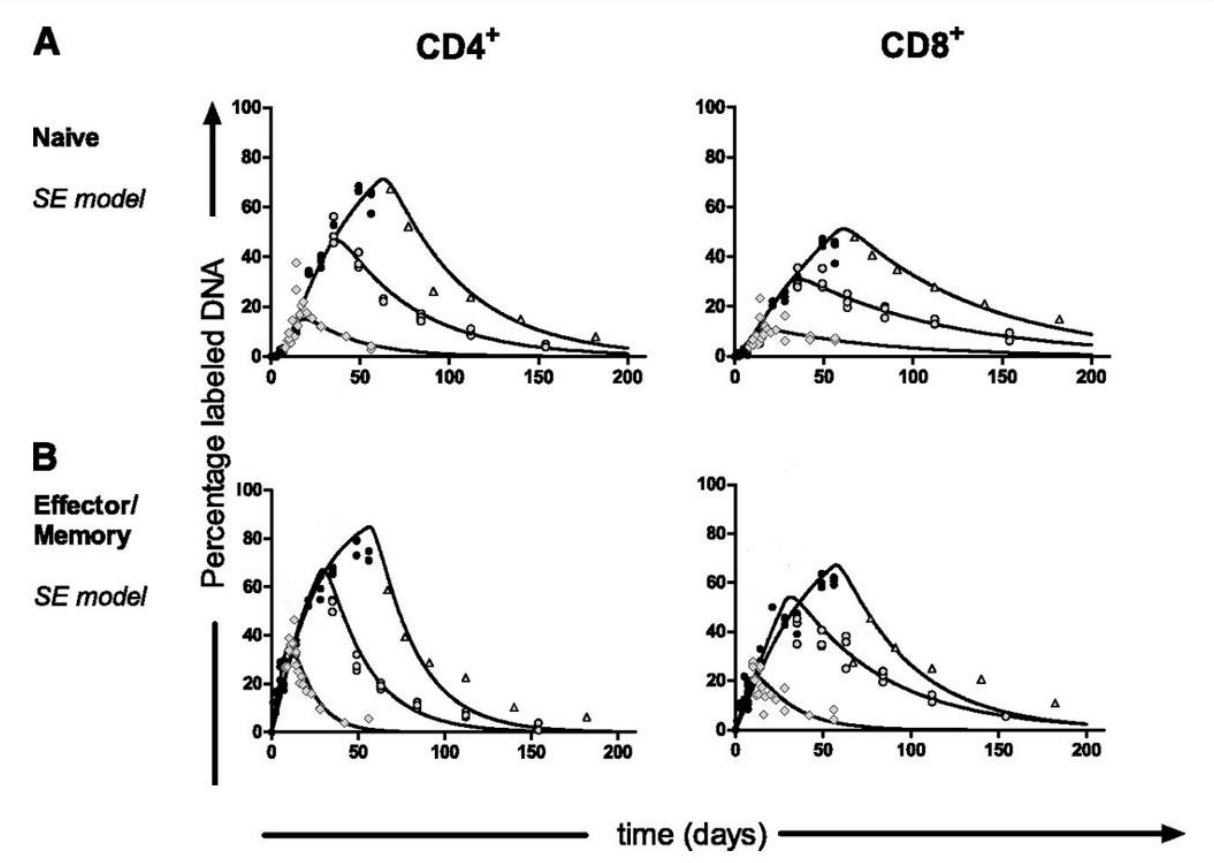

Figure 2.
Best fits of an exponential decay model to labeling experiments of different durations. At different time points during and after labeling, the percentage of labeled DNA of splenic (A) naïve and (B) effector/memory (E/M) CD4+ and CD8+ T-cells was determined. Dots represent measurements (i.e., individual mice) at different time points during labeling for 1, 4, and 8 weeks (overlaying curves). Data were fitted separately for each labeling period using a single-exponential (SE) model to estimate labeled cell kinetics for the corresponding labeling period. Figure and text edited from Westera *et al*. [ref 1].

Experimental observations

Studies of T-cell kinetics are of great interest for understanding the complex interactions of our immune system. The current central idea is that peripheral naïve T-cells rarely divide, and that populations are mostly renewed by new cells migrating from the thymus. This produces a situation where naïve T-cells regularly decay as they are replaced by new cells migrating from the thymus. However, studies indicate that the lifespan of naïve T-cells can develop as cells age, which causes an accumulation of long lived cells over time.

There are reports from multiple research groups showing that the dynamics of naïve CD4 and CD8 T-cells in adult mice and humans depend on cell age [ref 6-11]. These studies use a variety of labeling methods, including busulfan treated chimeras [ref 6-8], tamoxifen timestamp labeling [ref 9], measuring the natural abundance of nuclear bomb test–derived ^{14}C in genomic DNA [ref 10], or carboxyfluorescein diacetate succinimidyl ester (CFSE) labeling [ref 11]. All studies seem to agree with the idea that naïve T-cell survival is related to cell age, and that the net loss rate of cells gradually decreases with cell age.

A system of chimeric mice treated with busulfan can be used to measure the kinetics of naïve T-cells across the host mouse lifespan [ref 6-8]. This method consists of first partially depleting the hematopoietic stem cells in the bone marrow followed by a transplantation of T- and B-cell depleted bone marrow from a labelled congenic donor mouse. As a result, a chimerism is established for progenitor cells in the bone marrow and thymus which is maintained for the lifetime of the mouse (Figure 3) (methods detailed in [ref 12]). These studies find that the older host cell population is not completely replaced by the new donor cells. Thus indicating that there is a subpopulation of long lived self-renewing cells. This could imply that there are cell age related effects on either the cell mortality or self-renewal rate which leads to the persistence of older cells. Additional measurements of Ki67 expression show that naïve CD4 and CD8 T-cells divide very rarely. Observations show that over 60% of naïve T-cells express Ki67 early in their life. However, this declines to 2-3% at an age of 3 months [ref 6]. These results indicate that the persistence of old cells can be attributed to a decreased mortality instead of an increase in self-renewal.

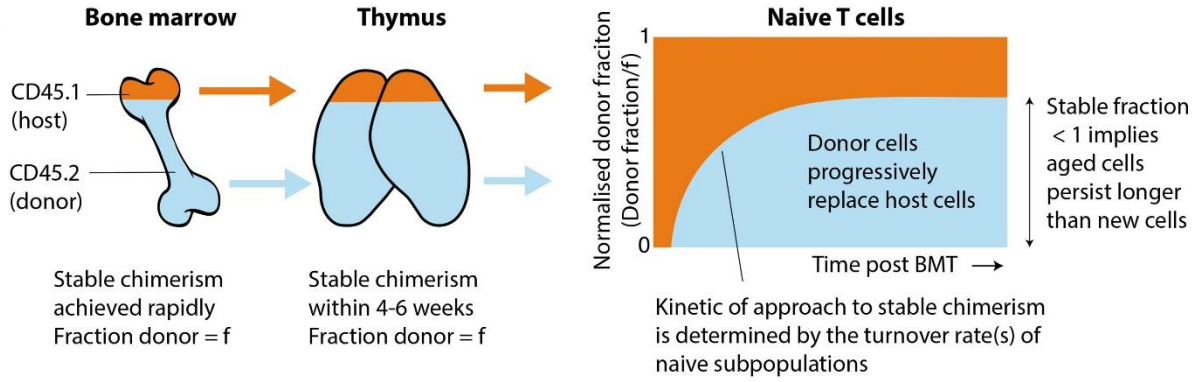

Figure 3
Schematic description of a busulfan treated chimera system, in which congenically labelled donor lymphocytes percolate into peripheral compartments following partial ablation of hematopoietic stem cells and bone marrow transplant (BMT). Figure and text taken from Rane *et al.* [ref 6].

This conclusion is supported by the findings of Reynaldi *et al.* [ref 9] who use a tamoxifen timestamping method to permanently stain newly produced naïve CD8 T-cells at different timepoints of host mouse age. Using this method it is possible to measure the decay of labeled cells while having an exact knowledge of their cell age (time since they left the thymus). As a result, it becomes possible to observe possible cell age related effects on cell decay. It is reported that not only cell age, but also host age, influences the decay rate of naïve CD8 T-cells. It can be seen that the decay of labeled cells does not follow the shape of exponential decay (Figure 4A). Instead, observations indicate that the loss rate of cells gradually decreases with time. Additionally, cells produced on the first day of life (host age) are rapidly lost while cells produced later in life have a slower initial rate of decay. However, in both cases the loss rate of cells can be seen to further slow down as cell age increases (Figure 4).

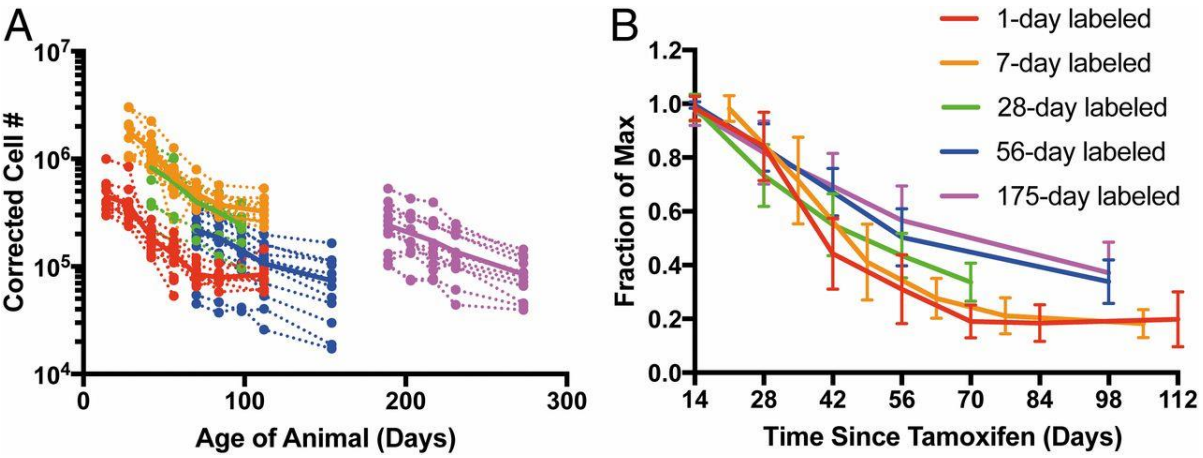

Figure 4.
Dynamics of timestamped CD8+ T-cells with age. (A) Corrected cell numbers of stamped CD8+ T-cells based on the percentage of labeled cells in blood. Dashed lines depict trajectories of individual animals (n = 12–17 per group), while the solid lines represent the arithmetic mean trajectory for each age group. (B) Survival of CD8+ T-cells based on time since production. The fraction of the maximum labeled CD8+ T-cells that persist at different times after tamoxifen administration (error bars represent SD from each group). The rate of decay of labeled CD8+ T-cells is not constant with age but rather it is decreasing with the age at stamping. Figure and text taken from Reynaldi *et al.* [ref 9].

The importance of cell age on cell survival is further supported by a study measuring the lifespans of naïve CD4 T-cells of young and aged mice [ref 11]. Here, naïve CD4 T-cells are isolated from young and aged mice. Afterwards, both populations are combined in equal ratios and transferred into a young host. A rapid loss of young cells is observed while aged cells show a slower rate of cell loss. The absolute number of aged donor cells 15 days post transplantation was 3-fold higher compared to the younger cells while both young and aged cells displayed no significant division. Thus, showing clear indications of a cell age related decrease in loss rate which is consistent with other experimental studies [ref 13]. Additionally, similar cell age related dynamics are also found in antigen-specific CD4 populations [ref 14]. Here, a busulfan treated chimera system is combined with BrdU labeling to measure the dynamics and longevity of circulating CD4 memory T-cells. It is reported that proliferative activity of CD4 T_{CM} and T_{EM} cells declines with cell age, while also showing that these cells become more persistent with increasing cell age. Thus further implying a cell age related decrease in loss rate. These findings for CD4 memory T-cells could suggest that a decreasing loss rate related to cell age is not limited to naïve cells, but instead is an intrinsic property of all T-cell types. All these results seem to point to the conclusion that the dynamics of (naïve) T-cells in mice are dependent on cell age with a decrease in cell loss as cell age increases. However, we still are unable to decisively conclude that T-cells display the same behaviour in human hosts.

Unconclusive results in human studies

While the previously discussed studies show promising results in mice, the results are less convincing in human studies. Nevertheless, there are some similar observations reported from human systems. Mold *et al.* [ref 10] were able to determine the dynamics of naïve CD4 and CD8 T-cells in healthy human adults using measurements of nuclear bomb test–derived ^{14}C in genomic DNA. Similar to mouse studies, they observed that turnover rates for CD4 and CD8 naïve T-cells decreased relative to donor age. However, contrary to mouse models, cell DNA age determinations indicate that the entire naïve T-cell pool undergoes constant turnover in healthy human adults. This is in stark contrast to the rarely dividing naïve T-cells reported from mouse studies [ref 15]. This discrepancy between human and mouse models complicates the hypothesis of a cell age related decline of loss rate. The presence of constant naïve T-cell turnover means that it can't be ruled out that long lived cells in humans persist due to a high rate of self-renewal instead of a low mortality rate. Furthermore, the findings of this study are challenged by another study tracking naïve T-cell turnover in elderly humans between 65 and 75 years of age [ref 16]. Here there were no reported age-related changes in turnover rate between elderly (65-75 years) and younger (20-25 years) donors. Thus contradicting the narrative that cell age related effects cause an accumulation of long lived cells with a slow turnover rate.

Model implementations

It is reported that the replacement kinetics from busulfan treated chimera experiments cannot be explained by models of homogeneous turnover [ref 8]. Additionally, results find that there is a kinetic heterogeneity in the populations of T-cells [ref 1,8,17]. This makes clear that some form of kinetic heterogeneity is needed to properly model T-cell populations. However, the question then remains whether this heterogeneity is caused by adaptive or selective forces. In the following section we will be discussing a few model implementations that have been used as an explanation for the observation of long lived cells accumulating over time. Here we will differentiate between cell based adaptation models, where individual cells experience a changing loss rate throughout their lifespan, and population based selection models, where the

heterogeneity of loss rates is caused due to an intrinsic variation of fixed loss rates throughout the population.

Adaptation models

In models of adaptation we assume that cell dynamics are not fixed at birth, but instead are dynamic and proportional to cell age. An example of such a model is given by Rane *et al.* [ref 6] where naïve T-cell dynamics are modeled to be continuous and directly proportional to cell age (Figure 5).

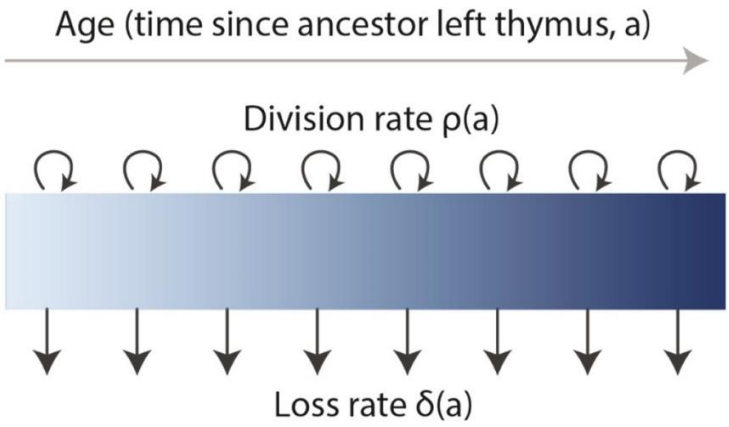

Figure 5.

Model of naïve T-cell dynamics. Loss or division rates vary with post-thymic cell age, a. Here we explicitly model the time-evolution of the population density of cells of post-thymic age a at mouse age t, N(a,t). Figure and text edited from Rane *et al.* [ref 6].

In this model, the loss or division rates of a cell continuously change with respect to its post-thymic age a. The expected population density $N(a,t)$ can be described by the following PDE:

$$\frac{\partial N(a,t)}{\partial a} + \frac{\partial N(a,t)}{\partial t} = -\lambda(a)N(a,t)$$

Where $\lambda(a)$ is the net loss rate dependent on the post-thymic age a, and the rate of thymic output $\theta(t)$ defines the production rate of cells with age zero, $N(0,t) = \theta(t)$. The total population size at host age t is given by the following equation where we integrate over all allowable cell ages. See [ref 7,8] for further technical details.

$$N(t) = \int N(a,t)da$$

A similar model is presented by Reynaldi *et al.* [ref 9] trying to describe the decay rate of naïve CD8 T-cells after labeling with tamoxifen. Here the decay rate of cells is modeled to be dependent on both cell age as well as host age. A system is described where new cells leaving the thymus are labeled at different moments of host age t. The population size of labeled cells $L(a)$ at time a after labeling is given by:

$$L(a) = L_0 e^{-(k(t)e^{-\delta a})a}$$

Where:

$$k(t) = k_b e^{-st}$$

Here, a denotes both the time after labeling, and the time since production of a cell in the thymus (cell age) as these processes happen at the same time. t denotes the host age at the time that a cell is produced in the thymus, and L_0 is the number of labeled cells at the start of the delabeling period $L(0) = L_0$. Each cell has an initial decay rate $k(t)$ based on the host age t at the moment that a cell was produced in the thymus. The initial decay rate $k(t)$ decreases for cells produced at an older host age t. This decrease happens at rate s from a baseline value of k_b. Additionally, an individual cell's initial decay rate further slows down at rate δ dependent on its cell age a. As a result, all cells decrease their decay rate as their cell age increases, and cells produced later in life start out at a lower initial decay rate.

Zarnitsyna *et al.* [ref 18] describe their findings following the CD8 T-cell responses to a yellow fever vaccine (YFV). A model is used to fit the frequency of YFV-specific CD8 T-cells over time after vaccination. The model uses a time dependent division $\alpha(t)$ and death rate $\delta(t)$ which are both in the form of

$$r(t) = r_1 + \frac{r_2}{t}$$

With r representing either α or δ for the division or death rate respectively. Interestingly, they report that the resulting decline in T-cell numbers in the fitted model exactly follows a power law function. Following that their best model fit gives $\alpha_1 = \delta_1$, which means that $\alpha(t) - \delta(t) = \frac{\alpha_2 - \delta_2}{t} = \frac{\lambda}{t}$, the frequency of YFV-specific cells f_N is described by the following ODE:

$$\frac{df_N}{dt} = \big(\alpha(t) - \delta(t)\big)N = \frac{\lambda}{t}N$$

Which can be solved to:

$$f_N(t) = t^{\lambda}$$

Which shows that the decay of YFV-specific CD8 T-cells can be described by a simple power law model.

A more explicit model is used by Johnson *et al.* [ref 19] to explain the reduced diversity of naïve CD4 T-cells in elderly humans. Here they use an agent based model in which naïve T-cells build up fitness with age through the accumulation of random mutations. The model uses parameters similar to what has been discussed for other models: New cells are supplied through thymic emigration $v(t)$, existing cells undergo division at rate λ, and cells are lost at rate δ. Additionally, there is a chance for random mutations to happen during division at rate μ per cell per division. The proliferation λ and death rate δ start out fixed in the population. However, random mutations are able to affect the division rate λ. As a result, high fitness mutants are selected over time that have a lower net loss rate as their division rate λ increased through random mutations while their death rate δ remained fixed. While this model does not directly address the assumption of exponential decay, it does provide another adaptive mechanism to explain the accumulation of high fitness cells over time. Additionally, one could imagine an alteration to the model where the death rate δ is also able to mutate upon cell division. Resulting in a decreased death rate over time.

Selection models

An alternative to the idea of cell based adaptation would be models of selection, in which each cell's survival capacity (loss rate) is determined during thymic development, drawn from a distribution, and subsequently fixed for its entire lifespan (seen in [ref 7,20-23]). Such a model would still assume exponential loss for each individual cell. However, due to the natural selection of intrinsically long lived cells, the average loss rate of the entire population would dynamically change over time. This gradual change in the loss rate at the population level could allow a selection based model to fit experimental data in a similar way to an adaptation based model.

An example of a simple selection model is given by Rane *et al.* [ref 7]. A natural variation in fitness is added to the source term of the population. It is assumed that each cell leaving the thymus draws their fitness value from a log-normal distribution $f_\theta(\lambda)$. This fitness is fixed for the lifespan of the cell, and is passed on to its daughter cells during division.

$$\frac{dN(\lambda, t)}{dt} = \theta(t) f_\theta(\lambda) - \lambda N(\lambda, t)$$

Here the cell population $N(\lambda, t)$ is supplied by a time-dependent thymic output $\theta(t)$, and cells are lost at a net loss rate λ (fitness) which is drawn from a log-normal distribution $f_\theta(\lambda)$ when cells leave the thymus. As a result of the natural fitness variation, cells with higher fitness (lower net loss rate λ) will accumulate in the population over time. This accumulation of high fitness cells over time is similar to what happens in the previously discussed adaptation models. However, the end state is reached through a different mechanism.

Explicit subpopulations

Another form of selection models are those where a select number of subpopulations are explicitly modelled such that there are distinct groups of cells each having their own defined cellular dynamics. These subpopulation models could be further divided into two main groups: Branched heterogeneity and linear heterogeneity (Figure 6).

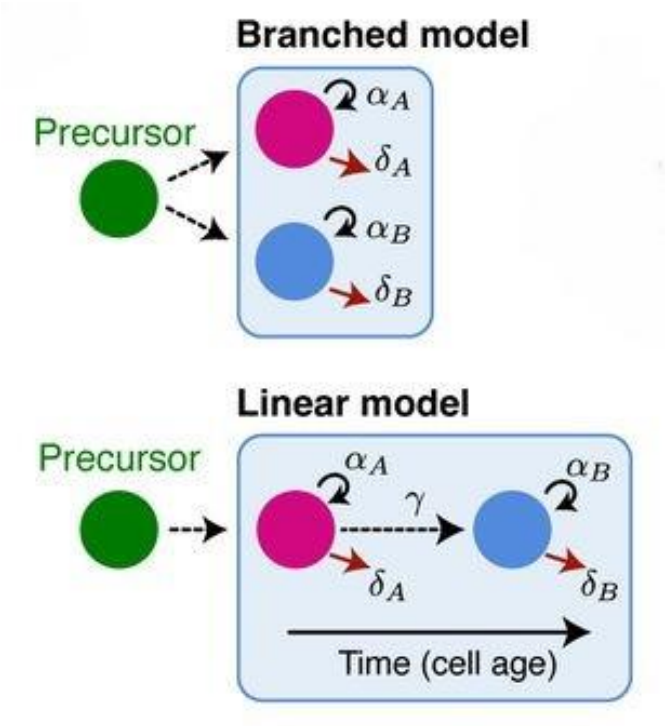

Figure 6.
Models of explicit kinetic heterogeneity within a cell population. Subpopulations A and B are explicitly modeled to have distinct parameters for their proliferation rate (α), death rate (δ), and maturation rate (γ). Figure taken from Bullock *et al.* [ref 14].

In models of branched heterogeneity, a precursor cell can branch into multiple subpopulations with distinct cellular dynamics. Implementations of such models can be found in [ref 1,6,8,14,21]. A simple model with 2 subpopulations A and B could be modeled using the following ODEs:

$$\frac{dA}{dt} = \theta_A + \alpha_A A - \delta_A A$$

$$\frac{dB}{dt} = \theta_B + \alpha_B B - \delta_B B$$

Where new cells are supplied through thymic output θ, cells divide at rate α, and die at rate δ. If the two subpopulations are defined as a population with either fast or slow turnover, it can be expected that over time selection forces will cause an enrichment of long lived cells in the total population.

A variation of branched heterogeneity uses a model of incumbent cells. Here, a subset of high fitness, self-renewing cells is created early in life, followed by lower fitness cells that are replaced by thymus emigrants (seen in [ref 7,8]). Once the production of early, high fitness cells has stopped, the system can be described as follows:

$$\frac{dA}{dt} = \alpha_A A - \delta_A A \qquad (early, high\ fitness\ cells)$$

$$\frac{dB}{dt} = \theta - \delta_B B \qquad (later, low\ fitness\ cells)$$

Here the thymic output θ only supplies new cells to the low fitness population while the high fitness population is kept alive through self-renewal with division rate α. Both populations lose cells at rate δ. In this scenario, a subset of long lived, self-renewing cells is able to persist from production early in life all the way throughout later life stages.

A different way to implement multiple subpopulations is to use a linear system where cells from group A mature into group B over time (Figure 6)(seen in [ref 6,14,24,25]). An example of how such linear heterogeneity could take shape is a model where recent thymic emigrants (A) and mature naïve cells (B) have distinct cellular dynamics. A simple model of this nature can be described using the following ODEs:

$$\frac{dA}{dt} = \theta + \alpha_A A - \gamma A - \delta_A A$$

$$\frac{dB}{dt} = \gamma A + \alpha_B B - \delta_B B$$

Recent thymic emigrants A are supplied through thymic output θ, and mature into mature naïve cells B at rate γ. Both groups divide at rate α, and die at rate δ. Such a model is fundamentally comparable to a model of adaptation. However, instead of a continuous aging process, the population is divided into a number of discrete age groups. As the number of explicit age groups increases towards infinity, and δ keeps decreasing with age, it can be seen that this model approaches the dynamics of an adaptation model where the loss rate is directly proportional to time.

Discussion

In this review we have described experimental observations that challenge the assumption of exponential cell loss. There are clear indications that T-cell life expectancy is dynamic and that mortality decreases with increased cell age. However, it is hard to definitively say that these effects are a direct result of individual cell based adaptation. Most experimental studies follow a labeled cell population and observe that over time the average rate of cell loss decreases. This could be explained by the adaptation of older cells decreasing their loss rate. However, another plausible explanation could be that each population has a natural variation in loss rates, and a subset of intrinsically long lived cells naturally accumulates over time. It is very difficult to differentiate between these mechanisms of adaptation and selection when only using experimental data that measures an entire population.

Reynaldi *et al.* [ref 9] try to resolve this problem by permanently staining newly produced naïve T-cells and following them throughout their lifespan. This method seems promising at first as they are able to know the exact age of their marked cells, and results show a clear increase of survival over time (Figure 4). Additionally, this method shows very convincing results that cell survival is related to host age. It can be seen that cells produced at an older host age decay slower than cells produced earlier in life. However, ultimately this method still measures the dynamics of an entire labeled population. The possibility still remains that the labeled population consist of cells with a static intrinsic loss rate following a certain distribution of life expectancies that get filtered out through natural selection. In order to definitively conclude the presence of cell age related adaptation, measurements would have to be made on a single-cell level. However, such an experiment is likely not yet feasible to perform.

While studies do show interesting results regarding the connection between cell age and cell mortality, it is important to note that most of these studies base their findings on experimental data taken from mice. Experimental results from mice are not always directly translatable to human systems. For example, if T-cells increase their survival capacity as they age, it would be expected that older hosts have T-cell populations that are enriched for long lived cells. However, a study tracking naïve T-cell turnover in human donors between 65 and 75 years of age reported no age-related changes in turnover relative to younger donors [ref 16]. Thus, it is important to keep in mind the differences between mice and human kinetics, and it would be beneficial to reproduce similar experiments in a human cohort where possible.

We can turn to mathematical models to further strengthen the hypothesis of either adaptation or selection based mechanisms. Results from busulfan treated chimera systems make clear that the observed replacement kinetics cannot be explained using models of homogeneous turnover [ref 8]. However, it is not clear which implementation of kinetic heterogeneity is the correct choice. Most studies seem to be in favor of age-dependent loss models. However, there are also reports of other models outperforming or competing with these adaptation models. A density dependent model is reported to best fit T-cell data from healthy and thymectomised mice, with adaptation models producing a visually similar fit [ref 7]. Additionally, there is a report from Hogan *et al.* [ref 8] where an age-dependent model produces worse fits and has significantly less statistical support compared to a model describing the persistence of incumbent cells created early in life. Ultimately, it is likely that the effects of age-related adaptation and selection are not mutually exclusive and that both processes play a role in the observed dynamic life expectancy of T-cells.

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