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Building a T cell compartment: how immune cell development shapes function

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Abstract

We are just beginning to understand the diversity of the peripheral T cell compartment, which arises from the specialization of different T cell subsets and the plasticity of individual naive T cells to adopt different fates. Although the progeny of a single T cell can differentiate into many phenotypes following infection, individual T cells are biased towards particular phenotypes. These biases are typically ascribed to random factors that occur during and after antigenic stimulation. However, the T cell compartment does not remain static with age, and shifting immune challenges during ontogeny give rise to T cells with distinct functional properties. Here, we argue that the developmental history of naive T cells creates a ‘hidden layer’ of diversity that persists into adulthood. Insight into this diversity can provide a new perspective on immunity and immunotherapy across the lifespan.

While much is known about T cell development on the individual cell level, we still lack critical information about how the T cell compartment is ‘put together’ as a whole. In general, it is thought that T cells are generated in the thymus, and a steady stream of T cells are exported to the periphery until the compartment is ‘full’[1,2]. Most of the variation in the peripheral T cell compartment is characterized on the basis of the antigenic experience of the cell. When a naive T cell encounters an antigen and undergoes progressive differentiation, it expresses a different set of surface markers, which can be used to distinguish naive T cells from effector and memory T cells[3,4]. Over the years, additional markers have been added to this classification scheme to identify new subsets of effector T cells (short-lived effector cells and memory precursor effector cells) and memory T cells (central memory cells, effector memory cells, long-lived effector cells and tissue-resident memory cells) on the

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basis of their distinct location and functional properties[5–9]. By contrast, naive T cells are often classified as a single subset of cells ($CD44^{low}CD62L^{hi}$ cells in mice and $CD45RA^{hi}CD45RO^{low}CCR7^{hi}$ cells in humans)[10]. As a result, the naive T cell compartment is typically viewed as a homogenous pool of cells.

Previous work has also viewed naive T cells as having equal potential to become effector or memory T cells, their fates determined by stochastic events in the host environment following microbial infection[11,12]. For example, individual T cell precursors from OT-I mice, which express an identical T cell receptor (TCR), display a wide range of effector phenotypes and clonal burst sizes after infection[12]. On the basis of these findings and other work, it has been proposed that the short-term and long-term fates of naive T cells are simply explained by the amount and type of stimulation they received during infection, which bias processes such as asymmetric cell division and differentiation[13–17]. Recent data, however, indicate that the differentiation trajectory of naive T cells is also influenced by when they were initially created in the host[18–21]. Naive T cells that are identical in every way except their developmental origin or age adopt different fates during infection, even when stimulated with equal amounts of an antigen and inflammation[22–25]. These studies suggest that not all naive T cells are created equal.

The link between T cell function and developmental origin has largely been confined to the field of neonatal immunity, where it has served as a useful explanation for why neonatal T cells behave differently to their adult counterparts. By contrast, studies of adult immune responses have generally not considered the developmental origins of cells, as this variable has not been considered relevant to immune responsiveness in adulthood. However, new studies in mice have shown that neonatal T cells persist into adulthood and retain their cell-intrinsic properties[26,27], indicating that the schism between the study of adult and neonatal responses needs to be overcome and that it is important to consider the developmental history of cells in the starting population.

These new studies have prompted us to reconsider our understanding of the structure and function of the naive T cell compartment. Instead of a continuous ‘stream’ of homogeneous cells, the naive T cell compartment appears to be built from a shifting palette of T cells that are produced at defined ages and periods of development[27,28]. These cells persist, leading to a highly dynamic and heterogeneous pool of cells with different functional properties[26,29,30]. However, a more comprehensive picture of T cell ontogeny is required to fully understand the diversity of T cell responses at different stages of life.

In this Perspective, we discuss how the production and function of naive T cells adapt to meet the challenges of a changing external environment during development. We explore how the phenotype of naive T cells changes at different ages and how alterations to the formation of the naive T cell compartment might contribute to individual immune variation across the lifespan. Although we largely focus on mechanistic studies in mice, the same developmental processes exist in humans and provide an exciting opportunity for future translational research.

Immune challenges in development

T cells produced at various stages of development are faced with different immune environments and challenges (FIG. 1). During fetal life, T cells emerge into a relatively sterile environment, in which they must maintain tolerance to maternal alloantigens. Given that the fetus expresses MHC molecules inherited from both parents, a primary goal of fetal T cells is to learn how to exist in a semiallogeneic host[31]. Fetal T cells must also become tolerant of other harmless antigens, such as food antigens that are transferred across the placenta[32,33]. Thus, in utero, there is less of a need for T cells to protect the host against harmful pathogens and more of a demand to maintain tolerance to harmless antigens.

Following birth, the fetus transitions from the more sterile environment of the uterus to the foreign antigen-rich environment of the outside world. During this time, the major goal of neonatal T cells is to learn the complicated task of tolerating commensal organisms, while also offering immune defence against dangerous microorganisms. Making matters more complicated, the total number of T cells is small, and effective T cell diversity is likely smaller still owing to increased homeostatic proliferation of more TCR-restricted neonatal clonotypes[34–39]. The neonatal T cell pool lacks immunological memory[40], placing further constraints on its ability to protect the host against the multitude of pathogens encountered in early life.

With advancing age, the major goal of T cells shifts to mounting appropriate responses against novel infections and protecting the host against reinfection with common pathogens. This goal becomes even more important in adulthood, as the production of new T cells wanes with the involution of the thymus[41–43]. As a consequence, existing T cells in the periphery must maintain their diversity to be capable of responding to any novel pathogens encountered in old age[44]. At the same time, adult T cells must contain high-avidity TCRs that can both respond to specific pathogens and limit autoreactive responses against self-antigens.

From fetal life to adulthood, the changing ecological landscape presents an evolving challenge for a properly functioning T cell compartment. An important question is how does the host mediate changes within the peripheral T cell compartment to adapt?

Immune solutions

In this section, we propose that a number of different programmes of T cell production and maintenance are conserved in mice and humans, which enable T cells to meet the rapidly changing demands of their environment (FIG. 1). These developmentally related solutions to environmental challenges are important drivers of functional heterogeneity in the naive T cell compartment.

Layered immune development.

One solution to the problem of needing T cells with different functions at various stages of development is to derive them from separate progenitors. During immune ontogeny, the thymus is first colonized by fetal haematopoietic stem cells (HSCs) and later by adult

HSCs[33,45–48]. Fetal HSCs give rise to fetal T cells that are biased towards becoming regulatory T (T_{reg}) cells after stimulation with allogeneic cells, which help to promote tolerance in utero[20,49]. Fetal progenitors continue to give rise to T cells in neonatal life, which exhibit distinct epigenomic profiles[50] and have an enhanced capacity to proliferate and differentiate during infection[21,23–25,51,52], potentially compensating for the less diverse naive T cell pool and absence of memory cells in early life. By contrast, adult-derived T cells respond to infection with slower kinetics, but they exhibit an enhanced capacity to form memory T cells, which protect the organism against reinfections[21,23–25,52]. The progressive transition from fetal-origin to adult-origin HSCs during early life leads to a spectrum of cell types that are poised to differentiate into cell types (effector or memory) most useful to the host at different stages of life[27].

TCR repertoire diversity.

Another way to alter T cell function at various stages of life is to change antigen recognition patterns. In early life, this is largely accomplished by delaying the expression of terminal deoxynucleotidyltransferase (TdT; the enzyme responsible for insertion of random nucleotide additions)[53,54]. As a result, the TCR repertoire in neonatal mice is less diverse and comprises more germline-encoded clonotypes[36,37,55,56]. It was initially assumed that restricting TCR repertoire diversity in early life limits pathogenic T cell responses during critical stages of growth and development. However, evidence suggests that even the more limited TCR repertoire in the developing fetus is diverse enough to recognize foreign pathogens[57]. Moreover, germline-encoded TCRs are more cross-reactive[58], providing a mechanism to maximize immune recognition by the small number of cells present in early life. While the delay in TdT expression leads to increased cross-reactivity, it may come at the cost of reduced TCR avidity[36,59]. Once TdT is active, T cells made later in life show both high avidity and specificity and thus are ideal for forming pathogen-specific memory responses.

Post-thymic maturation.

In addition to the ontogenic changes in T cell production, another solution for the rapidly changing immunological demands is to have T cell function evolve over the lifespan of the individual cell. Indeed, it is well established that $CD4^+$ and $CD8^+$ T cells express different markers and display different functions at various times after thymic egress[60]. Functional changes that occur during the post-thymic maturation period align well with the needs of the host during early stages of development. For example, the newly minted naive T cells (denoted ‘recent thymic emigrants’ (RTEs)) (BOX 1), which are most abundant in early life, have an enhanced capacity to migrate to peripheral organs and are more readily tolerized in the absence of inflammation[61–63].

Antigen versus inflammation sensitivity.

A major challenge for neonatal cells in early life is differentiating between commensal and pathogenic organisms after birth. That is, there is no easy way for the TCR to differentiate between healthy microbiota-derived peptides and potential pathogen-derived peptides on the basis of peptides alone. Only the ‘danger’ signals associated with pathogens allow any discrimination by the TCR. Thus, it is adaptive for neonatal cells to be more ‘inflammation

responsive'[27,63–69]. For example, human $CD8^+$ T cells in umbilical cord blood preferentially express Toll-like receptor 2 (TLR2) and TLR5, and human neonatal $CD4^+$ T cells are equipped to respond to TLR1 and TLR2 ligands[65–67]. In adults, RTEs also exhibit increased expression of innate-like receptors (TLRs, complement receptors and natural killer cell receptors), which may help them to discriminate between harmless and pathogenic microorganisms[63,68,69].

Homeostatic proliferation.

The differentiation trajectory of naive T cells is also influenced by their previous levels of homeostatic proliferation[70–73]. The current dogma is that T cells undergo increased rates of homeostatic proliferation in early life because they are exported to peripheral environments that are devoid of other T cells and, therefore, exposed to greater amounts of homeostatic cytokines (IL-7 and IL-15) on a per cell basis[35,74,75]. However, recent data demonstrate that cells made early in life have an inherent propensity to undergo homeostatic proliferation, probably owing to their HSC origin[27]. Naive T cells that have undergone extensive homeostatic proliferation upregulate markers and obtain functions that are typically associated with memory T cells induced by a foreign antigen[71,76,77] (BOX 1). Thus, in addition to rapidly filling the peripheral pool and providing some naive T cells with additional functional properties, homeostatic proliferation may also serve as a useful stop-gap defence mechanism until more true memory cells can be made. In adulthood, homeostatic proliferation may be reduced to maintain repertoire diversity[78].

Structure dictates function

Viewing the naive T cell compartment through the lens of immune development changes our perspective of the T cell response to infection with progressing age. In the past, the focus was on how age alters the cell-intrinsic properties of individual cells. For example, it is generally believed that $CD8^+$ T cells from aged individuals respond less vigorously to infection than younger cells because they have been subjected to years of protein misfolding and oxidative damage[79]. However, different drivers (HSC origin, post-thymic maturation or homeostatic proliferation) sculpt the peripheral T cell compartment during various windows of development, resulting in dramatic changes to the composition of the naive T cell pool at various stages of life. If we zoom out and consider how the distribution of naive T cell subsets varies over time, we can begin to appreciate how age-related changes in the starting population alter the host response to infection. The traditional 'neonatal' and 'adult' phenotypes represent just two snapshots in time across a changing immune landscape. In this section, we take into account the developmental biology of the peripheral T cell compartment and offer a different perspective on the 'neonatal' and 'adult' T cell responses to infection (FIG. 2).

The classical picture of T cell responses to novel pathogens assumes a long delay between the recognition of a peptide by a small number of naive antigen-specific precursors and their subsequent proliferation, differentiation and ability to mount an effector response. In the very young, in which nearly all infections are novel, this slow responsiveness represents a major risk to the individual. This risk is mitigated by the unique composition of T cells

present in early life. First, there is a larger relative number of virtual memory cells in the neonatal pool, which are sensitive to inflammation and can be activated by innate cytokines alone[23,27,64,80]. The ability of (non-antigen-specific) neonatal cells to respond to inflammatory stimuli means a larger proportion of T cells can respond to infection in a 'bystander' manner[81] (but only once the pathogen has caused sufficient tissue damage). Second, the broad cross-reactivity of germline-encoded clonotypes[58] may allow a larger proportion of neonatal T cells to recognize a particular epitope. Although the neonatal precursors may have lower avidity for a cognate antigen, this limitation is potentially overcome by the fact that most neonatal T cells are also RTEs and can therefore receive additional (costimulatory) signalling via TLRs[65–67]. Lastly, the virtual memory cells and RTEs in early life are derived from fetal HSCs, which enable them to divide and differentiate more rapidly than their adult-derived counterparts, and quickly contribute to the response[23,27,82,83]. The major drawback of the neonatal T cell response is the inability to form high-avidity, long-lived memory responses[24,25,36]. Although the bias towards effector cell differentiation in early life is often viewed as a defect, we propose that it is actually a useful adaptation that prioritizes immediate survival over future survival.

However, later in life, there is a shift from fighting infection with novel pathogens to fighting recurring exposure to common pathogens. The composition of the naive T cell pool in adulthood is well adapted to meet these demands. Adult-derived naive T cells are produced from a more diverse pool of TCRs and largely have a mature naive phenotype. Thus, they have the potential to be highly sensitive to an antigen and give rise to memory cells, but they tend to exist at low precursor numbers and exhibit slower proliferation rates[21,23–25,52,82,83]. Fortunately, the transition from neonatal to adult immunity does not involve the complete loss of neonatal cells. Neonatal phenotype cells persist throughout early life even as they are gradually replaced by adult phenotype cells[26]. Newly arrived adult cells also have an RTE phenotype, are sensitive to danger signals and offer some innate-like functions[63,68,69]. Thus, in adolescence, we see the presence of rapid early responses by neonatal virtual memory cells and adult-derived RTEs, followed by the development of mature (adult-derived) effector and memory responses. As the host accumulates a pool of memory cells for common pathogens, we see a shift from inflammation responsiveness to antigen-specific memory, which is accompanied by a decrease in the number of neonatal and RTE phenotype cells[26]. However, even in adult life, we observe that neonatal cells expand early in infection by novel pathogens, before being overtaken by the naive cell-derived adult response[27].

Variations in immune development

As discussed already, we propose that the naive T cell pool evolves over the lifespan of the individual. However, the evolution of the peripheral T cell compartment likely differs among individuals, depending on the unique set of conditions encountered during growth and development[84–86]. In anthropology, this concept is referred to as 'developmental acclimatization', and it has been used to explain how physiological systems adapt to certain conditions in early life[87]. Early life is a critical phase of rapid adaptation of the peripheral T cell compartment to the external environment, and thus stressors acting in this phase can act to alter either the number or the function of cells surviving into adulthood[88] (FIG. 3). As different proportions of neonatal, RTE and virtual memory cells alter how an individual

responds to inflammation and antigens (self, commensal or foreign), factors that affect immune cell production and survival in early life may have long-term effects on the susceptibility to infectious or autoimmune diseases.

One factor that likely alters the layered development of the peripheral T cell compartment is microbial exposure. Indeed, twin studies have shown that persistent infection with cytomegalovirus is a major driver of immune variation in humans[84], and population studies suggest that geographical location can profoundly affect immune development[89]. However, it is important to consider how the timing of exposure could impact the composition of the T cell compartment. Exposure to cytomegalovirus in infancy might lead to an outgrowth of neonatal T cells, while later exposure could favour the expansion of adult T cells[90–92]. Changing the distribution of subsets in the naive T cell compartment could alter an individual's inherent ability to form effector and memory T cells, as well as their response to new infections. Other types of pathogen can also alter the architecture of the peripheral T cell compartment and subsequent responsiveness to future infection. For example, mice exposed to helminths (such as *Heligmosomoides polygyrus*) have a larger population of virtual memory cells and are more resistant to bacterial pathogens[93,94]. Depending on the timing of infection, infection with *H. polygyrus* could lead to an outgrowth of neonatal or adult virtual memory cells and change the inflammatory response during early stages of infection.

It is also interesting to speculate how reductions in the overall number of infections affect immune development at the population level[95,96]. For example, the 'hygiene hypothesis' suggests that growing up in the unusually 'clean' environment of high-income countries may predispose individuals to allergic and autoimmune reactions[97–99]. Proponents of the hygiene hypothesis argue that in the absence of routine pathogen exposure, the immune system overreacts to what should be harmless. However, a developmentally driven interpretation might suggest that differential layering of T cells during ontogeny may contribute to these shifts in responsiveness. Factors such as malnutrition or obesity in early life may also have long-term effects on immunity if they perturb the overall structure of the peripheral T cell compartment[100–105].

The importance of naive T cell diversity may also be revealed in circumstances in which normal development is interrupted. For example, recovery from bone marrow transplants (or HIV-mediated depletion of $CD4^+$ T cells) is typically measured by replacement of total T cell numbers. However, what might appear as a superficially 'normal' repopulation may lack naturally occurring phenotypic diversity, owing to a loss of ontogenic layers. If cells produced at different times are building blocks in the establishment of a fully functional naive peripheral T cell compartment, removal of the original structure (via irradiation or chronic infection) could result in profound changes in how the new T cell compartment responds to infection.

Conclusion

Collectively, the studies discussed herein point towards a new model, in which different developmental histories in the naive T cell pool contribute to diversity in the T cell response

to infection. These observations are similar to those made with the ontogeny of B cells[106–108], macrophages[109,110], innate lymphoid cells[111] and γδ T cells[112,113]: successive waves of phenotypically distinct cells populate the periphery, persist into adulthood and respond to infection with distinct kinetics. There is now ample evidence to suggest that different subsets of naive T cells in adults exhibit unique roles during infection, which are linked to when they were initially created in the host. We believe the evidence warrants a reframing of how we view adult immunity. Rather than focusing solely on events that occur after priming, we need to better understand how the heterogeneity in the starting population of T cells affects both the response to acute infection and the quality of long-term memory responses.

Moving forwards, the challenge will be to generate models and tools to assess the proportions of neonatal versus adult cells, RTEs versus mature cells, and mature naive versus virtual memory phenotype cells that make up the naive pool in mice and humans at various stages of life (BOX 2). It will also be important to understand how these subsets respond to infection in neonatal and adult environments. In mice, we have the ability to use sophisticated fate-mapping mouse models to understand how extrinsic factors (such as diet and microorganisms) perturb the ontogeny of the T cell compartment and, consequently, the host response to infection. Such models may also prove to be useful in mapping out the developmental pathways of different subsets of naive T cells, as well as for developing testable hypotheses for future human studies.

In humans, it will be important to use the newer single-cell technologies (single-cell RNA sequencing and single-cell assay for transposase-accessible chromatin using sequencing) to identify reliable markers for different subsets of naive T cells and to better understand how the peripheral T cell compartment is altered at the individual cell level and the population level at various stages of development. If we can understand changes in the peripheral T cell pool from birth to old age, we may one day be able to predict infection outcomes on the basis of the structure of the naive T cell pool. A better understanding of the ontogeny of the naive T cell compartment may also yield advancements in the development of personalized medicine. For example, it may be possible to personalize the delivery of vaccines to different individuals to improve protective immunity, or to predict effectiveness and adverse outcomes associated with immunomodulatory therapies. Finally, we may find that certain subsets of naive T cells are particularly well suited for specific therapeutic applications, such as cancer immunotherapy.

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Box 1 |

Naive T cell subsets

Different programmes of T cell production and maintenance create naïveT cell subsets that are phenotypically and functionally distinct. Markers used to identify common naive T cell subsets in mice and humans are depicted in the table. Recent thymic emigrants (RTEs) are a well-known subset of naive T cells[60]. Historically, RTEs were characterized as 'hypofunctional', as they are generally less proliferative and exhibit diminished cytokine profiles compared with mature T cells after in vitro stimulation[18,114,115]. However, recent data indicate that RTEs may not be as defective as previously thought, as they undergo robust expansion and effector cell differentiation in the presence of inflammation[19,61]

Mature naive (MN) cells and virtual memory (VM) cells are two other subsets of naive T cells[71,76,116]. MN cells are what we might consider the 'classical' naive T cells, whereas VM cells are naive T cells that have undergone extensive homeostatic proliferation in the periphery. Functionally, VM cells respond more quickly to antigenic stimulation than MN cells and have a unique ability to undergo bystander activation in response to innate cytokines (IL-12 and IL-18) alone[72,73]. Thus, it is not surprising that the VM T cells are the first to respond to both inflammation and antigens during infection[72].

Subsets of naive T cells behave differently depending on their stem cell origin, providing an additional layer of diversity to the naive T cell pool. For example, neonatal and adult RTEs respond differently to homeostatic cues and produce different cytokines after stimulation[117]. Moreover, adult $CD8^+$ RTEs[19], but not neonatal $CD8^+$ RTEs[24], mount robust recall responses against secondary infection. Similarly, MN and VM cells derived from fetal haematopoietic stem cells adopt different fates after infection to their counterparts derived from adult haematopoietic stem cells [23]. These developmental differences were nicely illustrated in a series of dual adoptive experiments, which showed that naive T cells are biased towards terminal differentiation in the following order: neonatal VM cells > neonatal MN cells > adult VM cells > adult MN cells.

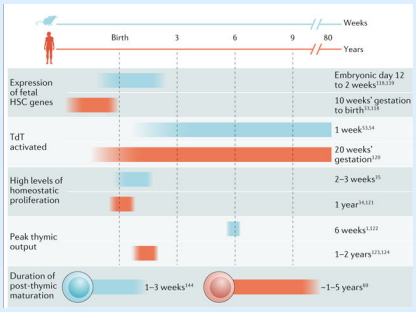
Species	RTEs		Mature naive T cells		Virtual memory T cells	
	Cell type	Phenotype	Cell type	Phenotype	Cell type	Phenotype
Mouse	$CD4^+$and $CD8^+$	$CD24^+$ $CD62L^+$	$CD4^+$and $CD8^+$	$CD44^-$ CD62L $^+Qa2^+$	$CD4^+$and $CD8^+$	$CD122^+CD44^+$ $CD49d^-$
Human	$CD4^+$ only	CD45RA* $CCR7^+$ $PTK7^+CD31$*	$CD4^+$and $CD8^+$	CD45RA* $CCR7^+$	$CD8^+$only	CD45RA*KIR $^+$ and/or NKC2A

CCR7, CC-chemokine receptor 7; KIR, killer cell immunoglobulin-like receptor; PTK7, protein-tyrosine kinase 7.

Box 2 |

Ontogeny of T cells in mice and humans

Much of our present knowledge of T cell ontogeny comes from studies in mice, in which marking and tracking of cells makes it possible to study their origins. The work on immune development in mice provides a framework in which to better understand the similarities and differences in humans (see the figure[118–124]). Although the underlying mechanisms of T cell development are conserved between species, notable distinctions are worth mentioning. First, the diversification of the repertoire occurs at an earlier stage of development in humans than in mice. Delayed expression of terminal deoxynucleotidyltransferase (TdT) extends the ‘fetal repertoire’ of mice into the first few weeks after birth[53,54]. Second, the post-thymic maturation period is shorter in mice. This difference in timing reflects the longer lifespan of T cells in humans than in mice[2]. Third, there is more detailed information on how developmental layering alters the naive T cell compartment in mice than in humans, as more sophisticated models are available to track the fates of T cells in mice. As a result, it is still not entirely clear when the developmental switch from fetal to adult haematopoietic stem cells (HSCs) occurs in humans. Lastly, some evidence suggests that mice rely more on thymic output to maintain the T cell compartment, whereas humans rely more on homeostatic proliferation[2]. Also, there are subsets of T cells with a memory-like phenotype that are present in newborn humans but not in newborn mice[125]. However, these studies involved mice housed in specific pathogen-free conditions, so it remains unclear whether these species-specific differences can be attributed to genetic or environmental factors.



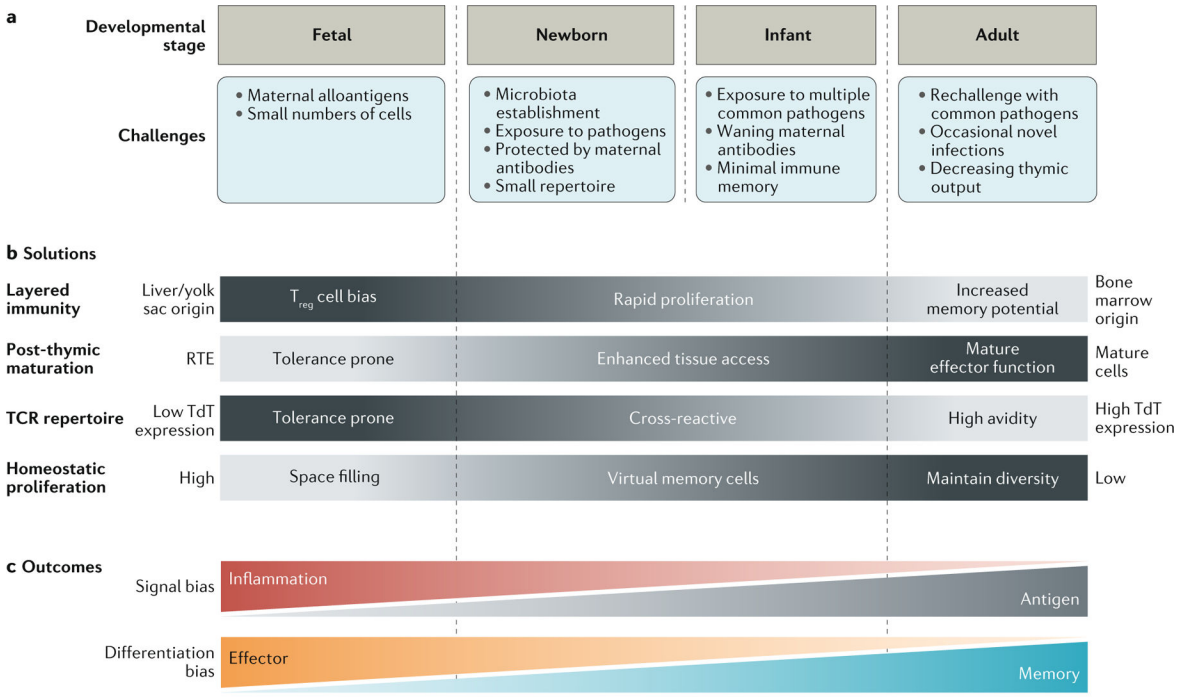


Fig. 1 |. Immune challenges and solutions during development.

a | Development from fetal life to adulthood requires progressive adaptation to environmental and infectious challenges. Prenatal life is characterized by the need for tolerance and the absence of infectious threats. Once born, an animal must cope with exposure to a diversity of novel antigens, learn to differentiate pathogenic colonization from commensal colonization and develop an effective memory response to common pathogens. **b** | The host adapts to these various immune challenges by alternating haematopoietic stem cell origins, changing the duration of post-thymic maturation, changing T cell receptor (TCR) diversity and varying the amounts of homeostatic proliferation. **c** | The interplay of specific challenges and solutions results in age-related biases in signal responsiveness and commitment to effector or memory fates. RTE, recent thymic emigrant; TdT, terminal deoxynucleotidyltransferase; T_{reg} cell, regulatory T cell.

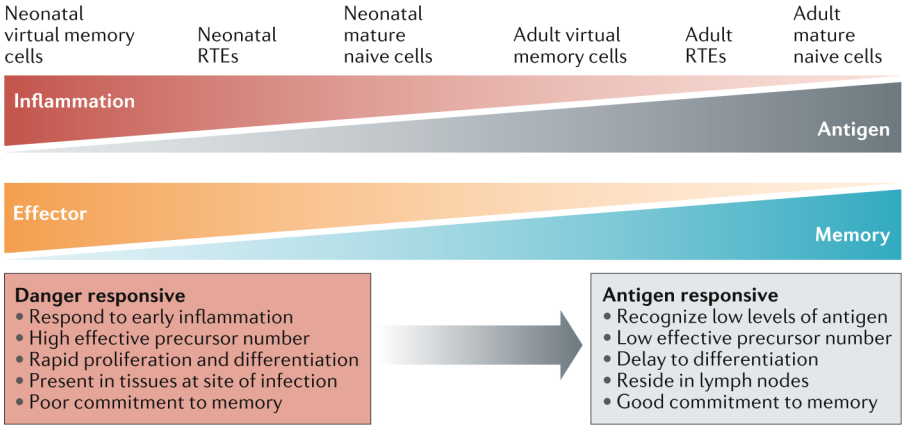


Fig. 2 |. Naive T cell subsets differ in their ability to respond to antigens and inflammation.
Immune challenges elicit a spectrum of responses from developmentally distinct subsets. Cells made early in life are more responsive to inflammatory signals and undergo rapid proliferation and differentiation. This allows rapid effector responses but is detrimental for the generation of robust memory. By contrast, cell subsets generated in adulthood respond to low levels of an antigen and make strong memory responses but require a significant time to become functional. RTEs, recent thymic emigrants.

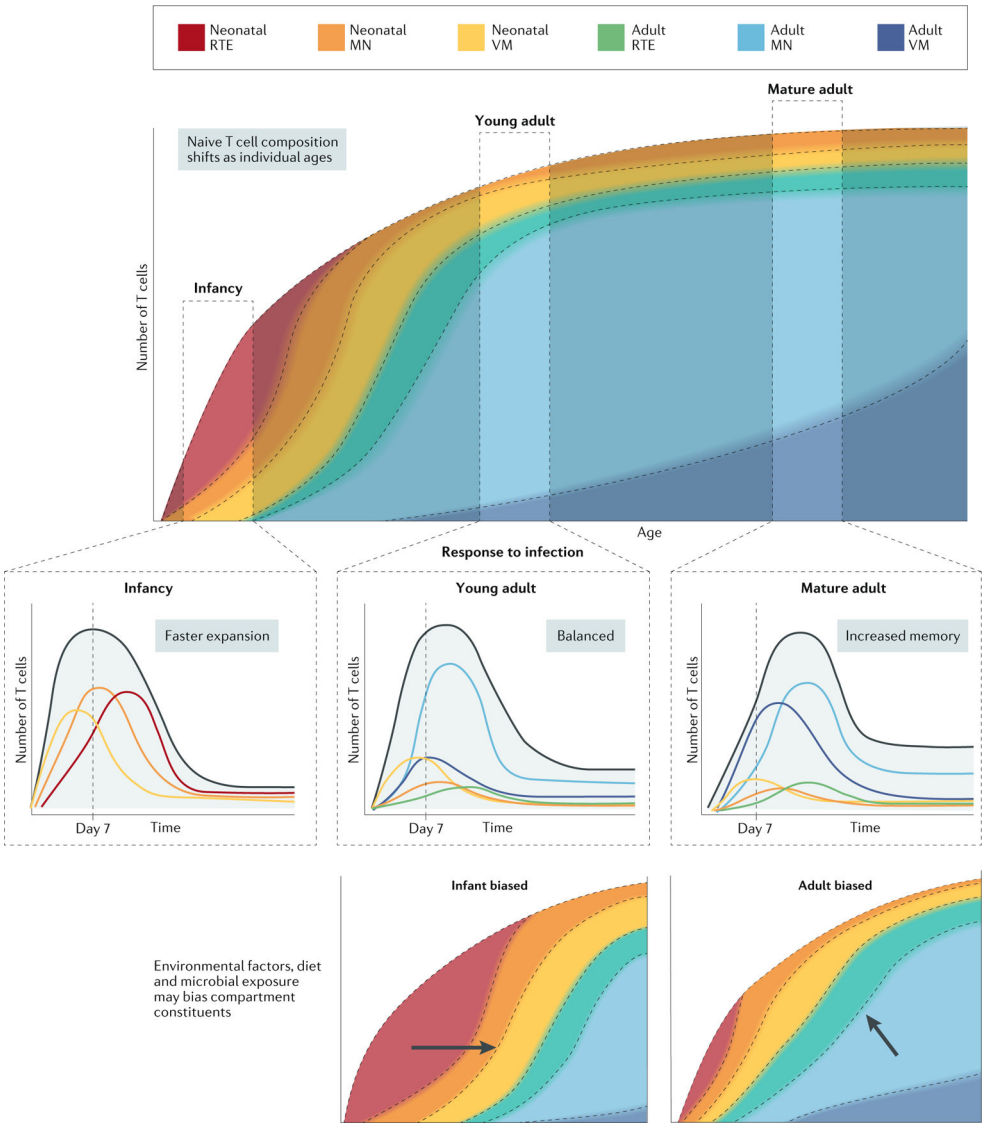


Fig. 3 |. Evolution and adaptation of the T cell compartment with progressing age.

The composition of the pool of naive T cells changes over time owing to changes in stem cell origin, T cell production, post-thymic T cell differentiation and survival. In infancy, the peripheral T cell pool is dominated by neonatal recent thymic emigrants (RTEs), which progressively differentiate to neonatal phenotype mature naive (MN) cells and virtual memory (VM) cells as a result of homeostatic proliferation. In time, these are complemented by the arrival of adult RTEs, which also differentiate over time into MN cells and VM cells, albeit at a slower rate than in infancy. At any given age, the composition of the responding naive T cell pool is unique and leads to changes in how the pool responds to novel infections. Shortly after birth, the response is dominated by fast-esponding, inflammation-sensitive subsets. Through infancy, fast-responding neonatal cells persist to provide protection, while newly arrived adult subsets begin to establish high-avidity immunological memory. In adulthood, the highly antigen-sensitive adult-derived subsets are mostly highly represented, leading to slower responses but enhanced memory formation. Perturbations in

normal immune development due to infection, malnutrition or environmental factors can perturb the T cell pool, resulting in it containing higher or lower levels of neonatal immune cells.