# Effects of Ageing on Adaptive Immune Responses

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**Abstract**

Persistent viral infections, reduced vaccination responses, increased autoimmunity, and a rise in inflammatory syndromes all typify immune ageing. As lifespan continues to extend, the demographic shift towards an older population will highlight the need to understand the mechanisms that drive age-related immune dysfunction, and to identify strategies to improve immune responsiveness in older people. These changes can be in part attributed to the accumulation of highly differentiated senescent T cells, characterised by their decreased proliferative capacity and the activation of senescence signaling pathways, together with alterations in the functional competence of regulatory cells, allowing inflammation to go unchecked. Moreover these defects that account for the decline in immune responsiveness also contribute to an increased prevalence in autoimmunity, through the reshaping of the peripheral T cell repertoire. This chapter discusses how the age-associated remodelling of the immune system leads to a lack of stability and subsequent decline in immune function.

**Keywords**

T cell • Lymphocyte differentiation • Senescence • Ageing • CD28 • TCR • mTOR • Regulatory • Immunosuppressive • Inflammation

## 2.1 Introduction

Immune function declines as we age resulting in an increased susceptibility to new infections and re-activation of latent pathogens to which we were once immune [1, 2]. Paradoxically, this dampened immune responsiveness observed during immune

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V. Bueno et al. (eds.), *The Ageing Immune System and Health*,
DOI 10.1007/978-3-319-43365-3_2

ageing is also associated with a low-grade chronic inflammation, termed 'inflammageing' [3, 4]. Although inflammation is critical for dealing with infections and tissue damage, inflammageing appears to be physiologically deleterious and predictive of all-cause mortality in multiple aged cohorts [5]. Immune senescence results from defects in different leukocyte populations, however the dysfunction is most profound in T cells [6, 7]. The responses of T cells from aged individuals are typically slower and of a lower magnitude than those of young individuals, whether the response is measured by proliferation [8], telomerase activity [8] or the induction of signalling events [9]. The T cell pool contains a number of functionally distinct subsets: $CD4^+$ T cells, $CD8^+$ T cells, and regulatory T cells together with non-conventional T cells, while not all equally affected by age, the overall T cell number does decline dramatically as a result of thymic atrophy [10, 11]. This reduced thymic output leads to the homeostatic expansion of peripheral T cells to regenerate the T cell pool, which together with the turnover of T cells in response to repeated antigenic stimulation eventually lead to the accumulation of oligoclonally expanded, functionally impaired T cells [1, 12]. Recent evidence suggests that the rise in homeostatic expansion during ageing may also be responsible for the abundance of memory-phenotype T cells specific for viral antigens in adults never previously infected [13]. Whatever the cause of these age-related changes to the T cell compartment, they all contribute to the inability of the aged immune system to respond to new antigenic challenge and mount effective responses following vaccination [14].

This chapter will examine how T cell memory is affected during ageing, the contribution of changes to the T cells themselves, as well as the consequence of an altered regulatory balance will be discussed, and will show how the generation of highly differentiated end-stage T cells contributes to age-associated disease.

## 2.2 Phenotypic Differentiation of T Cells During Ageing

There are numerous ways in which human T cell differentiation can be characterised [15, 16], the most common being listed in Table 2.1. However the most striking characteristic of highly differentiated T cells is the loss of the co-stimulatory molecules CD27 and CD28 and the re-expression of CD45RA, with $CD8^+$ T cells losing CD28 first followed by CD27 with the inverse being true for $CD4^+$ T cells [15, 17, 18]. Initially, it was thought that the loss of CD28 was the predominant factor controlling reduced activity in these cells [19]. However, highly differentiated T cells show considerable redundancy in co-stimulatory receptor usage, and alternative receptors, such as OX40 and 4-1BB can promote T cell activation in $CD28^-CD8^+$ populations [8, 20]. Highly differentiated T cells also increase during ageing with similar phenotypic changes occurring in both $CD4^+$ and $CD8^+$ T cells. However the rate at which these changes happen varies within each subset, with age-related changes being more pronounced on $CD8^+$ T cells, possibly due them exhibiting a greater homeostatic stability than $CD4^+$ T cells [21].

Highly differentiated T cells remain functional and secrete high levels of cytokines such as interferon-γ (IFNγ) and tumour necrosis factor (TNFα), together with high

**Table 2.1** Phenotypic and functional characteristics of differentiated human T cells

| | Early differentiated | | Mid differentiated | | Late differentiated | |
|---|---|---|---|---|---|---|
| Differentiation | CD45RA | +++ | CD45RA | +/– | CD45RA | –/+ |
| | CD27 | +++ | CD27 | + | CD27 | – |
| | CD28 | +++ | CD28 | +/– | CD28 | – |
| | CCR7 | +++ | CCR7 | +++ | CCR7 | – |
| | CD62L | +++ | CD62L | +++ | CD62L | – |
| | CD57 | + | CD57 | ++ | CD57 | +++ |
| | Cytotoxicity | + | Cytotoxicity | ++ | Cytotoxicity | +++ |
| | Proliferation | ++ | Proliferation | ++ | Proliferation | +/– |
| Senescence | KLRG1 | + | KLRG1 | ++ | KLRG1 | +++ |
| | Bcl-2 | +++ | Bcl-2 | ++ | Bcl-2 | + |
| | Telomere | +++ | Telomere | ++ | Telomere | + |
| | Telomerase | +++ | Telomerase | ++ | Telomerase | – |
| | P-Akt | +++ | P-Akt | ++ | P-Akt | – |
| | P-mTORC1 | ++ | P-mTORC1 | +++ | P-mTORC1 | – |
| | ROS | + | ROS | ++ | ROS | +++ |

levels of granzyme B and perforin expression, indicating that they have the potential to mediate high cytotoxic activity [16, 22–25]. Furthermore, highly differentiated $CD27^{-}CD28^{-}$ T cells remain polyfunctional secreting interleukin-2 (IL-2), IFNγ and TNFα, and expressing CD40 ligand, to the same extent as less differentiated memory T cell populations [22, 26, 27]. However, these cells have reduced capacity to replicate after activation [17, 27] and are susceptible to apoptosis ex vivo but it is possible that $CD27^{-}CD28^{-}$ T cells may persist in vivo in the presence of appropriate survival signals [28]. Taken together this suggests that highly differentiated T cell populations have characteristics of short-lived effector T cells, namely, potent effector function and susceptibility to apoptosis [29].

In addition, highly differentiated T cells become less reliant on specific antigen for stimulation and more prone to activation through innate receptors. Including killer immunoglobulin-like receptors (KIRs), killer cell lectin-like receptors (KLRs), and the immunoglobulin-like transcript receptors (ILT/CD85), more typically associated with NK cell function [30]. The acquisition of these receptors on highly differentiated T cells is more frequently seen on $CD8^{+}$ than $CD4^{+}$ T cells [31]. The majority of these NK receptors recognise MHC class I molecules [32], thereby circumventing the need for antigen recognition, which restricts clonal expansion and offers protection from undue repertoire skewing. Interestingly, NK receptors are not the only innate molecules to increase on end-stage T cells, recent evidence suggests that Toll-like receptor (TLRs) are also upregulated. TLRs appear to be more important for $CD4^{+}$ T cell function, displaying higher levels of TLR2/4 expression than $CD8^{+}$ T cells [33]. However the pattern recognition molecule retinoic acid inducible gene I (RIG-I)-like helicase was found to be more important for highly differentiated $CD8^{+}$ T cell function [33]. This suggests that differential expression of TLRs and RIG-1 on $CD4^{+}$ and $CD8^{+}$ T cells may reflect distinct modes of antigen-independent T cell priming.

## 2.3 Change in T Cell Signalling During Ageing

T cell differentiation is a highly complex process controlled not only by co-stimulation but also by the strength and duration of T cell receptor (TCR) signalling [34]. Nearly all TCR signalling pathways have been found altered during ageing (Fig. 2.1), with several studies suggesting aberrancies in early TCR mediated signalling events, such as changes to protein tyrosine phosphorylation, calcium mobilization and the translocation of protein kinase C to the plasma membrane [35–37]. In addition, there is also a decline in proximal and intermediate signalling events leading to decreased transcription factor activity, notably NF-kB and NF-AT [38]. Furthermore recent findings have shown the Lck pathway to be an important factor controlling T cell signalling [39]. Lck activity is regulated by two phosphotyrosine residues, Tyr394 which stabilises an open conformation and promotes kinase activity, and Tyr505 which results in a closed conformation decreasing activity. The lack of phosphorylation in either site can result in partial activation of lck [40]. The balance among these three pools of differentially phosphorylated lck is thought to determine the general level of enzymatic activity of lck in T cells [40]. Age-related changes in both Tyr394 and Tyr505 have been reported for $CD4^+$ T cells, both showing increased phosphorylation [36], confounding the authors as phosphorylation at these sites have opposing effects. However recent data suggests that the local concentration of active lck molecules is more important than the

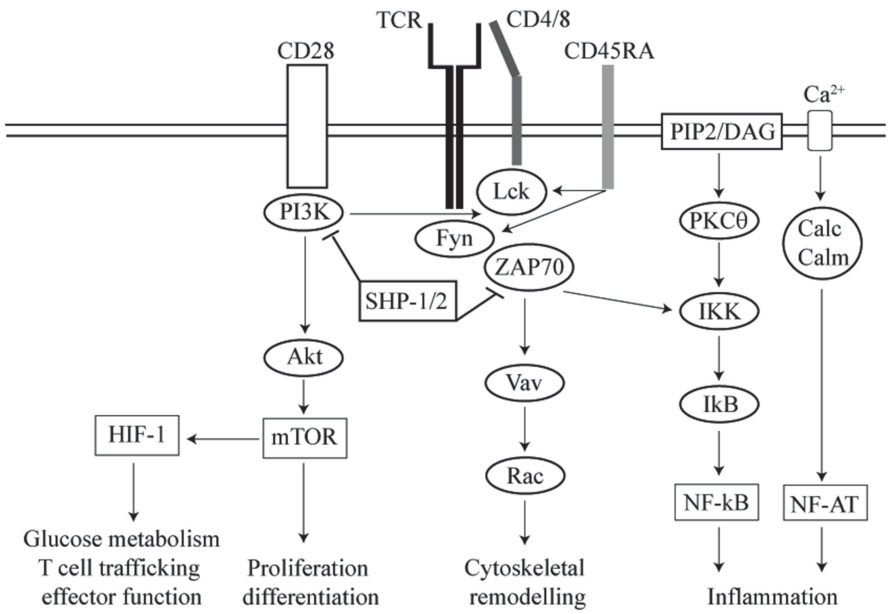


**Fig. 2.1** T cell receptor signalling pathways. This scheme highlights the most investigated signalling pathways in the context of ageing research

overall phosphorylated state of lck [41]. Therefore it remains to be determined whether highly differentiated T cells exhibit changes in either the location or movement of lck molecules in the membrane.

The immune microenvironment also plays a crucial role in shaping lineage commitment and ultimately the function of T cells (Fig. 2.1). There is now much evidence that mTOR (mammalian target of rapamycin), plays a central role controlling T cell function through its ability to connect immune signalling to metabolism [42]. The kinase mTOR belongs to the phosphatidylinositol 3-kinase (PI3K)-related kinase (PIKK) family of proteins that act as regulators of cellular growth and metabolism [43]. mTOR is the catalytic subunit of two distinct signalling complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), the activity of which are differentially regulated by distinct accessory proteins [42, 43]. Increased mTOR activity has been linked to senescence and ageing [44–47], however there is growing evidence to suggest that this increase is not universally observed in every cell type nor is it evident in older humans [27, 48–50]. Highly differentiated $CD4^+$ (unpublished observations) and $CD8^+$ T cells are unable to phosphorylate either the mTOCR1 [27] or the mTORC2 complex [51].

mTORC1 activity is a requirement for the generation of effector molecules [52], and despite highly differentiated $CD8^+$ T cells apparent lack of mTOR activity they are highly potent effectors [26, 27]. mTORC1 has also been shown to control transcriptional programs that determine $CD8^+$ effector fate via a HIF1-dependent mechanism [53]. However HIF1-null $CD8^+$ T cells were shown to have many characteristics of effector $CD8^+$ T cells such as high levels of IFNγ production, they lacked perforin and granzyme expression. A situation which is mirrored in highly differentiated $CD8^+$ T cells isolated from old individuals, where these cells display high levels of TNFα and IFNγ but lower levels of perforin and granzyme [25]. Furthermore when the mTORC1 inhibitor rapamycin was incubated with highly differentiated $CD8^+$ T cells it had no effect on IFNγ production [54]. Thus corroborating with the idea that mTOR may not play a role in T cell senescence.

An increasingly recognized pathway for modulating T cell signalling is via reactive oxygen species (ROS; Fig. 2.1) [55]. ROS influences the balance between protein tyrosine kinase and phosphatase activities through redox-dependent regulation of signalling [38]. During TCR stimulation there is a transient increase in ROS, which inactivates SHP-1 facilitating TCR signalling, however in continued ROS SHP-1 regulation is further altered, leading to the negative regulation of TCR function. High levels of ROS have been found in highly differentiated $CD8^+$ T cells [27] and during ageing [56], generated in part by impaired mitochondrial function [27]. Indeed the requirement for robust mitochondria in antigen-specific T cell expansion has been demonstrated using mice with T cell-specific alterations to complex III [57]. Thus, ageing increased oxidative stress, together with changes in tyrosine kinase and phosphatase activities all contribute to the altered T cell signalling observed during T cell differentiation and ageing.

## 2.4 Altered Regulatory Capacity During Ageing

Immune function is also controlled by regulatory T and B cells and myeloid-derived suppressor cells (MDSCs), with emerging data suggesting that the functional competence of these regulatory cells is altered during ageing (Fig. 2.2). The most characterised of the regulatory subsets are the natural regulatory T cells (nTregs), defined as $CD4^{+}CD25^{hi}Foxp3^{+}$ [58]. They are fundamental for maintaining peripheral tolerance and protection against autoimmunity, and also modulating immunity to infections and tumors [58]. Therefore, to maintain controlled immunity, it is important that this regulatory population is maintained throughout life. $CD4^{+}$ nTregs are derived from the thymus, however, the thymus involutes with age [10] suggesting that nTreg numbers might also be reduced during aging. However, there is ample data to suggest that nTreg numbers increase with age [59–62]. Therefore the number of nTregs must either be sustained through extensive proliferation or by generation from an extrathymic source [60, 63]. Human nTregs can express either CD45RA or CD45RO,

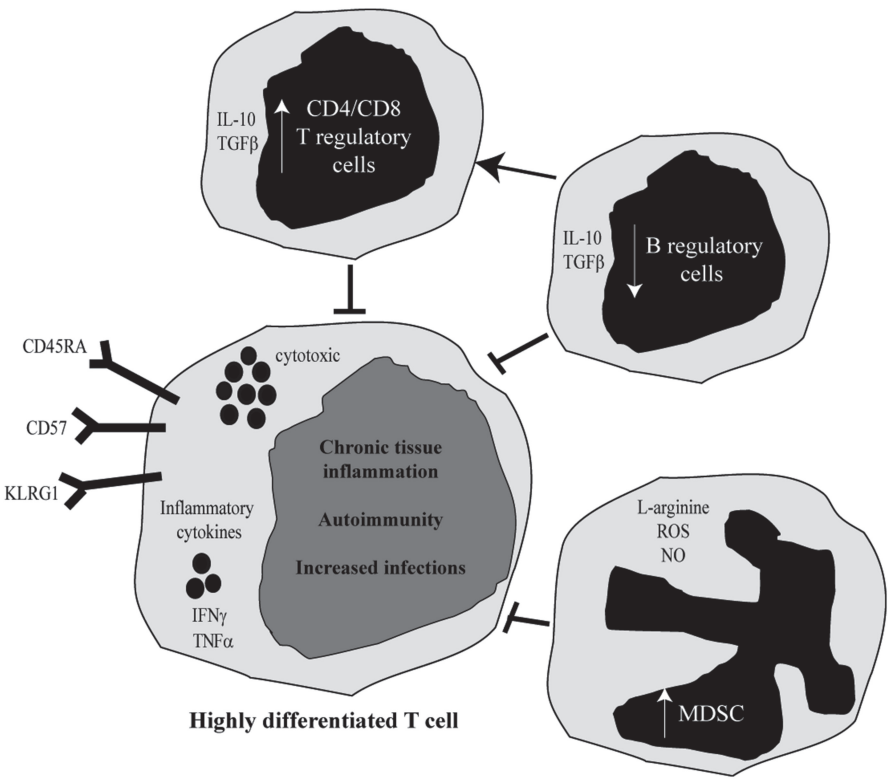


**Fig. 2.2** Altered regulation of highly differentiated T cells during ageing. Tregs and MDSCs increase with age whereas Breg numbers have been shown to decline, all alter immune control leading to a loss of peripheral tolerance and increased autoimmunity, as well as modulating immune responses to infections

with 90–95 % of adult nTregs displaying a $CD45RO^+$ phenotype [64]. It has been shown that human $CD45RO^+$ Tregs represent a highly differentiated population, characterised by short telomeres, a loss of telomerase activity and an increased susceptibility to apoptosis [60]. Indicating that these cells have limited capacity for self-renewal, suggesting that the Treg pool is not maintained through continuous turnover of pre-existing $CD45RO^+$ Tregs. Tregs can also be induced from $CD4^+CD25^-Foxp3^-$ conventional T cells in response to specific signals, such as TGFβ and retinoic acid, these so called inducible Tregs (iTregs) display the same suppressive function as nTregs [65]. It has been shown that human Tregs share a close TCR homology with $CD4^+CD25^-$ responder T cells [63, 66], supporting the hypothesis that the process of peripheral conversion from non-Tregs plays a significant role in the maintenance of the Treg population in humans. However mouse studies do not support this idea, when using non-immunised and non-lymphopenic mice, conversion was found not to play a significant role in the shaping of the peripheral Treg repertoire [67, 68]. Furthermore the induction of iTregs from aged mice was shown to be impaired [69]. However, the situation is likely to be different in humans, who undergo recurrent immunological challenges and have a much longer life span [65, 70].

Tregs belonging to the $CD8^+$ T cell compartment are equally important in regulating immune responses, although they are less well characterised than their $CD4^+$ counterparts [71]. Like $CD4^+$ Tregs, the percentage of $CD8^+Foxp3^+$ Tregs significantly increases in older individuals, with suppressor function remaining comparable to younger individuals [72]. Interestingly, these $CD8^+$ Tregs lacked expression of CD28, as discussed earlier the loss of CD28 is a hallmark of ageing. Thus suggesting that the increase in $CD8^+Foxp3^+CD28^-$ Tregs is consistent with the increase in overall numbers of $CD8^+CD28^-$ T cells.

Over the past decade, a population of immunosuppressive B cells or Bregs have come to prominence, having been shown to inhibit excessive inflammation [73]. Bregs function primarily by skewing T cell differentiation in favour of a regulatory phenotype in both mice [74] and humans [75], controlling Treg induction through direct cognate interactions between Bregs and T cells [76, 77]. Bregs can also suppress the expansion of pathogenic T cells through the production of IL-10, IL-35 and TGFβ [78]. Although the expression of IL-10 has been used to define populations of Bregs, many different surface markers have been used, leading to inherent problems in Breg subset definition, reviewed by Rosser and Mauri [73]. However two phenotypically distinct subsets of B cells: transitional $CD19^+CD24^{hi}CD38^{hi}$ B cells [79] and $CD19^+CD5^+CD1d^{hi}$ 'B10' B cells [80] have been demonstrated to exert immunosuppressive functions. The frequency and function of both these Breg subsets declines with age, owing to reduced $CD4^+$ T cell helper activity [81, 82]. The ability of Bregs isolated from old individuals to produce IL-10 following either ex vivo maturation or stimulation was also found to be reduced, and was linked to both impaired B cell signalling through CD40 and reduced expression of CD40L on $CD4^+$ T cells [81].

More recently myeloid-derived suppressor cells (MDSCs) have also been recognised as a population of immunosuppressive myeloid lineage cells capable of suppressing T cell functions [83]. MDSCs have been characterised in mice as belonging to either a monocytic, $CD11b^+Ly6G^-Ly6C^{high}$ or granulocytic, $CD11b^+LyG6^+Ly6C^{low}$

lineage, with an analogous population being identified in humans, defined as $CD33^{+}HLA\text{-}DR^{-}$ and lineage (CD3, CD19, CD56)-negative [84]. Reports have also shown human MDSCs to express CD11b and like their mouse counterparts have been subdivided into monocytic, $CD14^{+}$ and granulocytic, $CD15^{+}$ subtypes [85]. MDSCs suppress T cell responses principally through their ability to manipulate L-arginine metabolism, MDSCs produce arginase I, which catabolises L-arginine depriving T cells of this amino acid [83]. The loss of L-arginine from T cells in vitro inhibits their proliferation by arresting them in $G_0/G_1$ [86]. MDSCs can also inhibit $CD8^{+}$ T cells through the production of ROS and peroxynitrite, which catalyze the nitration of the TCR, thereby preventing T cell-MHC interactions [87]. Furthermore MDSC can indirectly effect T cell activation through the induction of Tregs, this requires MDSC production of IL-10 and arginase, but depending on the subpopulation of MDSCs can either be TGFβ dependent or independent [88]. The frequency of MDSCs increases in numerous cancers [89], chronic viral infections [90] and ageing [91]. The accumulation of MDSCs with age is thought to be driven by inflammation, the pro-inflammatory cytokines IL-1β and IL-6 and $PGE_2$ all being shown to induce the differentiation of MDSCs [91].

## 2.5 Conclusion

This chapter describes the many ways in which T cell responses are detrimentally affected by ageing, highlighting the intrinsic defects that occur to memory T cells and the extrinsic effects of altering the balance of regulatory cell activity, both limiting the responsiveness of T cells. The importance of understanding this interplay is underscored by highly differentiated T cells being found in high numbers not only during ageing but in chronic viral infections [92, 93], malignancies [94] and autoimmunity [31, 95]. Highly differentiated T cells have also been regarded as a causative factor in acute transplant rejection [96]. Additionally the low grade inflammatory state observed during ageing also plays a causal role in atherosclerosis [97] and type II diabetes [98]. The immune impairments in patients with chronic hyperglycemia resemble those seen during ageing, namely poor control of infections and reduced vaccination responses [99]. The ageing immune system in its attempt to endure and overcome the acquired defects may thus contribute to the development of an unstable state that predisposes to disease.

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The Ageing Immune System and Health
Bueno, V.; Lord, J.M.; Jackson, Th. (Eds.)
2017, XII, 182 p. 19 illus., 11 illus. in color., Hardcover
ISBN: 978-3-319-43363-9