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Mini review

Diversity of NKR expression in aging T cells and in T cells of the aged: The new frontier into the exploration of protective immunity in the elderly

Sameem Abedin[a], Joshua J. Michel[a], Bonnie Lemster[a,b], Abbe N. Vallejo[a,b,c,d,e,*]

[a]Division of Rheumatology, Children's Hospital of Pittsburgh, Pittsburgh, PA 15213, USA
[b]Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA
[c]Department of Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA
[d]The Cancer Institute, University of Pittsburgh Medical Center, Pittsburgh, PA 15232, USA
[e]McGowan Institute for Regenerative Medicine, University of Pittsburgh Medical Centre, Pittsburgh, PA 15219, USA

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Abstract

Aging in the immune system is characterized by the contraction of the lymphocyte repertoire, exemplified by long-lived oligoclonal T cells that pervade the peripheral circulation. T-cell receptor (TCR) repertoire contraction likely explains the decline in immunity with chronological age as evidenced by the increased morbidity and mortality to common and new infections, and the low rates of protective responses to vaccination in the elderly. Interestingly, in vitro senescence models and cross sectional ex vivo studies have consistently demonstrated that senescent (or pre-senescent) T cells and T cells of the aged express unusually high densities of receptors that are normally found on natural killer (NK) cells, the killer cell immunoglobulin-like receptors (KIR) being the most diverse NK receptors (NKR). Molecular studies also show that T cells are programmed to express NKRs/KIRs, and T-cell clonal lineages express a variety of NKRs towards the end stages of their replicative lifespan. We propose that NKR/KIR induction in aging T cells is an adaptational diversification of the immune repertoire. We suggest that NKR/KIR expression in oligoclonal senescent and pre-senescent T cells is a compensatory adaptation to maintain immune competence despite the overall contraction in TCR diversity with aging. NKRs comprise a diverse superfamily of receptors. Mounting evidence for NKR/KIR signaling pathways in T cells divergent from those seen in NK cells indicate that senescent NKR^+T cells are unique immune effectors. We suggest that appreciation of the functional diversity of these unusual NK-like T cells is central to the creative development of new strategies to enhance protective immunity in the aged.

Keywords: Aging; Immune repertoire; KIR; Replicative senescence

1. Introduction

Decline of immune function with chronological (or calendar) age is well documented. Regardless of geographical and ethnic/racial backgrounds, elderly persons (age ≥ 65 years) have increased morbidity and mortality to infections, with a generally low rate of protective response to vaccination, and have high incidence of malignancies and autoimmune disorders (Castle, 2000; Ramos-Casals et al., 2003; Denduluri and Ershler, 2004; Simonsen et al., 2005). Mechanisms underlying immune anomalies in old age are pleiotropic and complex, but are thought to be related to general perturbation of physiological functions consistent with the notion of systems failure associated with aging (Gavrilov and Gavrilova, 2003). Cellular studies on lymphocytes from elderly humans and aged rodents suggest defects in T-cell receptor (TCR) signaling. Aging T cells appear to have inefficient polarization/triggering of the TCR-CD3 complex (Garcia and Miller, 2001; Larbi et al., 2004) that may be exacerbated by the characteristic down regulation of the CD4 and CD8 co-receptors (Bryl et al., 2001; Vallejo, 2005). Other studies suggest that TCR signaling deficits could be related to age-associated impairment of the antigen (Ag) presenting function of dendritic cells (DCs) and macrophages (Plackett et al.,

* Corresponding author. Address: Children's Hospital Rangos Research Center, University of Pittsburgh School of Medicine, 3705 Fifth Ave., Pittsburgh, PA 15213, USA
E-mail address: abbe.vallejo@chp.edu (A.N. Vallejo).

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2004; Plowden et al., 2004). Consequently, T cells of elderly persons and of aged mice exhibit various defects in cytokine production (Linton and Dorshkind, 2004; Huang et al., 2005) and have lost classical T-helper and T-cytotoxic functions (Weyand et al., 1998; Deng et al., 2004). Similar deterioration in B-cell function with chronological aging in both humans and mice has been reported. Among these are defects in B-cell receptor signaling and proliferation (Johnson et al., 2002b), loss of B-cell precursors and associated defects in B-cell maturation (Miller and Allman, 2003), inefficiencies in immunoglobulin (Ig) recombination and isotype switching (Frasca et al., 2004), and disturbances in germinal center formation (Aydar et al., 2003).

Aging-related immunological anomalies could also be attributed to gain-(and/or loss-) of-function properties of aging lymphocytes (Vallejo, 2005) consistent with the notion of physiological remodeling with aging as a consequence of extended lifespan in the absence of natural selection (Franceschi et al., 2000). Physiological remodeling suggests mechanisms of biological adaptation that are either beneficial or maladaptive. For instance, some studies suggest that chronological aging is accompanied by the progressive accumulation of T cells that have the phenotypic characteristics of suppressor or regulatory T cells (Shimizu and Moriizumi, 2003), a T-cell subset considered to promote tolerance and curb autoimmunity in the young. However, functional studies demonstrate that suppressive activity generally ascribed to so-called regulatory T cells is in fact lost during the normal course of aging (Tsaknaridis et al., 2003). In the B-cell/plasma-cell compartment, age-dependent increased production of autoantibodies is associated with the differential selection and survival of certain B-cell subsets and with defects in the affinity maturation of Igs (Johnson et al., 2002a,b). There also appears to be preferential expansion of B1 B-cells that do not require T-cell help (Colonna-Romano et al., 2003), presumably because of inherent T-helper defects (Weyand et al., 1998).

Clearly, perturbation of lymphocyte function underlies immune deficits in old age. Unraveling the pathways leading to the loss- and gain-of-function properties in the immune system with age will be pivotal to the understanding of aging phenotypes as well as to the creative development of strategies to enhance immunity in the elderly.

2. TCR repertoire contraction: system failure underlying immune incompetence in old age

Alterations of T-cell function with chronological aging are indicative of a broader perturbation of the TCR repertoire. It has long been recognized that there is age-related skewing of the immune repertoire towards the memory compartment (Wack et al., 1998). Because of the rapid degeneration of the thymus after birth (George and Ritter, 1996), production of naïve T cells is impaired with advancing age (Ye and Kirschner, 2002; Fig. 1). Therefore, Ag exposure through life predictably leads to the expansion of the memory T-cell pool. Indeed, several studies have unequivocally demonstrated the age-related preponderance of memory/effector T cells that have Ag-specificities against common pathogens such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Herpes simplex virus (Davenport et al., 2002; Khan et al., 2004). Similar age-related low level of T-cell clonal expansions have also been indicated for the influenza virus (Deng et al., 2004) and for various adenoviral strains (Olive et al., 2001; Tang et al., 2004).

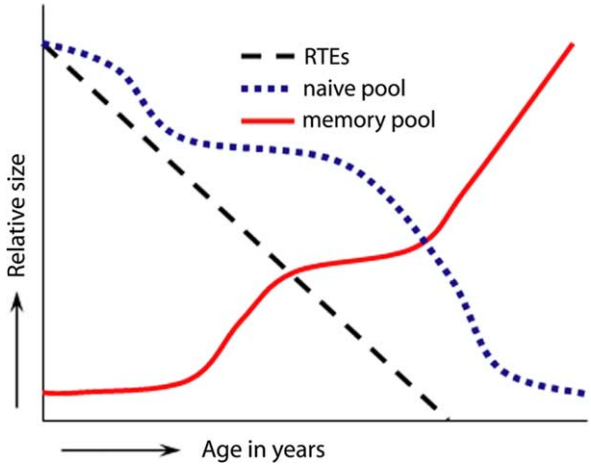

Fig. 1. The TCR repertoire contracts with age. Repertoire contraction is brought by three age-related changes in the immune system. First is the rapid postnatal degeneration of thymus that impairs T-cell production (black dashed line). New T-cells, or so-called recent thymic emigrants (RTEs), are characterized by the presence of TCR excision circles (TREC), which are non-replicating episomal DNA elements that were excised from the genome during TCR rearrangement as T cells mature in the thymus (Ye and Kirschner, 2002). Absolute numbers of TRECs decreases exponentially with age. The second is the expansion of the memory compartment due to a lifetime exposure to Ags (red solid line). The memory compartment in old age consists of large clonal populations of T cells (Schwab et al., 1997), many of which have TCR specificities against common persistent pathogens. The third is the depletion of the naïve T cell pool (blue dotted line) due to lack of replishment of RTEs and to the lifetime exposure to Ags that convert naïve cells into memory cells (Fagnoni et al., 2000). There is also increased homeostatic Ag-independent expansion with age that contributes to the severe contraction of the TCR repertoire in both naïve and memory compartments in old age (Naylor et al., 2005).

The expansion of the memory compartment, along with thymic involution, also leads to the inevitable restriction and/or depletion of the naïve reserve with age (Fagnoni et al., 2000; Fig. 1). Because the threshold of activation of memory T cells is lower than that of naïve T cells (Chandok and Farber, 2004), it has been suggested that memory T cells have growth advantage. Accumulation of memory T cells with age, due to Ag exposure through life, could crowd out naïve cells that limit their activation whenever a new Ag is encountered (Stockinger et al., 2004). Recent work on quantitative measurements of the TCR repertoire (Naylor et al., 2005) has demonstrated severe contraction in the naive