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Review

DNA damage, metabolism and aging in pro-inflammatory T cells Rheumatoid arthritis as a model system

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ABSTRACT

The aging process is the major driver of morbidity and mortality, steeply increasing the risk to succumb to cancer, cardiovascular disease, infection and neurodegeneration. Inflammation is a common denominator in age-related pathologies, identifying the immune system as a gatekeeper in aging overall. Among immune cells, T cells are long-lived and exposed to intense replication pressure, making them sensitive to aging-related abnormalities. In successful T cell aging, numbers of naïve cells, repertoire diversity and activation thresholds are preserved as long as possible; in maladaptive T cell aging, protective T cell functions decline and pro-inflammatory effector cells are enriched. Here, we review in the model system of rheumatoid arthritis (RA) how maladaptive T cell aging renders the host susceptible to chronic, tissue-damaging inflammation. In T cells from RA patients, known to be about 20 years pre-aged, three interconnected functional domains are altered: DNA damage repair, metabolic activity generating energy and biosynthetic precursor molecules, and shaping of plasma membranes to promote T cell motility. In each of these domains, key molecules and pathways have now been identified, including the glycolytic enzymes PFKFB3 and G6PD; the DNA repair molecules ATM, DNA-PKcs and MRE11A; and the podosome marker protein TKS5. Some of these molecules may help in defining targetable pathways to slow the T cell aging process.

1. Introduction

The DNA in each of the trillions of cells in our body is under constant assault by exogenous and endogenous toxins, genotoxic chemicals and cellular metabolism inducing damage to the genetic material (Ciccia and Elledge, 2010; Lindahl and Barnes, 2000). To maintain DNA integrity, cells elicit a highly specific intracellular and intercellular response network to sense, signal and repair DNA lesions, thus preventing the generation of nucleotide alterations, single-strand breaks and double-strand breaks (Jackson and Bartek, 2009). The conglomerate of hierarchical pathways protecting DNA integrity has been termed DNA damage response (DDR). Declining efficiency of DNA repair systems will lead to the accumulation of damaged DNA which causes functional failure or cell death. Notably, DNA damage accumulation or repair system defects promote cellular senescence or apoptosis (Childs et al., 2015). Thus, preserving DNA intactness is a cardinal feature of health and a decline in DDR is considered a major contributor to organismal aging (Pan et al., 2016). Aging is characterized as a time-dependent progressive functional decline, leading to loss of organismal homeostasis, increased human pathologies and eventually death (Fulop et al., 2011; Lopez-Otin et al., 2013). The decline of immune protective adeptness, often referred to as immune aging, is one of the key processes associated with advancing age and contributes to numerous age-related morbidities. Immune aging impairs the host's

Abbreviations: EC, endothelial cell; ROS, reactive oxygen species; ATP, adenosine 5′-triphosphate; ER, endoplasmic reticulum; mtDNA, mitochondrial DNA; ETC, electron transport chain; mROS, mitochondrial ROS; NADPH, nicotinamide adenine dinucleotide phosphate; TNF-α, tumor necrosis factor-α; AMPK, AMP-activated protein kinase; VEGF, vascular endothelial growth factor; NF-κB, nuclear factor-kappa B; DDR, DNA damage response; SASP, senescence-associated secretory phenotype; RA, rheumatoid arthritis; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biophosphatase 3; G6PD, glucose-6-phosphate dehydrogenase; ATM, ataxia telangiectasia mutated; DSB, double-strand breaks; ATR, ATM and RAD3-related; PIKKs, phosphatidylinositol-3-OH-kinase-like kinase; PPP, pentose phosphate pathway; STING, stimulator of interferon genes; DNA-PK, DNA-dependent protein kinase; NHEJ, non-homologous end joining; HR, homologous recombination; SCID, severe combined immunodeficiency; VCAM, vascular cell adhesion molecule; MRE11A, meiotic recombination 11 homolog A; A-TLD, ataxia-telangiectasia-like disorder; NBS, Nijmegen breakage syndrome; TGF, tumor growth factor; DAMP, damage-associated molecular pattern; TLR, toll like receptor; NLRP3, Nod like receptor family pyrin domain containing 3; NET, neutrophil extracellular traps; SLE, systemic lupus erythematosus; TRF2, telomeric repeat-binding factor 2; IFN, interferon; KIR, killer immunoglobulin-like receptors

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protection against pathogen invasion, renders the host susceptible to malignancies, weakens wound healing and tissue repair, while increasing the risk for chronic inflammation and autoimmune disease development (Goronzy et al., 2013; Goronzy and Weyand, 2013; Palmer, 2013). Immune system aging is one of the key components leading to inflammaging; a process of smoldering inflammation in the elderly, but other age-related changes, such as accumulation of infections and senescent cells, metabolic syndrome, etc. may also contribute.

In patients with rheumatoid arthritis (RA), the immune aging process is accelerated; best captured in prematurely aged T cells that lose CD28, have shortened and damaged telomeres, impaired DNA repair systems and excessive production of cytokines (Goronzy and Weyand, 2012; Schmidt et al., 1996b; Weyand et al., 2014). RA T cells are metabolically reprogrammed, affecting their differentiation, function, and longevity (Weyand et al., 2017). In this review, we will use the inflammatory syndrome RA as a model system to discuss how DNA damage accelerates T cell aging and how old T cells promote and sustain tissue inflammation. Defining molecular targets at the interface of immune cell aging and inflammation may allow the development of novel interventions counteracting the detrimental effects of organismal aging and inflammatory disease.

2. Maladaptive T cell aging in rheumatoid arthritis

T cells from RA patients have an array of features that identifies them as being prematurely aged: the accumulation of $CD28^-$ effector T cells, telomere fragility and attrition, inefficient DNA damage repair, metabolic reprogramming, and excess production of cytokines compatible with a senescence-associated secretory phenotype (SASP) (Fig. 1). To keep immune homeostasis, e.g. securing population density, diversity and cellular competence, the T cell compartment develops adaptive strategies to generate new T cells, protect long-term survival of existing T cells and monitor functional adeptness of individual T cells (Goronzy and Weyand, 2017). In mice, survival times of naïve T cells are short and their generation entirely depends on the thymus (Bains et al., 2009; den Braber et al., 2012; Tsukamoto et al., 2009). In contrast, due to the involution of the thymus during the first third of life, humans had to adopt a completely different strategy to generate and maintain their T cell compartment: they generate new T cells by homeostatic proliferation of already selected T cells. Over a lifetime, continuous peripheral proliferation, progressive T cell differentiation and persistent stimulation by infectious agents will eventually build a T cell compartment with contracted diversity, partial cellular differentiation and reduced cellular competence (Czesnikiewicz-Guzik et al., 2008; Moskowitz et al., 2017; Sauce et al., 2012).

The T cell memory compartment, characterized by cell inflation and TCR repertoire shifts, serves the aging host by optimizing anti-viral immunity, particularly to CMV and VZV infections (Derhovanessian et al., 2014; Goronzy et al., 2001; Levin et al., 2003). Changes in the frequencies and composition of regulatory T cell (Treg) are also associated with aging. In older individuals, the population of naïve-like $CD4^+CD45RA^+CD25^+$ Treg cells is fading and $CD4^+CD45RO^+CD25^{hi}$ memory-like Treg cells are increasing (Seddiki et al., 2006; Valmori et al., 2005). Notably, the number of $CD45RA^+CCR7^+NOX2^+$ naïve-like $CD8^+$ Treg cells decreases with age as well (Wen et al., 2016). $NOX2^+$ CD8 Treg cells exert anti-inflammatory functions by controlling the size of the CD4 T cell compartment and their age-related decline favors unopposed tissue inflammation. Thus, healthy immune aging results from a multitude of adaptive mechanisms, all geared to optimize immune protection while maintaining homeostasis. In patients with RA, the process of immune aging is maladaptive, resulting in the accumulation of pro-inflammatory effector cells and susceptibility of the host to suffer from unopposed tissue inflammation (Fig. 1).

Unfavorable outcomes of immune aging include inefficient protection against infection, impaired vaccine responses, susceptibility to cancer development and compromised wound healing. Studying T cells from RA patients has been informative in exploring the role of old T cells in tissue inflammation. Most of these studies were performed with purified naïve CD4 T cells from RA patients that were stimulated to enter effector cell differentiation. Thus, abnormal phenotypes and functional behaviors should not be a consequence of the inflammatory disease process, as naïve T cells have no role in tissue inflammation. Focusing on the naïve CD4 T cell population, however, has allowed functional and molecular studies prior to such T cells entering the rheumatoid disease process. In this review, reference to RA T cells relates to stimulated naïve CD4 T cells that have converted into effector cells.

An important conceptual progress has been that the aged T cells from RA patients are not in permanent cell cycle arrest and thus do not

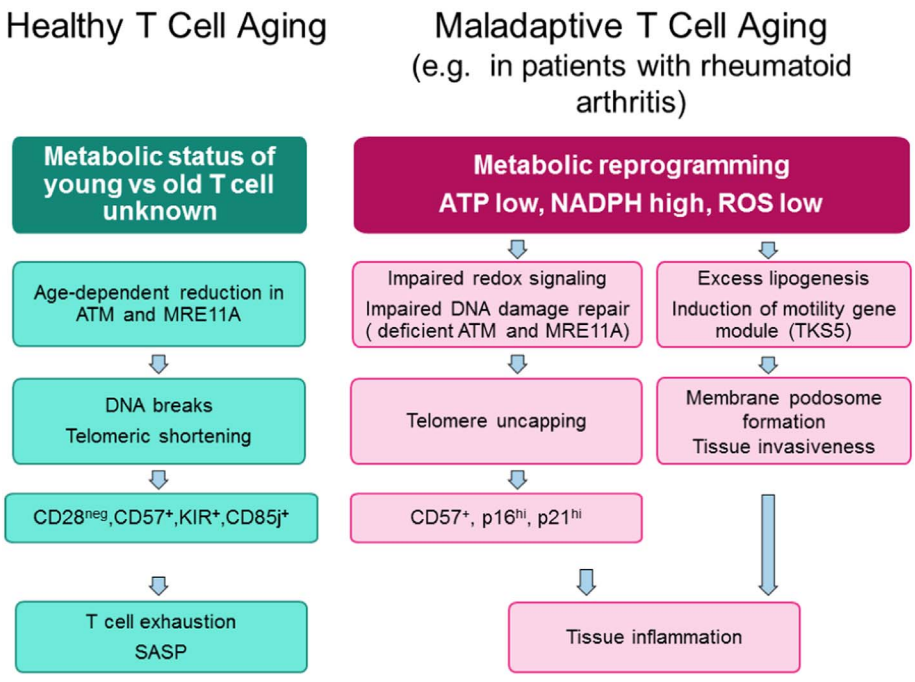

Fig. 1. Healthy and maladaptive T cell aging.
T cells from patients with the inflammatory syndrome rheumatoid arthritis (RA) age at an accelerated pace. Naïve CD4 T cells from RA patients are metabolically reprogrammed. Due to suppressed glycolysis, they produce less ATP and shunt glucose into the pentose phosphate pathway, yielding high levels of NADPH and low levels of reactive oxygen species (ROS). One outcome is increased lipogenesis, lipid droplet formation, membrane ruffling and accelerated T cell motility. A second outcome is insufficient activation of the DNA repair machinery, affecting the kinase ATM and the nuclease MRE11A. As a consequence, telomeres are uncapped and T cells enter the senescence program. Aged cells express CD57 and upregulate p16 and p21. Damaged telomeres and membrane podosome formation enable T cells to invade into the synovial tissue and cause chronic synovitis.
RA T cells serve as a model system to explore the aging process in healthy T cells, in which phenotypes are less pronounced but molecular mechanisms may be shared.