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Activation-induced and damage-induced cell death in aging human T cells

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ABSTRACT

In multicellular organisms the proper system functionality is ensured by the balance between cell division, differentiation, senescence and death. This balance is changed during aging. Immunosenescence plays a crucial role in aging and leads to the shrinkage of T cell repertoire and the propensity to apoptosis. The elimination of expanded T cells at the end of immune response is crucial to maintain homeostasis and avoid any uncontrolled inflammation. Resting mature T lymphocytes, when activated *via* their antigen-specific receptor (TCR) and CD28 co-receptor, start to proliferate and then undergo the so called activation induced cell death (AICD), which mechanistically is triggered by the death receptor and leads to apoptosis. T lymphocytes, like other cells, are also exposed to damage, which can trigger the so called damage-induced cell death (DICD). It was hypothesized that oxidative stress and chronic antigenic load increasing with age reduced lymphocyte susceptibility to DICD and enhanced a proinflamatory status leading to increased AICD. However, data collected so far are inconsistent and does not support this assumption. Systematic and comprehensive studies are still needed for conclusive elucidation of the role of AICD and DICD in human immunosenescence, including the role of autophagy and necroptosis in the processes.

1. Introduction

In multicellular organisms, the proper system functionality is ensured by the balance of cell division, differentiation, senescence and death. This functionality changes during ontogenesis and aging. In the period of organism development, there is a dominance of cell growth and differentiation although cell death and senescence also take place. Programmed cell death, termed apoptosis, has been recognized many years ago as a process involved in morphogenesis (Lockshin and Zakeri, 2001). This is an evolutionarily conserved cell suicide program that is strictly regulated and executed through finely controlled signaling pathways. Recently, also programmed cellular senescence has been documented in mouse embryo (Munoz-Espin et al., 2013; Storer et al., 2013). Cellular senescence denotes a permanent proliferation arrest, which, like apoptosis, is controlled by signaling pathways, but does not result in cell death (Rodier and Campisi, 2011). Both cell fates seem to play the same role in morphogenesis ensuring the clearance of unneeded cells by the immune system.

Postnatal programmed cell death is a vital part of thymocyte maturation. Thymocytes undergo a process of positive and negative selection, which ensures the release to the periphery of properly differentiated non-autoreactive lymphocytes. Apoptosis is also necessary to keep homeostasis of the immune system by lymphocyte elimination. During the so called contraction period, which follows the antigenic load and is a critical element in the defense against autoimmune disease, lymphocytes are eliminated *via* apoptosis (Giovannetti et al., 2008). It was revealed that mice with mutations in *lpr* and *gld* genes encoding Fas (CD95) and Fas ligand (CD95L) proteins, respectively have autoimmune disease. (Takahashi et al., 1994; Watanabe-Fukunaga et al., 1992).

Apoptosis can be both beneficial, in ridding of pre-neoplastic damaged and mutated cells, but also harmful when cell loss exceeds the ability of stem cells to restore and maintain tissue homeostasis (Joaquin and Gollapudi, 2001).

Senescent cells are alive but metabolically altered. They secrete a lot of factors, such as proteases (*e.g.*, metaloproteases-MMP-1, 3, 10), chemokines (growth-related oncogene- GROα, IL-8, monocyte chemoattractant protein-1-MMC-1), cytokines (IL-1α, Il-6, IL-7) and many others (Freund et al., 2010). These factors can influence the tissue surveillance in a way which could promote tissue repair, prevent fibrosis, signal to the innate immune system to clear the senescent cells, but also reinforce senescence and promote cancer

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development and other age-related diseases associated with low grade inflammatory state (Hoare and Narita, 2013). On the other hand, senescence is a barrier to cancer as it stops division of damaged cells (Campisi, 2003). The number of senescent cells increase with age which can result in decreased tissue function, increased low grade inflammation (the so called inflammaging, (Franceschi et al., 2000)) and exhaustion of stem cells. In this way cell senescence can influence or even cause organismal aging (Sikora et al., 2011). Moreover, it is believed that senescence prevents cells from apoptosis and, indeed, resistance to apoptosis was documented for several types of cells *in vitro* (Salminen et al., 2011). Thus, accumulation of senescent cells with age, including senescent stem cells counteracts tissue regeneration.

Replicative senescence refers to the limit of population divisions due to telomere erosion (Hayflick, 2000). Another type of cell senescence is called stress- or-oncogene induced senescence (SIPS and OIS, respectively) and is telomere erosion-independent (Kuilman et al., 2010). Short telomeres, as a hallmark of cellular senescence, have been correlated with age and many age-dependent pathologies (Sikora et al., 2011). Senescent cells identified according to other markers, such as activity of SA-β-galactosidase, DNA damage foci or cell cycle inhibitors, p16 and p21, were shown to be present in various organs of mice and humans and their numbers were documented to increase with age (Jeyapalan and Sedivy, 2008; Wang et al., 2009). Logically thinking, if the number of senescent cells is increasing with age and senescent cells are resistant to apoptosis, thus the level of cell death should decrease with age. However, the results published so far are inconsistent as they report both increased and decreased apoptosis with age. Aberrations in apoptosis are observed in a number of age-related pathologies, such as osteoporosis, retinal degeneration, autoimmunity, ischemia, neurodegeneration, cardiovascular diseases, sarcopenia and the so called segmental aging syndromes for instance Werner's and Bloom syndrome (Warner, 1999, 2007).

Aging is an essential physiological phenomenon characterized by progressive accumulation of deleterious molecular damage in cells, that decreases cell viability to survive and increases the risk of death. There is an ongoing debate whether aging is a simple destruction, namely a stochastic or entropic process, or a continuation of the developmental program or even a quasi-program (Zimniak, 2012). Irrespective of which theory better describes the evolutional origin of aging, the functionality of an organism is changing with age and the cell propensity to apoptosis and senescence is also a subject of age-dependent changes.

In this review, we will focus on lymphocyte propensity to undergo apoptosis and its relation to cell senescence and the aging process.

2. Cell death of T cells

Apoptosis serves to eliminate severely damaged cells, which acquired lesions mainly in DNA, due to the action of stress inducing factors such as reactive oxygen species, UVB, hyperproliferation and metabolism. This type of cell death can be called damaged-induced cell death (DICD). Immune cells, just like other cells, are exposed to the various insults (*e.g.*, DNA damaging factors, glucocorticoids, reactive oxygen species, cytokine deprivation) which can induce DICD (Ginaldi et al., 2004). However, in the immune system, apoptosis plays a unique role restricted only to this system. Namely, it ensures selection of T-cell repertoire in the thymus, deletion of self-reactive T and B lymphocytes both in the central and peripheral lymphoid compartments, the killing of target cells by cytotoxic T lymphocytes and natural killer cells as well as elimination of T (CD3+) cell clones resulted as a response to antigen (Osborne, 1996).

Precursors of CD3+ cells from the bone marrow enter the thymus, where they undergo negative or positive selection to produce CD4+ and CD8+ mature cells with diverse functions in the peripheral immune system (Palmer, 2003). In the periphery, T cells are resting until they encounter foreign antigens and gain the ability to proliferate, differentiate into effector cells, produce cytokines and eliminate target cells. T-cell activation is induced by signals received through the TCR (T Cell Receptor) activated by the antigen presented by APC (antigen presenting cells) in MHC (major histocompatibility complex) context, and by co-stimulatory molecules, including CD28, adhesion molecules and interleukins (IL) (IL-2, IL-13, IL-15). This clonal expansion phase is followed by the contraction phase in which T cell numbers decline to maintain homeostasis and avoid any uncontrolled inflammation. The majority of activated T cells die by apoptosis and only a few T cells that have been exposed to the antigen remain. These cells develop into memory T cells. The process in which expanded cells are eventually eliminated is called activation-induced cell death (AICD), which mechanistically occurs *via* the so called extrinsic apoptotic signaling pathway (Krueger et al., 2003; Sprent and Tough, 2001).

The extrinsic apoptotic pathway is triggered by signals originating from cell-surface death receptors belonging to the TNF (tumor necrosis factor) receptor (TNFR) superfamily that are activated by several ligands such as CD95L (FasL), TNF or TNF-related apoptosis-inducing ligand (TRAIL). Transduction of the apoptotic signal from the death receptors starts with the formation of a large protein complex at the cell membrane, known as the death inducing signaling complex – DISC. This complex facilitates in the assembly of pro-caspases 8 and 10 and their autoproteolytic activation followed by so called executor caspases activation. Upon stimulation of activated T cells, CD95L mRNA and protein expression are rapidly induced. CD95L is secreted and binds to the CD95 receptor on the same cell or on neighboring cells, and triggers CD95-dependent apoptosis. (Krammer et al., 2007). This signaling pathway should suffice to induce executor caspases and eventual cell death. However, the level of CD95, DISC and active caspase 8 may be too low and the signal requires an additional amplification loop involving the cleavage of a BH3-only BCL-2 (B-cell lymphoma 2) family protein, BID (BH3-interacting domain death agonist), by caspase 8 to form truncated BID (tBID). tBID, in turn, aggregates BAX (BCL-2 associated X protein) or BAK (BCL-2 agonist/killer), which leads to mitochondrial membrane permeabilization, cytochrome c release (Krammer et al., 2007) and activation of the second intrinsic apoptotic signaling pathway.

The intrinsic apoptotic pathway crucially depends on permeabilization of the outer mitochondrial membrane and mitochondria seem to be integrators of many apoptotic signals coming from the outside and inside of the cell. After receiving an apoptotic signal, mitochondria release a variety of molecules, including cytochrome c, which together with the cytoplasmic apoptotic-protease-activating factor 1 (APAF1) forms the apoptosome. In the apoptosome the initiator caspase 9 is activated. Mitochondrial membrane permeability is controlled primarily by a balance between the antagonistic actions of the pro-apoptotic and anti-apoptotic members of the BCL-2 family (Krammer et al., 2007). The intrinsic apoptotic pathway is the mechanism of DICD and can be triggered by DNA damage, thus DNA damage response pathway (DDR) with its key protein, p53 is involved in this type of apoptosis. The p53 protein acts as a transcriptional activator of pro-apoptotic or a suppressor of anti-apoptotic proteins from the BCL-2 family. P53 also directly interacts with the BCL-2 proteins influencing mitochondrial outer membrane permeabilization (Chipuk and Green, 2006).

One of the final events of the apoptotic signaling pathways is activation of specific endonucleases that cleave DNA into oligunucleosomal fragments: Endonuclease G and DFF/CAD. The latter

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