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Cellular senescence and apoptosis: how cellular responses might influence aging phenotypes

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Abstract

Aging in complex multicellular organisms such as mammals entails distinctive changes in cells and molecules that ultimately compromise the fitness of adult organisms. These cellular and molecular changes lead to the phenotypes we recognize as aging. This review discusses some of the cellular and molecular changes that occur with age, specifically changes that occur as a result of cellular responses that evolved to ameliorate the inevitable damage that is caused by endogenous and environmental insults. Because the force of natural selection declines with age, it is likely that these processes were never optimized during their evolution to benefit old organisms. That is, some age-related changes may be the result of gene activities that were selected for their beneficial effects in young organisms, but the same gene activities may have unselected, deleterious effects in old organisms, a phenomenon termed antagonistic pleiotropy. Two cellular processes, apoptosis and cellular senescence, may be examples of antagonistic pleiotropy. Both processes are essential for the viability and fitness of young organisms, but may contribute to aging phenotypes, including certain age-related diseases.

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1. Introduction

Aging, ultimately, is a phenomenon of intact organisms. Nonetheless, it results from biochemical reactions, cellular responses and the action of genes, which, in multicellular organisms, may have different effects in different tissues. According to current evolutionary theories of aging, the primary causes are thought to derive from the unselected action of specific genes, which evolved under ancestral environments that differ substantially from modern environment. Thus, aging phenotypes very likely arise because the force of natural selection declines with age. This decline can have two effects. First, it can allow the accumulation of late-acting deleterious mutations, which would compromise the fitness of old, but not young, organisms (mutation accumulation). In addition or alternatively, the declining force of natural

selection with age can permit processes that were selected for their beneficial effects early in life to have unselected deleterious effects in old organisms, a phenomenon termed antagonistic pleiotropy (Kirkwood and Austad, 2000).

For complex multicellular organisms such as mammals, on which this review focuses, it would take several volumes to review all of the cellular and molecular changes that have been reported to occur as a function of age. Therefore, this review makes no attempt to be comprehensive. Rather, it focuses on two cellular responses that occur in mammals and other organisms, which may be important for embryonic development and/or maintaining the health of adult tissues, yet may also cause or contribute to aging phenotypes. It also discusses the role of genomic maintenance systems for preserving the health of cells, tissues and ultimately the organism, and speculates on how cellular and genomic changes might lead to aging phenotypes and certain age-related diseases.

2. Cellular processes that may contribute to aging

Individual cells undergo a wide range of structural and functional changes during organismal aging. Here, however, two cellular processes are discussed, each of which results in striking structural and function changes in cells. These processes are apoptosis, or programmed cell death, and cellular senescence, or the senescence response.

Apoptosis and cellular senescence are the cellular responses to a variety of intrinsic and extrinsic signals. It is well established that both processes are critically important for the health and function of many tissues in the adults of complex organisms (such as mammals). Nonetheless, apoptosis and cellular senescence have also been proposed to contribute to aging phenotypes and/or the development of certain age-related diseases (Campisi, 2000; Zhang and Herman, 2002). How might these processes be both beneficial and detrimental to complex organisms, and how might they contribute to aging? There are, at present, no definitive answers

to these questions. However, in the last decade, considerable progress has been made in understanding the regulation and biological consequences of apoptosis and cellular senescence. In addition, substantial progress has been made in understanding some of the root causes of aging and certain age-related diseases. The convergence of these two bodies of knowledge makes it now possible to speculate – and much of the following discussion is speculation -- on how apoptosis and cellular senescence might impact the aging of complex organisms.

2.1 Apoptosis

Apoptosis is the rapid, highly conserved process of controlled, programmed cell death. Cell death by apoptosis (as opposed to necrosis) ensures that the contents of dying cells are encapsulated and removed by scavenging cells. In this way, apoptosis prevents the release of degradative enzymes and their destruction of neighboring cells, and, in complex organisms, it prevents subsequent inflammation reactions (Arends and Wyllie, 1991; Ellis et al., 1991).

Apoptosis is essential for normal embryonic development in both simple eukaryotes, such as *Caenorhabditis elegans* (nematodes) and *Drosophila melanogaster* (flies), and complex eukaryotes. Many of its features are evolutionarily conserved (Vaux and Korsmeyer, 1999; Meier et al., 2000). Of perhaps greater relevance to aging, apoptosis is also essential for normal tissue homeostasis in the adults of complex organisms. In adult tissues, apoptosis can occur as a consequence of normal differentiation, in which cases it is generally induced by intrinsic signals. In addition, apoptosis serves to remove unwanted or damaged cells from tissues, in which cases it is generally induced by extrinsic signals [Ellis, 1991 #347; Cohen, 1992 #348;(Li and Yuan, 1999; Medh and Thompson, 2000).

Given the importance of apoptosis for normal tissue function, it not surprising that defects in its regulation have been shown to cause or contribute to a panoply of degenerative and hyperproliferative diseases (Arends and Wyllie, 1991; Thompson, 1995; Fadeel et al., 1999;

Reed, 1999; Martin, 2001). The most striking example is the development of cancer. Cancer cells almost invariably acquire mutations that allow them to evade the normal signals and mechanisms that cause apoptotic cell death. Indeed, it has been argued that resistance to apoptosis is a necessary, although insufficient, step for malignant progression (Hanahan and Weinberg, 2000). Thus, for example, genetically modified mice that are compromised in their ability to engage one or more apoptotic pathway (and survive to adulthood) generally die prematurely of cancer (Ghebranious and Donehower, 1998; Hakem and Mak, 2001; Wu and Pandolfi, 2001). Consistent with a vital role for apoptosis in preventing cancer, p53, a critically important mammalian tumor suppressor protein, is also a key positive regulator of apoptosis (Amundson et al., 1998; Kaelin, 1999; Pluquet and Hainaut, 2001). On the other hand, inappropriate or overactive apoptosis can lead to tissue atrophy or degeneration. The most severe effects of inappropriate apoptosis are seen in tissues composed largely of post-mitotic cells, such as the brain and peripheral nervous system (Arends and Wyllie, 1991; Thompson, 1995; Fadeel et al., 1999; Martin, 2001). In these tissues, the replacement of post-mitotic neurons is very likely rare, and may not occur at all in some regions (Almeida-Porada et al., 2001; Weissman et al., 2001).

A generalized defect in the control of apoptosis has been proposed to cause or contribute to aging (Joaquin and Gollapudi, 2001; Zhang and Herman, 2002). Although this idea is not as well developed or supported by data as the proposed role for apoptosis in specific diseases, evidence for this idea is mounting (Muskhelishvili et al., 1995; Kajstura et al., 1996; Higami et al., 1997; Adams and Horton, 1998; Mather and Rottenberg, 2000; Suh et al., 2002). One might imagine two scenarios by which the cellular process of apoptosis might be interconnected with the intrinsic process of aging and/or the development of specific aging phenotypes.

First, an upstream, fundamental mechanism of aging (for example, a change in neuroendocrine hormones, or change in the hormonal/cytokine milieu) might alter the control of

apoptosis, which, in turn, would lead to aging phenotypes and age-related disease. That is, one or more basic aging process might alter the regulation of the apoptotic response, at least in certain cell types. There is some evidence for this scenario. For example, when the livers of young rats were challenged with a direct acting DNA damaging agent, there was an expected striking increase in the number of hepatocytes that underwent apoptosis. This apoptotic response presumably removed hepatocytes that were badly damaged and, hence, had become dysfunctional or at risk for neoplastic transformation. In identically treated old animals, however, many fewer hepatocytes underwent apoptosis, suggesting a generalized blunting of the apoptotic response (Suh et al., 2002). Moreover, caloric restriction, which extends the life span and retards most if not all age-related pathology in these animals, increased both the basal and damage-induced levels of apoptosis, and the elimination of preneoplastic cells. in aged liver (Grasi-Kraupp et al., 1994). Thus, aging appears to suppress the apoptotic response, at least in the liver and in response to DNA damage, and suppression is retarded by regimens (caloric restriction) that retard aging. On the other hand, aging has been reported to sensitize hepatocytes to apoptosis induced by the endogenous ligand Fas, and this sensitization was reversed by caloric restriction (Higami et al., 1997). In addition, the basal rate at which chrondrocytes undergo apoptosis in articular cartilage was reported to increase with age, and this increase was proposed to contribute the age-related development of osteoarthritis (Adams and Horton, 1998).

Taken together, these findings suggest that one or more fundamental process that is responsible for aging may alter the regulation of apoptosis. However, whether the apoptotic response is increased or decreased by aging may depend on the both the inducing signal and the tissue or cell type.

Second, it is also possible that the normal (homeostatic) apoptotic responses and their regulation might, over time, lead directly to aging phenotypes and/or age-related pathology. For example, apoptosis normally acts to remove cells that are damaged or dysfunctional. As mentioned earlier, this function of apoptosis is critical for protecting mammalian organisms from

cancer (Reed, 1999; Hanahan and Weinberg, 2000). However, apoptosis can also act on damaged or dysfunctional post-mitotic cells, such as neurons. Post-mitotic cells can be damaged by endogenous processes, such the reactive oxygen species that are generated by mitochondrial metabolism, or by external agents, such as certain neurotransmitters or environmental toxins. Damaged neurons can be eliminated by apoptosis, which may have little or no phenotypic consequences for young organisms, in which synaptic plasticity allows the neuronal network to compensate for occasional cell loss. In old organisms, however, neuronal loss owing to apoptosis may eventually outpace the ability of the remaining neurons to establish compensatory synapses. This would, of course, result in the deleterious neuronal insufficiency and neurodegeneration.

2.2 Cellular senescence

Cellular senescence refers to the response of mitotically competent cells (that is, cells that are not terminally differentiated, and hence have the ability to divide) to a stimulus that has the potential to cause neoplastic transformation. In recent years, many senescence-inducing stimuli have been identified, including short, dysfunctional telomeres, DNA damage, and the expression of certain oncogenes (discussed further below).

Like apoptosis, cellular senescence may be an evolutionarily ancient response. It occurs in simple unicellular organisms, such as the yeast *Saccharomyces melanogaster* (Jazwinski, 1996), and in the stem cells of simple multicellular eukaryotes, such as the *Drosophila melanogaster* ovary (Margolis and Spradling, 1995). In addition, like apoptosis, the senescence response is critical for suppressing tumorigenesis in complex eukaryotes (Sager, 1991; Campisi, 2001). Thus, genetically engineered mice comprised of cells that cannot undergo a normal senescence response typically die prematurely of cancer (Donehower et al., 1992; Harvey et al., 1993; Ghebranious and Donehower, 1998; Hakem and Mak, 2001). Consistent with its important role in preventing cancer, cellular senescence is controlled by several well-recognized

tumor suppressor genes, including that encoding p53 (Bringold and Serrano, 2000; Campisi, 2001; Itahana et al., 2001). In sharp contrast to apoptosis, however, cellular senescence does not eliminate cells that are dysfunctional, damaged or potentially neoplastic. Rather, the senescence response irreversibly arrests the proliferation of such cells. Thus, cellular senescence renders cells incapable of forming a tumor (by permanently arresting cell growth), but senescent cells may persist in tissues.

Cellular senescence, like apoptosis, has also been implicated in aging. Early ideas proposed that, because senescent cells are incapable of self-renewal, cellular senescence might cause or contribute to aging phenotypes such as immune failure, poor would healing, skin atrophy, the decline gastrointestinal function, and so forth – phenotypes that are presumed to arise owing to a loss of cell proliferative (and hence tissue regenerative) capacity. These ideas arose primarily because the first stimulus that was recognized to cause cellular senescence was repeated cell division (replicative senescence) (Cristofalo and Pignolo, 1993; Campisi et al., 1996; Smith and Pereira-Smith, 1996). Subsequent studies showed that replicative senescence is caused, in large measure, by the progressive shortening of telomeres that occurs with each cell cycle in cells that do not express the enzyme telomerase (Levy et al., 1992; Bodnar et al., 1998; Shay and Wright, 2001). Most mammals do not express telomerase in their somatic cells, although there are some exceptions, and there are species-specific differences in the stringency with which telomerase is repressed in the soma /reviewed in (Campisi, 2001). In species that have relatively short telomeres and stringently regulate telomerase expression (humans, for example), dividing cells eventually acquire one or more critically short and presumably dysfunctional telomere (Chiu and Harley, 1997; Sedivy, 1998; Blackburn, 2000; Weng and Hodes, 2000; Shay and Wright, 2001). Dysfunctional telomeres, which may resemble damaged (broken) DNA in cells, then trigger the irreversible senescence growth arrest. The role of telomeres in triggering the senescence response gave rise to the so-called “telomere hypothesis

of aging", which should really be called the "cellular senescence hypothesis of aging" (Campisi et al., 2001).

In recent years, it has become apparent that telomere dysfunction is but one of many stimuli that can induce a senescence response (Sherr and DePinho, 2000; Campisi, 2001; Serrano and Blasco, 2001) (other inducers were discussed above). These stimuli include direct DNA damage (oxidative lesions, as well as double strand breaks), the expression of certain oncogenes (such as activated RAS or RAF), supraphysiological mitogenic signals, and the disruption of chromatin organization /reviewed in (Howard, 1996; Blackburn, 2000; Campisi, 2000; Serrano and Blasco, 2001; Shay and Wright, 2001). The findings that the senescence response can be induced by many stimuli, not solely repeated cell division and dysfunctional telomeres, suggest that the occurrence of senescent cells *in vivo* need not be confined to highly proliferative tissues or compartments. In addition, these findings suggest that cellular senescence can occur in species that have relatively long telomeres and promiscuous control of telomerase (laboratory mice, for example).

Of perhaps even greater relevance to aging than the inducers of senescence, it is now recognized that the senescence response also results in selected changes in cellular behavior and function. Upon senescence, at least some cell types become resistant to certain apoptotic signals (Wang et al., 1994; Linskens et al., 1995; Seluanov et al., 2001). This resistance to apoptosis may explain why senescent cells can accumulate in tissues with age (Dimri et al., 1995; Pendergrass et al., 1999; Choi et al., 2000; Ding et al., 2001; Paradis et al., 2001). Equally important, senescent cells tend to overexpress secreted molecules, which can act at a distance within tissues and disrupt the local microenvironment. Among the molecules that are secreted by senescent cells are several matrix metalloproteinases and other degradative enzymes, inflammatory cytokines, and certain growth factors (Campisi, 1996; Campisi, 2000; Jennings et al., 2000; Leung and Pereira-Smith, 2001).

The functional changes associated with cellular senescence suggest an additional mechanism by which this process might contribute to aging. As dysfunctional senescent cells accumulate *in vivo* (Dimri et al., 1995; Pendergrass et al., 1999; Choi et al., 2000; Ding et al., 2001; Paradis et al., 2001), their secretory phenotype might lead to disruption of the local tissue microenvironment. This disruption might explain the loss of tissue integrity and function that is a hallmark of aging (Campisi, 1997; Campisi, 2000). Moreover, it might also initiate or promote to certain age-related diseases. For example, atherosclerosis has been proposed to be initiated by the secretions produced by senescent endothelial cells (Chang and Harley, 1995; Vasile et al., 2001). In addition, senescent cells have been proposed to stimulate the progression of cancer (Krtolica et al., 2001), which requires both oncogenic mutations and a disrupted cellular microenvironment in which mutant cells can express their neoplastic phenotype.

3. Tumor suppression and aging

Apoptosis and cellular senescence have at least two features in common: they both are important mechanisms for suppressing tumorigenesis, and they both have the potential, at least in theory, to contribute to aging phenotypes and age-related disease. These dual features suggest the intriguing possibility that both of these cellular processes are examples of antagonistic pleiotropy. That is, while apoptosis and cellular senescence are clearly beneficial in young organisms, they may have unselected deleterious effects late in life, thereby compromising the fitness and contributing to the aging of old organisms.

This idea is illustrated in its simplest form in Figure 1. We presume that the processes of apoptosis and cellular senescence act throughout life (indeed, most likely from embryogenesis), although their regulation and robustness may vary with the age and physiology of the organism, and will certainly vary depending on the tissue. During young adulthood (shaded box), both processes have net positive effects on health and fitness as they eliminate damaged or dysfunctional cells. As damage and time (age) increase, however, cell loss due to apoptosis, or

tissue disruption owing to the presence of senescent cells, may reach threshold levels at which the health of the tissue is compromised. Tissues may differ in how much cell loss or disruption can be tolerated before tissue function declines. The deleterious effects of apoptosis and cellular senescence are proposed to occur relatively late in the life span, during which time the force of natural selection is weak.

Because evolution acts on organisms through genes, it should be possible to identify gene variants that alter the propensity of cells to undergo apoptosis and/or cellular senescence, alter susceptibility to cancer, and also alter aging in at least some tissues. There are, of course, a number of genetic manipulations that alter apoptosis, cellular senescence and cancer susceptibility. However, most manipulations that blunt apoptosis or senescence cause early death due to cancer – that is, the subjects tend to die of cancer before any possible effects on aging can be observed. Very recently, however, a novel mutation was described in the gene encoding murine p53. When present as a single genomic copy, this mutation (mutant p53) appeared to increase the animals' resistance to tumorigenesis. Strikingly, it also accelerated aging in some tissues, and modestly decreased the life span (Tyner et al., 2002). Thus, compared to wild-type animals, heterozygous mutant p53 mice had a 6- to 7-fold lower incidence of spontaneous cancer. However, they also had a 20-30% shorter life span.

The mutant p53 mice often died with no obvious pathology. However, they exhibited premature immune senescence, osteoporosis, skin atrophy, and other selected signs of aging. How might the mutant p53 protein provide super-protection from cancer while accelerating certain aging phenotypes? Wild-type p53 is known to be a tetrameric transcription factor that interacts with many other cellular proteins, and controls the expression of many genes. Among the p53-inducible genes, are several that promote or participate in the apoptotic response. Biochemically, the mutant p53 protein is thought to form hetero-tetramers with wild-type 53, and increase the transactivation activity of the p53 complex. At the cellular level, the mutant p53 protein appeared to sensitize cells to apoptotic stimuli. The greater propensity of cells to

undergo apoptosis might explain both the increased protection from cancer and decreased longevity of the mutant mice. There may, of course, be additional explanations. For example, the mutant p53 protein might also increase the propensity of cells to undergo a senescence arrest, a possibility that has yet to be tested.

If hyper-p53 activity increases tumor suppression and accelerates aging, one might predict that hypo-p53 activity would decrease both tumor suppression and aging (at least in tissues that use p53-mediated apoptosis and senescence to avoid cancer). Indeed, in both mice and humans, p53 deficiency markedly increases the risk of cancer (Donehower et al., 1992; Harvey et al., 1993; Jacks et al., 1994). Unfortunately, cancer is a major cause of death in these organisms, as in many other mammals, and p53-deficient mice (and humans) typically die of cancer prematurely, before signs of retarded aging would be apparent. Therefore, the only way to test the idea that reduced p53 activity can lead to reduced aging (in at least some tissues) is to examine a cohort of p53-deficient mice that do not die of cancer. Lamentably, these mice are very rare. It is intriguing, however, that in humans a polymorphism that predisposes p53 to degradation, and is associated with an increased cancer risk, is as prevalent in centenarians as it is in young subjects (Bonafe et al., 1999). Might subtly reduced p53 levels contribute to the longevity of these centenarians (who presumably resist cancer via other tumor suppressor pathways)?

4. Concluding remarks

The processes of apoptosis and cellular senescence arose early in evolution, most likely to eliminate defective or damaged cells from the germ line and embryos. Both processes (but especially apoptosis) have been shown to occur in largely post-mitotic organisms (such as *Caenorhabditis elegans* and *Drosophila melanogaster*), which do not develop cancer as adults (Ellis et al., 1991; Margolis and Spradling, 1995; Vaux and Korsmeyer, 1999; Meier et al., 2000). As complex organisms with renewable tissues evolved, however, so did the problem of

cancer – the unregulated proliferation of cells that retain the ability to divide and their mutational evolution towards increasingly malignant phenotypes. Apoptosis and cellular senescence appear to have taken on at lease one additional function during the evolution of complex organisms: that of suppressing the development of cancer (Sager, 1991; Reed, 1999; Campisi, 2001; Hakem and Mak, 2001). There is strong evidence to support the idea that apoptosis and cellular senescence are important mechanisms for suppressing tumorigenesis in mammals. However, both processes may also contribute to mammalian aging and certain late-life pathologies. There is incomplete but mounting evidence to support this idea. If correct, it would further suggest that apoptosis and cellular senescence can have antagonistically pleiotropic actions. Clearly, much more work is needed to understand whether and how the tumor suppressive activities of apoptosis and cellular senescence are balanced against aging phenotypes. However, a deeper understanding of these relationships will be essential if we are to develop rational strategies for intervening in aging processes.

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Figure 1. Model for antagonistic pleiotropy of apoptosis and cellular senescence. Apoptosis and cellular senescence occur throughout life (although their regulation and robustness may vary with the age and physiology). During young adulthood (shaded box), as they eliminate damaged or dysfunctional cells, both processes have net positive effects, and thus overall health and fitness are high. As damage and time (age) increase, however, cell loss due to apoptosis, or tissue disruption owing to the presence of senescent cells, may reach threshold levels at which point the health of the tissue may be compromised. Tissues may differ in how much cell loss or disruption can be tolerated before function declines, and thus there may be multiple threshold levels.