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Saturated fatty acid metabolism is key link between cell division, cancer, and senescence in cellular and whole organism aging

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Abstract Cellular senescence is an in vivo and in vitro phenomenon, accompanied by physiological changes including cessation of division and disturbances of organelle structure and function. Review of the literature was undertaken to determine whether there is evidence that whole organism aging and cell senescence share a common initiation pathway. In vivo aged cells of different lineages, including aged T lymphocytes, show high expression of the *INK4A-p16* gene. In cell culture when telomeres are shortened past a key length or state, the *Arf/Ink* gene system (*p16/p14* humans, *p16/p19* mice) switches on and activates *p53,* which suppresses further cell division. The *p53* gene is a key tumor suppressor and its deletion or mutation allows cancerous growth. The switching on of *p53* also causes changes in fatty acid metabolism, especially down-regulation of both *fatty acid synthase* and *stearoyl-CoA* (*delta-9*) *desaturase*. The co-suppression of these genes together with enhanced uptake of extracellular fatty acids, leads to raised levels of cellular palmitate and induction of either apoptosis or senescence. In senescent cells, the fatty acid composition of the cellular membranes alters and leads to changes in both structure and function of organelles, especially mitochondria. Animal models of accelerated aging exhibit repression of *stearoyl-CoA desaturase* activity while anti-aging calorie restriction stimulates the same enzyme system. It is concluded that aging in cells and whole organisms share a common initiation pathway and that cellular senescence is protective against cancer. Healthy longevity is likely to be most enhanced by factors that actively suppress excessive cell division.

Keywords Aging · p53 · Ink4a · Arf · p16 · fasn · Stearoyl-Coenzyme A-desaturase · Stearoyl-CoA-desaturase · Delta-9 desaturase · Telomere · Senescence · Calorie restriction · Palmitate · Palmitic acid · Cancer

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Aging: a balance of senescence and cancer

Aging and the age-related decline in health is one of the most critical problems of modern civilization. Although considerable advances have been made in researching aging, progress in understanding this complex phenomenon is hampered by the volume of research in the different sub-disciplines and the difficulty of cross-discipline communication. This paper attempts to address one of these gaps by bringing together some of the literature from tumor cell biology and whole organism aging. The understanding that the *p53* tumor suppressor gene plays a critical role in the prevention of human cancer (Oren 2003) is fundamental to the argument. It is concluded that changes in the *p53* pathway induced at the

cellular level at the time when cells reach a critical telomere state, and which switch off cell division, also induce permanent changes in fatty acid metabolism. Switching off or reducing the function of the *stearoyl-CoA-desaturase 1* gene underlies changes in cellular membrane fatty acids that affect the structure and function of mitochondria and other organelles. Similar changes in fatty acids are seen in all rodent and human models of aging.

Telomeres, *INK4A-Arf* locus, and the *p53* transcription factor

The observations that normal human fibroblasts have a limited lifespan in culture and that this seemed to be strongly influenced by the age of the donor, led to the Hayflick theory of cellular aging (Hayflick 1976). The maximum lifespan of the culture was known as the Hayflick limit after which senescent cells went into apoptosis (programmed cell death) or senescence. The relationship between donor age and cellular lifespan was later shown to be simplistic (Cristofalo et al. 1998) and it now appears that growth arrest is regulated by telomere state rather than by telomere length per se (Karlseder et al. 2002). However, although telomere regulation is a major inducer of senescence, activated oncogenes, DNA damage, oxidative stress, and inappropriate cell culture conditions can each rapidly induce senescence in cultured cells (Shay and Wright 2001).

In humans, both the *p53* gene and the *RB1* (retinoblastoma) gene monitor telomere function but in mice the *p53* gene seems to be the only gene involved (Smogorzewska and de Lange 2002). The mechanism appears to be similar to other mechanisms that detect DNA damage and clearly involves the ATM (Ataxia telangectasia mutated gene)-*p53* pathway (Takai et al. 2003). When telomeres shorten to a critical point, the *p53* pathway is activated.

The *INK4A-Arf* locus has two gene products, $p16^{Ink4a}$ in both man and mouse and $p14^{Arf}$ in humans and $p19^{Arf}$ in mice. Both *INK* and *Arf* genes are potent tumor suppressors and both play a critical role in regulating the activities of the *RBI* and *p53* genes. *Ink4A/Arf* was shown to be a robust biomarker of aging in mice (Krishnamurthy et al. 2004). Studies of senescence in vivo showed markedly increased expression of the genes in almost all rodent tissues with advancing age while there was little detectable change in other markers. Gene activation was restricted to well-defined areas in different organs but in each organ, cells of different lineage including epithelial and stromal cells were involved.

Further experiments with *BubR1* insufficient mice suggest that the two *INK4A-Arf* genes may play different roles in senescence. When the two genes were separately inactivated, $p16^{Ink4a}$ exacerbated senescence while $p19^{Arf}$ attenuated senescence in skeletal muscle (Baker et al. 2008). The role of $p16^{Ink4a}$ is supported in human studies: expression of $p16^{Ink4a}$ increases sharply in aging human cells and high expression can be detected in peripheral blood T lymphocytes (Liu et al. 2009).

Arf genes activate *p53* and cells move into either senescence (G1 arrest) or apoptosis (Lowe and Sherr 2003). Modulation by the *Arf* genes is complex and experiments using cells taken from mice with modified gene expression suggest that *Arf* acts rather like a circuit breaker that monitors the strength of mitotic signals. Under some circumstances cell division is allowed but where inappropriate oncogenic signals are received, *p53* is induced. Loss of *Arf* or *p53* function overwhelms normal tumor surveillance and genetic deficiencies result in increased susceptibility to cancer.

The p53 gene and tumor suppression

There is considerable evidence that the *p53* gene is a component of the cellular response to DNA damage in mitosis as well as in response to telomere shortening. In either type of situation it causes cell cycle arrest at one of the cell cycle checkpoints (Harris 1996). Since chromosomes with very short telomeres have a strong tendency to both make divisional errors (aneuploidy) and to interchange DNA with other chromosomes causing structural chromosomal changes, the monitoring role reduces the cellular incidence of DNA and chromosomal error. The key role of *p53*, however, appears to be shutting down cell division completely. When a cell undergoes changes that could potentially lead to cancer, *p53* is involved in activating appropriate repair mechanisms or in stimulating the chain of reactions that result in apoptosis or senescence, either of which effectively inhibits the cell from ever replicating again (Oren 2003). It is not surprising

therefore that p53 mutation, deletion and/or suppression, is involved in a very wide range of tumors and that p53 antibodies, mostly to missense mutations, are found in human patients with a wide range of cancers (Soussi 2000).

Palmitic acid: key roles in cell metabolism, cell division, senescence, and apoptosis

p53, fasn, and senescence signaling

The *p53* gene family consists of three genes in vertebrates but in invertebrates only a single gene is present. It is likely that this gene is the most important of the three *p53* genes and its target gene *fasn-1*, fatty acid synthase, is conserved in all organisms from the nematode worm *Caenorhabditis elegans* to humans (D'Erchia et al. 2006). Not only is the gene conserved but the *fasn-1* gene has been shown to have roles in both cellular proliferation and in apoptosis in germ cells. The key reaction product of the *fasn-1* gene is palmitic acid (Smith 1994).

A recent study of fatty acid biosynthesis in senescent cells showed that a profound modification of fatty acid biosynthesis and fatty acid desaturation occurred in the senescence process in cultured human fibroblasts (Maeda et al. 2009). Cells were cultured to 80–90% confluence to induce senescence (G1 arrest) and tested for the expression of senescence associated B-galactosidase. Both *fatty acid synthase* and *stearoyl-CoA-desaturase 1* (also known as *delta 9 desaturase*), the enzyme that converts saturated fatty acids palmitic and stearic to their monosaturated forms palmitoleic and oleic acids (Nakamura and Nara 2004), were markedly decreased in the senescent cells. However, exogenous fatty acids were preferentially incorporated into the triacylglycerol pool leading to relatively high levels of palmitic acid within the pool.

The cytoskeleton associated protein-4 (CKAP4) that links the endoplasmic reticulum to the cytoskeleton is reversibly palmitoylated and phosphorylated (Planey et al. 2009). Palmitoylation (the covalent attachment of palmitic acid to cysteine residues of membrane proteins) of CKAP4 plays a key role in opposing the expression of genes which are otherwise expressed during cell proliferation including tumorigenesis.

The cellular response to *p53* inhibition of *fasn* is either senescence or apoptosis. The experiments of (Baker et al. 2008) suggest that this 'decision' is influenced by slightly different functionality of the two *Arf* genes. However, Chen et al. (2000) found that in H_2O_2-treated human diploid fibroblasts the cellular response depended on the stage of the cycle at the time of *p53* activation. Apoptotic cells were mainly distributed in S phase while growth arrested cells were in G1 or G2/metaphase distributions. Apoptotic cells also exhibited much higher levels of *p53* and reduction of *p53* with human papilloma virus *E6* protein inhibited the activation of *caspase-3* and decreased the number of apoptotic cells. It seems that the determination of whether apoptosis or senescence occurs lies within the interaction between the *Arf* and *p53* genes and the degree of activation of *p53*.

Role of palmitic acid in metabolic regulation, apoptosis, and senescence

It is commonly recognized that saturated fatty acids play a role in debilitating age-related illness such as type-2 diabetes and coronary heart disease but it is less well known that palmitic acid plays a key regulating role in the expression of a large number of genes. Palmitic acid was shown to affect the expression of 162 genes in liver cells (Swagell et al. 2005) but palmitic acid is also a regulator of genes that are not found in the liver nor apparently related to fat metabolism.

Elevated concentrations of palmitic acid are toxic to mitochondria and endoplasmic reticulum and can induce apoptosis without the involvement of reactive oxygen species. This has been demonstrated in many different cell types including cardiomycocytes (Hickson-Bick et al. 2002), hematopoietic cells (Paumen et al. 1997), pancreatic B-cells (Shimabukuro et al. 1998), and astrocytes (Blazquez et al. 2000). Relatively minor changes in palmitate concentration cause dramatic changes. For example incubation of BRIN-BD11 cells with increasing concentrations of palmitate (0.1–0.5 mM) resulted in a dose-dependent loss of cell viability. A 50% rate in cell death occurred between 0 and 0.15 mM and a further 30% cell death between 0.15 and 0.3 mM (Welters et al. 2006). Average palmitate levels in human serum are 0.125±0.04 mM (Richieri and Kleinfeld 1995) indicating that toxic effects could occur within slightly elevated physiological ranges. It is also well established that fatty acid metabolites of cycloxygenase, lipoxygenase, and cytochrome P450

are essential components of programmed cell death (Tang et al. 2002). Thus signaling that increases cellular levels of palmitic acid can induce programmed cell death by more than one mechanism, including the induction of *caspase* (Ulloth et al. 2003).

Senescent cells are permanently growth arrested but are still functional at some level. In vitro induced senescent cells have the same changes in gene expression that are seen with age in human mesenchymal and hematopoietic cells (Wagner et al. 2009). Senescence particularly affects the structure and functions of organelles. Electron microscopic changes are observed in the mitochondria of senescence accelerated OXYS rats (Kolosova et al. 2001) and the fatty acid composition of both mitochondrial and microsomal membranes occur with aging in rats on an ad libitum diet and are modified by lifelong calorie restriction. The fatty acid changes with aging are consistent with reduction in the activity of the *stearoyl-CoA-desaturase* 1 gene and consequent increases in palmitic and stearic acids relative to palmitoleic and oleic acid.

Taken together, data on the fatty acid composition of organelles with aging and changes in the appearance of mitochondria with aging confirm that the reduced activity of *stearoyl-CoA-desaturase 1* is an outcome of *p53* activation that has an ongoing effect on mitochondrial function and cell function (Fig. 1).

Fatty acid metabolism and aging

Changes in fatty acid metabolism, in particular increases in saturated fatty acids and their metabolic products, are characteristic of many age-related human diseases including cardiovascular disease and cancer (Volpe and Vagelos 1976). They also occur in the changes in gray matter that occur with advanced age (McNamara et al. 2008). These diseases are often regarded as lifestyle diseases and although there is little doubt that lifestyle plays a critical role in their etiology, the current findings on the changes in fatty acid metabolism that occur in response to *p53* activation demonstrate that at least some of the changes in fatty acids are critical to survival.

A recent study has shown that changes in fatty acids consistent with the loss of *stearoyl-CoA-desaturase 1 (*delta-9) and delta-5 and 6 desaturase enzymic activity occur in adipose tissue in the mid-30 age group in fertile human females (Ford and Tavendale 2009). Similar dramatic changes in fatty acid synthesis have been shown to occur in mid-life in rats (Murthy et al. 1986) and these parallel the changes in *stearoyl-CoA-desaturase 1* found in the membranes of aging organelles.

Key phenomena of aging and their (possible) relationship to altered fatty acid synthesis

Given that raised levels of saturated fatty acids, especially palmitic acid, occur as a result of *p53* activation and that these fatty acids can cause both apoptosis and the mitochondrial changes seen in senescence, is this consistent with other models of mammalian aging?

Calorie restriction

Calorie restriction is the only factor that has reliably been shown to reduce aging but there is no consensus yet as to how this extends lifespan. In addition to the study on organelle membrane composition, several studies on calorie restriction have examined the effect on fatty acid metabolism. These data show highly significant decreases in the levels of long-chain fatty acids (Ayala et al. 2007). Energy restricted diets in rats specifically stimulate *stearoyl-CoA-desaturase* and effect massive decreases in levels of long-chain fatty acids (Hardy et al. 2002). Similarly, dietary protein and energy restriction in young pigs also induces *stearoyl-CoA-desaturase* (da Costa et al. 2004).

Senescence-accelerated mice

Senescence-accelerated mice (SAM) mice have been used as models of aging. The SAM mice seem to start life with normal development and maturation but due to rapid progression of senescence after maturity, the median survival time of the SAM mice is between 37% and 73% of the corresponding wild-type strains. The degree of senescence at 8 months of age is about 1.5 to 3.5 times normal. One of the SAM strains SAMP8 has been proposed as a possible model for Alzheimer disease (Morley 2002). SAMP8 mice have a marked decrease in *stearoyl-CoA-desaturase* and its mRNA by 10 months of age (Kumar et al. 1999) and

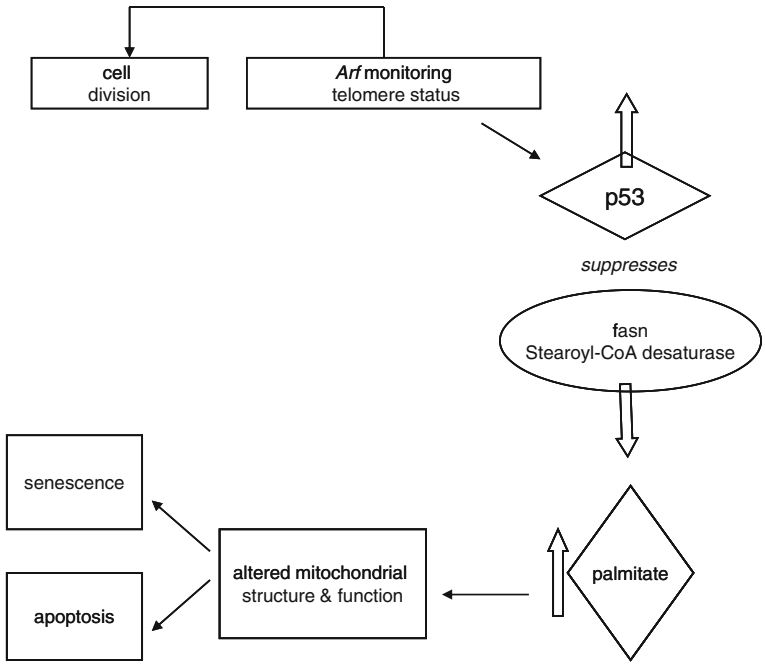

Fig. 1 Key stages of cellular aging include monitoring of cell division by the *ARF/Ink* gene complex. When telomeres reach a certain stage of shortening or function, *Inkp16* signals and *p53* is switched on. Activation of *p53* inhibits the function of *fatty acid synthase (fasn)* and *Stearoyl-CoA desaturase*. This leads to raised cellular levels of palmitate which is taken up by cell membranes and organelles leading to either apoptosis or senescence

it is thought that this may be involved in age-related impairments through its effects on membrane fluidity and cellular signaling pathways.

Human premature aging syndromes

Progeria is the most well known of a small number of premature aging syndromes in humans. Progeria was first described in 1886 and like other rare progeroid syndromes, involves a mutation in a gene whose function is related to DNA repair or metabolism. Some authors have interpreted the involvement of DNA repair dysfunction in these rare syndromes as evidence supporting the reactive oxygen species theory of aging, however the involvement of DNA repair genes is more likely to be involved in the activation of the *p53* system as described above.

Fatty acids have not generally been the subject of research into the advanced-aging syndromes but long-term studies of serum lipids in a girl with progeria (Macnamara et al. 1970) showed extremely elevated levels of serum lipids. Total serum lipids were exceptionally high when the child was fed a diet including animal fat but regardless of diet, lipemia was excessive and there was delayed clearance of fats. This early paper did not define the specific fatty acids.

Mammalian aging, cell division, and fatty acids: implications for prevention of age-related illnesses

As has long been observed, aging is associated with both an increase in the incidence of most cancers and a range of chronic diseases and disability. It is also well known that many of the chronic diseases and disability are associated with fats and fatty acid metabolism. While physicians, physiologists, and epidemiologists have been undertaking considerable work in proving these associations, cell biologists and geneticists have been defining the genes and mechanisms that control the cell cycle and the transitions between the cell cycle and the onset of cancer. The work reviewed in this paper has shown that there is a signaling mechanism that switches on the *p53* gene at the time of critical telomere shortening (or functional limitation) that causes crucial changes in fatty acid metabolism. Synthesis of fatty acids, in particular palmitic acid is shut down but levels of this fatty acid are maintained through the shutting down of the key enzyme *stearoyl-CoA-desaturase* whose role is to convert saturated fatty acids into monosaturated fatty acids. Other *desaturase* enzymes are also affected and these key changes go some way to explaining why fish oil supplementation is of such benefit in a range of age-related chronic illnesses (Yosefy et al. 1999).

Since reaching the point of telomere limitation is key to both the onset of cancer and senescence, it seems most likely that limiting unnecessary cell division is the key to longevity. Presumably, healthy aging will be enhanced by any behavior that reduces unnecessary cell division.

Calorie restriction is the one lifestyle option that is known to increase longevity and decrease age-related diseases. Calorie restriction significantly reduces cell division in vivo (Heller et al. 1990; Lok et al. 1990) but provides robust cellular proliferative responses when appropriate (Apte et al. 2002). There is no doubt that calorie restriction from a young age is greatly beneficial and enhances both longevity and healthy aging: the Japanese Okinawans provide an excellent example of such an outcome (Willcox et al. 2006). A recent study on caloric restriction in elderly humans demonstrates that memory performance can be enhanced by even later life caloric restriction (Witte et al. 2009). This study performed over 3 months in 50 normal to overweight subjects of mean age 60.5 years, showed a significant increase in verbal memory scores after caloric restriction, together with decreases in fasting insulin and high-sensitive C-reactive protein. Controls who ate their normal diet or a diet enhanced with unsaturated fatty acids showed no changes.

The papers reviewed in this paper show that there is evidence linking telomeres, cell division, cancer, and senescence through fatty acid metabolism. To date, changes in fatty acid metabolism have not been regarded as an intrinsic part of the cell division, telomere reduction-senescence pathway. The recognition that not only is fatty acid metabolism critical to this process but that this underlies the initial age-related damage observed in mitochondria, allows us to understand why some interventions, such as supplementation with fish oil, might improve some age-related problems but not others. The model presented that shows how these processes are linked through a series of checkpoints issues a strong warning against stimulation of cell division as a possible anti-aging therapy.

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