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Caveolin-1, cellular senescence and age-related diseases

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Abstract

According to the “free radical theory” of aging, normal aging occurs as the result of tissue damages inflicted by reactive oxygen species (ROS) when ROS production exceeds the antioxidant capacity of the cell. ROS induce cellular dysfunctions such as stress-induced premature senescence (SIPS), which is believed to contribute to normal organismal aging and play a role in age-related diseases. Consistent with this hypothesis, increased oxidative damage of DNA, proteins, and lipids have been reported in aged animals and senescent cells accumulate *in vivo* with advancing age. Caveolin-1 acts as a scaffolding protein that concentrates and functionally regulates signaling molecules. Recently, great progress has been made toward understanding of the role of caveolin-1 in stress-induced premature senescence. Data show that caveolin-mediated signaling may contribute to explain, at the molecular level, how oxidative stress promotes the deleterious effects of cellular senescence such as aging and age-related diseases. In this review, we discuss the cellular mechanisms and functions of caveolin-1 in the context of SIPS and their relevance to the biology of aging.

Keywords

caveolin; senescence; p53; aging; oxidative stress

1. Caveolae and caveolin-1

Caveolae are 50 to 100 nm flask-shaped invaginations of the plasma membrane enriched in cholesterol and glycosphingolipids. Caveolae can exist as individual invaginations or can be found in detached grape-like clusters and long tubular structures derived from the fusion of single caveolae. Caveolin-1 is a structural protein component of caveolae in most cell types (Kurzchalia et al., 1992). Deletion mutagenesis studies show that caveolin-1 contains an oligomerization domain mapping to residues 61-101, which mediates the homo-oligomerization of 14–16 individual caveolin-1 molecules. Consistent with these findings, caveolin-1 forms high-molecular-mass oligomers of 400 kDa, as demonstrated by velocity gradient centrifugation (Monier et al., 1995; Sargiacomo et al., 1995), which are insoluble in cold non-ionic detergents (Kurzchalia et al., 1992).

The “caveolin scaffolding domain” (CSD), which is represented by residues 82-101, mediates direct protein-protein interactions between caveolin-1 and a variety of signaling molecules carrying the caveolin binding domain (CBD : ΦXΦXXXXΦ, ΦXXXXΦXXΦ, or

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ΦXΦXXXXΦXXΦ where Φ represents an aromatic amino acid and X represents any amino acid) (Couet et al., 1997a; Jagannadham et al., 2002; Song et al., 1997). The direct interaction with caveolin-1 generally results in the sequestration of a given signaling molecule within caveolar membranes and modulation of its signaling activity. These signaling proteins include G-protein alpha subunits, H-Ras, Nitric Oxide Synthase (NOS), Epidermal Growth Factor Receptor (EGFR), Src-like Nonreceptor Tyrosine Kinases (NRTK), Protein Kinase C (PKC) and Protein Kinase A (PKA) (Couet et al., 1997b; Feron et al., 1996; Ju et al., 1997; Li et al., 1996; Li et al., 1995; Lisanti et al., 1994; Liu et al., 1997; Mineo et al., 1996; Schnitzer et al., 1995; Segal et al., 1999; Shenoy-Scaria et al., 1994; Smart et al., 1993; Song et al., 1996; Sonnino and Prinetti, 2009). Based simply on their ultrastructural appearance as plasma membrane invaginations, caveolae were originally thought to function as macromolecular transport vesicles (Matveev et al., 2001). Since then, their role has expanded to signal transduction, cellular metabolism, cholesterol homeostasis, endocytosis, tumor promotion and tumor suppression (Galbiati et al., 2001a; Galbiati et al., 2001b; Parton and Richards, 2003; Razani et al., 2000; Watanabe et al., 2009; Williams et al., 2005; Williams and Lisanti, 2004).

2. Reactive oxygen species and aging

Reactive oxygen species are molecules containing the oxygen atom and they are highly reactive due to the presence of unpaired electrons. ROS represent natural byproducts of the normal metabolism of oxygen. They are formed in mitochondria and as intermediates in enzyme reactions as part of normal aerobic life. Oxygen radicals can be overproduced in white blood cells and cells exposed to environmental stresses such as ionizing radiation, UV light, smoking and air pollution. ROS are implicated in a variety of cellular processes, including proliferation, differentiation, host defense and wound repair mechanisms. These cellular responses depend on the amount and/or duration of ROS generation. Excessive production of ROS is usually counteracted by enzymatic antioxidants such as superoxide dismutase, glutathione peroxidase and catalase, and non-enzymatic antioxidants such as vitamin E, vitamin C and glutathione. A redox imbalance occurs when ROS production exceeds the antioxidant capacity of the cell. Elevated levels of ROS can damage macromolecules, including proteins, nucleic acids and lipids (Marnett, 2000; Stadtman and Levine, 2000; Yla-Herttuala, 1999) and lead to cellular dysfunctions such as apoptosis and senescence (Chen and Ames, 1994; Chen et al., 1998; Finkel, 2003; Frippiat et al., 2001; Frippiat et al., 2002; Martindale and Holbrook, 2002).

Aging is a complex phenomenon that is characterized by structural changes and functional deterioration of organs over time. Although it was well-accepted that free radicals were too unstable to exist in biological systems, it was only in the 1950s that researchers started to consider the possibility that free radicals may be linked to the aging process. Denham Harman was the first to propose the “free-radical theory” of aging, where aging *per se* is described as a free radical event (Harman, 1956). According to this theory, reactive oxygen species promote oxidative stress which, in turn, leads to tissue damages and functional dysfunctions which contribute to aging and age-related diseases. In support of this theory, aged animals have been shown to produce higher levels of ROS, compared to younger animals, due to defective mitochondria. In addition, increased oxidative damage of DNA, proteins, and lipids has been reported in aged animals (Chen, 2000).

3. Cellular senescence and aging

Most cells cannot divide indefinitely due to a process termed cellular senescence (Black et al., 2000; Dimri et al., 1995; Kim et al., 1994; Lee et al., 1998; Lundberg et al., 2000; Sherr and DePinho, 2000; Wynford-Thomas, 1999). Cellular senescence is a fundamental feature

of somatic cells, with the exception of most tumor cells and certain stem cells. Cellular senescence was first described in an *in vitro* cell culture study when Hayflick and colleagues observed that human diploid fibroblasts permanently stopped dividing after a finite number of cell divisions, becoming irreversibly arrested in the G1 phase of the cell cycle (Hayflick and Moorhead, 1961). Growth arrest is associated with well-defined biochemical alterations. These include cell cycle arrest, increased p53 activity, increased $p21^{Waf1/Cip1}$ and p16 protein expression, and hypo-phosphorylation of pRb (Black et al., 2000; Dimri et al., 1995; Lundberg et al., 2000; Sherr and DePinho, 2000; Wynford-Thomas, 1999).

Senescent cells remain viable and metabolically active for a long period of time despite their inability to proliferate (Matsumura et al., 1979). This is mainly attributed to the fact that senescent cells no longer respond to external stimuli including both growth factors and apoptotic agents (Cristofalo et al., 1989; Wang, 1995). Such resistance to external stimuli distinguishes them from quiescent cells, which resume proliferation in response to appropriate signals after spending long intervals in a reversibly arrested state. In addition, senescent cells can be experimentally identified by their enlarged and flattened morphology, as well as positive staining for β-galactosidase activity at pH 6 (Dimri et al., 1995).

Cellular senescence is a basic cellular mechanism developed by organisms to prevent the propagation of cells with damaged DNA and potentially carrying oncogenic mutations. Therefore, cellular senescence is considered a powerful tumor suppressor mechanism. However, senescent cells accumulate over time (Dimri et al., 1995; Herbig et al., 2006; Jeyapalan et al., 2007; Kishi, 2004; Melk et al., 2003) and they are believed to contribute to aging and age-related pathologies (Campisi, 1997). In fact, the inability of senescent cells to proliferate contributes to reduced tissue function in aging organs. In addition, senescent cells secreting metalloproteinases and inflammatory cytokines (Linskens et al., 1995; Millis et al., 1992; West et al., 1989) may also play a role in tissue aging by influencing the neighboring tissue microenvironment (Campisi, 1997; Campisi, 2005).

Cellular senescence can be divided into two categories: replicative senescence and stress-induced premature senescence. Replicative senescence is dependent on the number of divisions the cell has completed. This type of senescence is spontaneously achieved by somatic cells. It is now known that the cell division counting is controlled by telomere shortening, an unavoidable consequence of genome duplication (Bodnar et al., 1998; Harley et al., 1990; Kim et al., 1994; Lansdorp, 2000; Martens et al., 2000). Senescence can be accelerated by a number of stressful stimuli, such as oncogene activation, DNA damage, cytotoxic drugs and oxidative stress (Chen et al., 1995; Frippiat et al., 2001; Robles and Adami, 1998; Serrano et al., 1997; Zhu et al., 1998). This type of senescence is referred to as stress induced premature senescence. SIPS is independent of telomere status but shares many molecular and functional features with replicative senescence. Since increased oxidative damage has been reported in aged animals and oxidants can induce premature senescence in cells, understanding the molecular mechanisms that regulate stress-induced premature senescence of eukaryotic cells is therefore fundamental for gaining insight into the aging process. Over the last decade, an increasing number of reports have shown that caveolin-1 plays a major role in controlling cellular senescence. In the following sections, we review the function of caveolin-1 in replicative senescence and stress-induced premature senescence.

4. Caveolin-1 and replicative senescence

Early studies showed that in non-transformed NIH 3T3 cells, caveolin-1 levels are down-regulated in rapidly dividing cells, but dramatically elevated in confluent cells, where caveolin-1 is concentrated at the areas of cell-cell contact (Galbiati et al., 1998). In addition,

overexpression of caveolin-1 in mouse embryonic fibroblasts (MEFs) is sufficient to block these cells in the G0/G1 phase of the cell cycle through modulation of the p53/p21$^{waf1/Cip1}$ pathway (Galbiati et al., 2001c). Since the blockage of cellular proliferation and inhibition of cell cycle progression are two fundamental steps in achieving cellular senescence, these data suggest that caveolin-1 may be involved in mediating cellular senescence. Indeed, MEFs transgenically over-expressing caveolin-1 have a shorter proliferative lifespan when grown in culture as compared to MEFs derived from normal control littermate embryos. In addition, caveolin-1-overexpressing MEFs display a large, flat morphology and express high levels of senescence-associated β-galactosidase activity (Volonte et al., 2002).

The importance of caveolin-1 in replicative senescence was also supported by studies showing that old human diploid fibroblasts express higher levels of caveolin-1 compared to younger cells (Park et al., 2000; Wheaton et al., 2001) and that caveolin-1 expression is increased in replicative senescent mesenchymal stem cells (Park et al., 2005) and bone marrow stromal cells (Sun et al., 2009). In addition, upregulation of caveolin-1 positively correlates with shortening of chondrocyte replicative lifespan after treatment with interleukin (IL)-1β (Yudoh et al., 2009). Consistent with these findings, caveolin-1 expression is upregulated in the lung, spleen and brain of old rats (Kang et al., 2006; Park et al., 2000) and in skeletal muscles of old mice (Oh et al., 2008). In aged mice, the level of caveolin-1 expression in the brain remains controversial. While a report showed increased caveolin-1 expression in hippocampal tissue in aged wild type mice (Gaudreault et al., 2004), a separate study found that loss of caveolin-1 in mice accelerated neurodegeneration and aging phenotypes (Head et al., 2010). In humans, caveolin-1 expression is elevated with age in both smooth muscle and epithelium of the prostate (Herbert et al., 2007) and in elderly cerebral cortex (Kang et al., 2006). Moreover, increased caveolin-1 protein level in the hippocampus and caveolin-1 mRNA in the frontal cortex were described in patients with Alzheimer's disease (Gaudreault et al., 2004).

5. Caveolin-1 and SIPS

Several independent reports, using both cell culture and animal models, have shown that caveolin-1 plays a key role in stress-induced premature senescence. Subcytotoxic level of hydrogen peroxide increases endogenous caveolin-1 expression and induces premature senescence in NIH 3T3 cells (Volonte et al., 2002). Quercetin and vitamin E, two antioxidant agents, successfully prevent the premature senescent phenotype and the up-regulation of caveolin-1 induced by hydrogen peroxide (Volonte et al., 2002). Moreover, premature senescence induced by hydrogen peroxide is greatly inhibited in NIH 3T3 cells harboring antisense caveolin-1 and in mouse embryonic fibroblasts (MEFs) derived from caveolin-1 null mice, which do not express caveolin-1 (Bartholomew et al., 2009; Volonte et al., 2002). Induction of premature senescence by oxidative stress is recovered when caveolin-1 levels are restored (Volonte et al., 2002). Besides sub-lethal hydrogen peroxide, other stressors have been shown to induce premature senescence in cells, including bleomycin and UV light. Bleomycin upregulates caveolin-1 expression and downregulation of caveolin-1 by shRNA inhibits bleomycin-induced premature senescence in A549 human lung adenocarcinoma epithelial cells (Linge et al., 2007). In addition, sub-lethal UV-C light increases caveolin-1 levels and induces premature senescence in fibroblasts (Volonte et al., 2002). Interestingly, downregulation of caveolin-1 by siRNA in IMR-90 human diploid fibroblasts did not inhibit SIPS (Chretien et al., 2008). This data may be explained considering that caveolin-1 was mainly found in the nucleus of IMR-90 cells, in contrast to its usual localization at the plasma membrane and in Triton-insoluble microdomains in the cytoplasm. These observations further support the concept that the caveolin-1-mediated regulation of signaling molecules within caveolar membranes is required for the

development of premature senescence following sub-lethal oxidative stress, as described in details in section 7.

In vivo studies on cigarette smoking-induced pulmonary emphysema, atherosclerosis, osteoarthritis, microbial infections, human intervertebral disc degeneration, wound healing and fibrosis have supported the critical role of caveolin-1 in SIPS and age-related pathologies (Figure 1), as discussed in the following sections.

5.1. Pulmonary Emphysema

Pulmonary emphysema is an age-related lung disease that occurs after a prolonged period of cigarette smoking. Oxidative stress is believed to be a key element in the pathogenesis of emphysema since cigarette smoke is enriched in potent oxidants (MacNee, 2005). Cigarette smoke promotes premature senescence of lung fibroblasts in culture, which can be prevented by the co-treatment with antioxidants (Nyunoya et al., 2006; Volonte et al., 2009). In addition, lung fibroblasts obtained from patients with emphysema have a reduced proliferation rate and an increased senescence-associated β-galactosidase activity (Holz et al., 2004; Muller et al., 2006). Interestingly, evidence shows that cigarette smoke-induced premature senescence of lung fibroblasts is dependent on caveolin-1. In these studies, the number of senescent cells is dramatically reduced in both lung fibroblast cultures derived from caveolin-1 null mice after treatment with cigarette smoke extracts and in caveolin-1 null mice exposed to cigarette smoking for either 6 weeks or 6 months (Volonte et al., 2009). More interestingly, the development of pulmonary emphysema is significantly inhibited in caveolin-1 null mice compared to wild type mice after 6 months of exposure to cigarette smoking (Volonte et al., 2009). Senescent lung fibroblasts in wild type mice were observed as early as 6 weeks after exposure to cigarette smoke while pulmonary emphysema was only morphologically detectable after 6 months of exposure. Since lung fibroblasts provide part of the structural support and matrix of the lung that is essential for its integrity, these results suggest that oxidants contained in cigarette smoke induce premature senescence of lung fibroblasts in a caveolin-1 dependent manner and that senescent lung fibroblasts may contribute to the pathogenesis of pulmonary emphysema by affecting tissue microbalance and the structural maintenance of the lung.

5.2. Atherosclerosis

Cigarette smoking is also a known risk factor for cardiovascular diseases. Smoking has been associated with the development of inflammation and accelerated atherosclerosis as a consequence of prooxidant-antioxidant imbalance. Studies show that endothelial cells isolated from chronic smokers with premature atherosclerosis display senescent features, increased oxidative stress and elevated caveolin-1 expression, as compared to endothelial cells isolated from nonsmokers (Farhat et al., 2008). Consistent with these data, cellular senescence in endothelial cells isolated from patients with severe coronary artery disease is accelerated by oxidative stress associated with risk factors for cardiovascular diseases (Voghel et al., 2007). In these cells, caveolin-1 expression is elevated (Voghel et al., 2007). Thus, these data support the idea that caveolin-1 may link oxidative stress-induced premature senescence to cardiovascular diseases.

5.3. Osteoarthritis

Articular chondrocyte senescence is believed to contribute to the increased incidence of osteoarthritis with increasing age and catabolic stresses such as cytokines and oxidative stress have been shown to mediate the pathogenesis of osteoarthritis (Martin and Buckwalter, 2001). Interestingly, both IL-1β and hydrogen peroxide up-regulate caveolin-1 mRNA and protein expression and induce premature senescence in articular chondrocytes (Dai et al., 2006). Downregulation of caveolin-1 expression with antisense oligonucleotides

significantly prevents the induction of chondrocyte senescence induced by IL-1β and hydrogen peroxide (Dai et al., 2006), suggesting that caveolin-1 may play a role in the pathogenesis of osteoarthritis by mediating chondrocyte senescence.

5.4. Microbial infections

Microbial infections are more likely to occur in elderly individuals. Data show that the entry of Salmonella typhimurium is increased in nonphagocytotic senescent host cells expressing elevated caveolin-1, as compared to nonsenescent host cells with lower caveolin-1 expression (Lim et al., 2010). When caveolin-1 is overexpressed in non-senescent host cells, Salmonella invasion is increased (Lim et al., 2010). In contrast, when caveolin-1 expression in senescent cells is reduced by siRNA, Salmonella invasion is also decreased. In addition, caveolin-1 expression is elevated in Peyer's patch and spleen of aged mice, targets for infection by Salmonellae (Lim et al., 2010). Thus, elevated caveolin-1 expression in senescent host cells may explain the increased susceptibility to microbial infections that occurs with age.

5.5. Intervertebral disc degeneration (IVD)

Chronic low back pain can be due to age-related intervertebral disc degeneration (Luoma et al., 2000). Cellular senescence has been proposed as a possible contributor of IVD degeneration (Gruber et al., 2007; Le Maitre et al., 2007; Roberts et al., 2006). Human cells from the nucleus pulposus (NP) of degenerate discs show evidence of cellular senescence and express high levels of caveolin-1 (Heathfield et al., 2008; Le Maitre et al., 2007). Since upregulation of caveolin-1 is sufficient to induce premature senescence in cells (Galbiati et al., 2001c; Volonte et al., 2002), these findings suggest that caveolin-1-mediated cellular senescence may play a role in the pathogenesis of IVD degeneration.

5.6. Wound healing and fibrosis

Synthesis and deposition of extracellular matrix (ECM), mostly by myofibroblasts, is fundamental to maintain tissue integrity during wound healing. Excessive ECM deposition may lead to fibrosis, scarring and loss of tissue function. Studies show that senescence of myofibroblasts at late stages of wound healing limits the extent of fibrogenesis associated with wound healing. Upon liver injury, hepatic stellate cells are the main sources of myofibroblasts, which initially proliferate and secrete ECM components to support hepatocyte proliferation and organ repair. Then, these cells undergo senescence and secrete several matrix metalloproteinases (MMPs), which degrade ECM proteins and contribute to resolving the fibrotic scar (Krizhanovsky et al., 2008). Consistent with this scenario, when the ability of stellate cells to undergo senescence is compromised in mice (through the genetic deficiency of p53 or $p16^{INK4a}$), severe fibrosis occurs after liver injury (Krizhanovsky et al., 2008). Similarly, during skin wound healing, the initial proliferation of myofibroblasts and deposition of ECM is followed by the secretion of MMPs by myofibroblasts that undergo senescence in a process that is dependent on the matricellular protein CCN1 (Jun and Lau, 2010). Myofibroblasts are converted into anti-fibrotic senescent cells that degrade ECM components later in the skin wound healing process, as shown by excessively fibrotic skin wounds in mice lacking wild type CCN1 (Jun and Lau, 2010). Thus, cellular senescence plays an important role in tissue repair.

Wound healing capacities are compromised in aged organisms. Interestingly, elderly individuals have higher caveolin-1, p53 and $p21^{Waf1/Cip1}$ levels in the corneal epithelial cells than young adults and the time of wound healing after laser epithelial keratomileusis (LASEK) positively correlates with the expression level of caveolin-1 in the cornea, suggesting that elevated caveolin-1 expression may contribute to explain the delayed wound healing in elderly individuals (Rhim et al., 2010). In addition, overexpression of caveolin-1

in corneal epithelial cells inhibited the activation of ERK by EGF, one of the growth factors involved in wound healing processes (Rhim et al., 2010). Consistent with these data, accelerated skin wound healing was reported in caveolin-1 null mice, through a mechanism involving increased nitric oxide production and nitration of MMP-13, whose release from endothelial cells accelerates angiogenesis (Lizarbe et al., 2008). Moreover, downregulation of caveolin-1 occurs during muscle repair in satellite cells/myogenic precursor cells and hepatocyte growth factor, which is produced after muscle injury, downregulates caveolin-1 expression (Volonte et al., 2005). In contrast, overexpression of caveolin-1 inhibits muscle repair mechanisms both in cell culture studies and *in vivo* (Volonte et al., 2005).

Although these data indicate that caveolin-1 is a regulator of tissue repair mechanisms, the precise physiological role of caveolin-1 in tissue repair remains to be fully established. However, one can speculate that an initial downregulation of caveolin-1 expression at the site of damage promotes the growth factor-mediated proliferative and migratory phase, in which cells accumulate at the wound site to initiate repair and replacement. This is followed by a later phase in which increased caveolin-1 expression contributes to the accumulation of senescent cells and limits excessive fibrosis. Consistent with this scenario, an anti-fibrotic potential of caveolin-1 was reported in mice, as shown by inhibition of bleomycin-induced pulmonary fibrosis and TGF-β1-induced ECM production by caveolin-1 gene transfer (Wang et al., 2006). Furthermore, increased matrix deposition and α-smooth muscle actin and redistribution of collagen expression in lung parenchyma was reported in caveolin-1 null mice (Maniatis et al., 2008). Finally, caveolin-1 expression is reduced in lung tissues and in primary pulmonary fibroblasts from idiopathic pulmonary fibrosis patients, compared with controls, a condition characterized by activation of fibroblasts and overproduction of extracellular matrix (Wang et al., 2006), and in the skin and lung samples from patients with systemic sclerosis (SSc) (Castello-Cros et al., 2011). Restoration of caveolin-1 function in skin fibroblasts from SSc patients reverses their pro-fibrotic phenotype while skin from caveolin-1 null mice exhibits many characteristics found in the skin of SSc patients (Castello-Cros et al., 2011). Thus, increased caveolin-1 expression in aged organisms may inhibit the initial proliferative and migratory phase and contribute to explain their compromised wound healing capacities.

Altogether, these findings indicate that caveolin-1 is a critical mediator of premature senescence induced by exogenous stress and that caveolin-1-dependent senescence contributes to oxidant-initiated and age-related pathologies.

6. Signaling upstream of caveolin-1 in cellular senescence

As described above, oxidative stress has been shown to upregulate caveolin-1 protein expression and upregulation of caveolin-1 expression plays a central role in SIPS. What is the molecular mechanism that regulates the oxidant-induced increase of caveolin-1? Studies show that caveolin-1 expression in senescent cells is regulated by p38 mitogen-activated protein kinase (MAPK), Sp1, NF-κB, phosphatidylcholine-specific phospholipase C (PC-PLC) and cyclooxygenase-2 (COX2).

6.1. p38 MAPK-Sp1

Sub-cytotoxic oxidative stress has been shown to stimulate caveolin-1 protein expression through activation of the caveolin-1 gene promoter (Dasari et al., 2006). Functional deletion analysis mapped the oxidative stress response elements of the mouse caveolin-1 promoter to the sequences −244/−222 and −124/−101 (Dasari et al., 2006). The antioxidant quercetin prevents the oxidant-mediated activation of both Cav-1 (−244/−222) and Cav-1 (−124/−101) (Dasari et al., 2006). Using electrophoretic mobility shift studies and chromatin immunoprecipitation analysis, Sp1 was identified as the transcription factor that

mediates the activation of the caveolin-1 promoter after oxidative stress through binding to GC-boxes contained in the Cav-1 (−244/−222) and Cav-1 (−124/−101) sequences (Dasari et al., 2006).

How is the oxidant-initiated and Sp1-mediated transcription of the caveolin-1 gene promoter regulated? Signaling studies demonstrate that the p38 mitogen-activated protein kinase (MAPK) is the upstream regulator of Sp1-mediated activation of the caveolin-1 promoter following oxidative stress. Inhibition of p38 MAPK inhibits the oxidant-induced Sp1-mediated upregulation of caveolin-1 protein expression and development of premature senescence (Dasari et al., 2006). Consistent with these data, the p38 MAPK-mediated upregulation of caveolin-1 and induction of premature senescence after oxidative stress occur in normal human mammary epithelial cells but not in MCF-7 breast cancer cells, which lack caveolin-1 expression (Dasari et al., 2006). These studies detail at the molecular level the oxidant-mediated regulation of caveolin-1 expression and bring new insights into the redox control of cellular senescence in normal and cancer cells. Interestingly, the p38 MAPK-dependent increased phosphorylation of caveolin-1 on tyrosine 14 was demonstrated in IMR-90 human diploid fibroblasts following sub-lethal oxidative stress, suggesting that p38 MAPK regulates caveolin-1 both at the transcriptional and post-translational levels (Chretien et al., 2008).

6.2. NF-κB

Several independent studies have linked NF-κB to aging, including reports of increased NF-κB activity in nuclear extracts derived from a variety of aged tissues such as brain, lungs, kidney, and heart (Gosselin and Abbadie, 2003; Spencer et al., 1997; Toliver-Kinsky et al., 1997). Interestingly, the intronic region of caveolin-1 contains NF-κB consensus sites and data show that LPS activation of endothelial cells increases caveolin-1 protein expression in an NF-κB-dependent manner (Tiruppathi et al., 2008). Since oxidative stress is a known activator of NF-κB, it is possible that the oxidant-induced and NF-κB-mediated transcription of the caveolin-1 gene promoter contributes to caveolin-1-mediated SIPS.

6.3. Phosphatidylcholine-specific phospholipase C

The activity of PC-PLC is dramatically increased and caveolin-1 expression is upregulated during replicative senescence of bone marrow stromal cells (BMSCs) (Sun et al., 2009). Inhibition of PC-PLC activity by the specific inhibitor D609 reduces the upregulation of caveolin-1 expression and the number of replicative senescent BMSCs, suggesting that PC-PLC mediates senescence of BMSCs possibly with a mechanism involving caveolin-1-dependent signaling (Sun et al., 2009). Since senescence of BMSCs greatly limits their use in transplants for the treatment of a variety of diseases, manipulation of caveolin-1 expression in BMSCs may represent an alternative approach to improve the therapeutic use of these cells.

6.4. Cyclooxygenase-2

Pro-inflammatory genes such as COX2 have been proposed to play an important role in the aging process. Data show that NS-398, a selective COX2 inhibitor, prevents the upregulation of caveolin-1 expression and the development of cellular senescence in human dermal fibroblasts (Kim et al., 2008). Since a selective COX2 inhibitor has been shown to prevent the Sp1 proteins from binding to SP1 sites (Wu et al., 2008), inhibition of COX2 may inhibit the caveolin-1-mediated development of premature senescence following oxidative stress by limiting the Sp1-mediated activation of the caveolin-1 promoter.

7. Signaling downstream of caveolin-1 in cellular senescence

Independent investigations have shown that caveolin-1 regulates a variety of signaling pathways in senescent cells, such as the p53/p21$^{Waf\text{-}1/Cip1}$, epidermal growth factor receptor (EGFR), focal adhesion kinase (FAK) and small Rho GTPase pathways.

7.1. Regulation of the p53 pathway by caveolin-1 in stress-induced premature senescence

The p53 tumor suppressor protein becomes functionally active in response to stress signals and promotes a transient cell cycle arrest, apoptosis or cellular senescence. In most cell types, activation of p53 is fundamental for initiating the senescence response following exogenous stress. p53 action has been linked to the aging process. Mouse models of gain of p53 function show increased tumor suppression but decreased longevity and early aging phenotypes (Maier et al., 2004; Tyner et al., 2002). Interestingly, data from mouse models of accelerated aging demonstrate that the harmful effects of p53 on aging are not attributable only to the p53 gene but involve also the NAD^+-dependent deacetylase SIRT1 (Ungewitter and Scrable, 2009), suggesting that genes that have modifying effects on p53 activity but evolve independently may contribute to the deleterious actions of p53 late in life.

The activity of p53 is highly regulated by phosphorylation, protein-protein interactions and protein stability. Since overexpression of caveolin-1 is sufficient to induce premature senescence and activate the p53 pathway (Galbiati et al., 2001c; Volonte et al., 2002), investigations have focused on determining the molecular mechanisms underlying the caveolin-1-mediated activation of p53 in the context of SIPS. In the following sections, we review findings showing that caveolin-1 activates p53 during SIPS by modulating molecules that regulate p53 signaling, such as Mdm2, thioredoxin reductase 1 (TrxR1) and ataxia telangiectasia-mutated (ATM).

7.1.1. Regulation of Mdm2 by caveolin-1 in SIPS—Mdm2 is a negative regulator of p53. p53 is a target of the E3 ubiquitin ligase activity of Mdm2, resulting in proteosomal degradation of p53 (Kubbutat et al., 1997). Mdm2 also suppresses p53 transcriptional activity and shuttles p53 out of the nucleus (Momand et al., 1992). As mentioned earlier, caveolin-1 binds to signaling molecules through a direct interaction between the caveolin scaffolding domain of caveolin-1 (residues 82-101) and caveolin binding motifs of signaling molecules. Caveolin binding motifs include crucial aromatic amino acid residues that are separated by a variable number of X residues (Couet et al., 1997a). GST pull down experiments demonstrate that caveolin-1 is a novel binding protein for Mdm2 and that both mouse and human Mdm2 have a caveolin binding motif between amino acids 48 and 60 (Bartholomew et al., 2009). Following oxidative stress, Mdm2 is sequestered by caveolin-1 into caveolar membranes, away from p53, in WI-38 human diploid fibroblasts (Bartholomew et al., 2009). Thus, by binding to Mdm2, caveolin-1 limits the interaction between p53 and Mdm2. This is consistent with the observation that the caveolin-1 binding motif of Mdm2 overlaps with the p53 binding domain of Mdm2 (amino acids 23-108). Data show that the oxidant-induced sequestration of Mdm2 by caveolin-1 leads to stabilization of p53, upregulation of p21$^{Waf1/Cip1}$, a p53 downstream target that is responsible for cell-cycle arrest, and induction of premature senescence in WI-38 cells and mouse embryonic fibroblasts (Bartholomew et al., 2009). Stabilization of p53, upregulation of p21$^{Waf1/Cip1}$ and induction of premature senescence following oxidative stress is dramatically inhibited in MEFs derived from caveolin-1 null mice, which do not express caveolin-1 (Bartholomew et al., 2009) and in bleomycin-treated A549 cells in which caveolin-1 expression is downregulated by shRNA (Linge et al., 2007). Together, these findings show that, under conditions of oxidative stress that induce premature senescence, caveolin-1 positively regulates p53 function by preventing the negative action of Mdm2 on p53.

7.1.2. Regulation of TrxR1 by caveolin-1 in SIPS—In cells, excessive production of ROS is usually counteracted by antioxidants, including the thioredoxin-thioredoxin reductase system. Thioredoxin reductase 1 is an essential antioxidant enzyme (Behne and Kyriakopoulos, 2001) that reduces thioredoxin by using nicotinamide adenine dinucleotide phosphate (Mustacich and Powis, 2000). By using a proteomic-based approach, TrxR1 was identified as a caveolar membrane-resident protein (Volonte and Galbiati, 2009). *In vitro* experiments show that the caveolin scaffolding domain of caveolin-1 directly interacts with the caveolin binding motif (amino acids 454-463) of TrxR1 (Volonte and Galbiati, 2009). Data demonstrate that caveolin-1 is a novel endogenous inhibitor of TrxR1. In fact, overexpression of caveolin-1 inhibits TrxR activity, whereas a lack of caveolin-1 activates TrxR, both *in vitro* and *in vivo* (Volonte and Galbiati, 2009). Since oxidants can activate p53 and induce premature senescence and TrxR1 is an antioxidant enzyme, what is the functional significance of the inhibition of TrxR1 by caveolin-1 in the context of activation of p53 and SIPS? Data show that oxidative stress fails to activate the p53/$p21^{Waf1/Cip1}$ pathway and induce premature senescence in cells expressing a mutant form of TrxR1 that cannot bind to caveolin-1 and is constitutively active (Volonte and Galbiati, 2009). Evidence indicates that p53 is a redox-dependent transcription factor and that the expression and activity of p53 are regulated by the TrxR system. In fact, downregulation of TrxR expression increases p53 messenger RNA (Gan et al., 2005) and protein levels, and enhances the DNA-binding activity of p53 (Seemann and Hainaut, 2005). Thus, through inhibition of TrxR1 after oxidative stress, caveolin-1 stimulates p53-dependent signaling and promotes SIPS.

7.1.3. Regulation of ATM by caveolin-1 in SIPS—The ATM protein kinase is a key regulator of the p53 pathway in response to genotoxic stress. Reactive oxygen species have been shown to activate ATM (Shackelford et al., 2001) and p53 in an ATM-dependent manner in different cell types (Chen et al., 2003; Moiseeva et al., 2006). Activation of ATM occurs when oxidative stress promotes autophosphorylation of multimeric ATM at serine 1981, which dissociates into active monomers and then rapidly phosphorylates and activates numerous substrates, including p53 (Bakkenist and Kastan, 2003). Caveolin-1 was found to be a novel activator of ATM, as shown by reduced activation of ATM in cells lacking caveolin-1 (Volonte et al., 2009). How does caveolin-1 activate ATM? Protein phosphatase 2A (PP2A) belongs to the conserved phosphoprotein phosphatase family of serine/threonine protein phosphatases, which regulates a variety of cellular processes (reviewed in (Cohen, 2002; Honkanen and Golden, 2002)). PP2A is a holoenzyme composed of a catalytic C subunit (PP2A-C), a scaffolding A subunit (PP2A-A), and a regulatory B subunit (PP2A-B). PP2A is a negative regulator of ATM autophosphorylation and activity *in vivo* (Goodarzi et al., 2004). Data show that by sequestering the ATM inhibitor PP2A-C into caveolar membranes after oxidative stress, caveolin-1 activates the ATM-p53-$p21^{Waf1/Cip1}$ pathway and induces premature senescence in fibroblasts (Volonte et al., 2009). Thus, a novel signaling pathway exists that links oxidative stress to caveolin-1-mediated activation of ATM, which in turns leads to activation of p53, up-regulation of $p21^{Waf1/Cip1}$ and induction of premature senescence of fibroblasts (Volonte et al., 2009).

7.2. Regulation of EGF signaling by caveolin-1 in replicative cellular senescence

Response to growth factors such as epidermal growth factor is defective in senescent human diploid fibroblasts. Data show a correlation between increased caveolin-1 expression and reduced phosphorylation of ERK-1/2 after EGF stimulation in replicative senescent fibroblasts (Park et al., 2000). In addition, senescent diploid fibroblasts show a strong interaction between caveolin-1 and EGF receptor and overexpression of caveolin-1 in young human diploid fibroblasts suppress activation of ERK-1/2 upon EGF treatment.

Interestingly, the caveolin-1 status seems to be critical in maintaining the replicative senescence phenotype. Down-regulation of caveolin-1 restores normal growth factor responses of aging cells that are in a replicative senescent state, as shown by increased phosphorylation of ERK-1/2, nuclear translocation of p-ERK-1/2 and activation of p-Elk following stimulation with EGF (Cho et al., 2003). Moreover, DNA synthesis, re-entry of senescent cells into the cell cycle and downregulation of p53 and $p21^{Waf1/Cip1}$ occurred upon EGF stimulation in cells in which caveolin-1 was downregulated (Cho et al., 2003).

7.3. Regulation of focal adhesion kinase and small Rho GTPases by caveolin-1 in replicative cellular senescence

Because senescent cells have a large and flat shape, morphological changes contribute to the development of the senescent phenotype. Focal adhesion complexes and small GTPases play an important role in the determination of cell structure. Phosphorylation of FAK is increased in senescent human diploid fibroblasts (HDFs). Downregulation of caveolin-1 in replicative senescent human diploid fibroblasts results in reduced phosphorylation of FAK (Cho et al., 2004), which is consistent with data showing reduced FAK activity by downregulation of caveolin-1 (Teixeira et al., 1999). The formation of focal adhesion and actin stress fibers was reduced in caveolin-1 siRNA-transfected senescent cells via the caveolin-1-mediated inactivation of FAK (Cho et al., 2004). Moreover, the Rho family GTPases Rac1 and Cdc42 are localized to caveolar membranes and interact with caveolin-1 in replicative senescent human diploid fibroblasts. Since senescent HDFs display elevated Rac1 and Cdc42 GTPase activity, these results suggest that caveolin-1, through the activation of Rho GTPases, may contribute to cytoskeletal reorganization. Interestingly, downregulation of caveolin-1 in senescent HDFs results in morphological adjustment to a young cell-like shape (Cho et al., 2004). Together, these results suggest that caveolin-1 is a key regulator of the morphological changes that occur in senescent cells.

8. Oxidative stress, caveolin-1 and the tumor microenvironment

Cancer is considered an age-associated disease. The tumor microenvironment plays a central role in tumorigenesis in many types of human cancers (Bissell and Radisky, 2001). Within the tumor microenvironment, cancer-associated fibroblasts (CAFs) are believed to contribute to the outcome of human cancers, including breast cancer. Lisanti and colleagues have recently proposed the “The Reverse Warburg Effect” to explain tumor growth and progression (Pavlides et al., 2009). According to this model, aerobic glycolysis takes place in cancer-associated fibroblasts and not in cancer cells. Data show that cancer cells induce oxidative stress in the adjacent fibroblasts, which leads to the activation of NF-κB and HIF1α, transcription factors involved in inflammation and aerobic glycolysis, respectively (Martinez-Outschoorn et al., 2010a; Martinez-Outschoorn et al., 2010b). Their combined effect drives autophagy in the tumor stroma (Martinez-Outschoorn et al., 2011), which results in the production of high energy nutrients and the stimulation of oxidative mitochondrial metabolism in cancer cells. As a result, the increased production of ATP in cancer cells drives tumor growth and metastasis.

A loss of caveolin-1 was recently identified as a marker of the cancer-associated fibroblast phenotype. In fact, downregulation of caveolin-1 expression was found in CAFs from 8 out of 11 breast cancer patients (Mercier et al., 2008). In addition, a loss of stromal caveolin-1 is a predictor of tumor recurrence, lymph node metastasis, resistance to tamoxifen and poor clinical outcome in human breast cancer patients (Witkiewicz et al., 2009). Proteomic analysis in stromal cells demonstrates that a loss of caveolin-1 is associated with oxidative stress, as shown by increased expression of catalase and peroxiredoxin1, two markers of oxidative stress (Pavlides et al., 2009). Data show that a loss of stromal caveolin-1 in a co-culture system is prevented by the treatment with antioxidants, autophagy inhibitors and

HIF1 and NF-κB inhibitors (Martinez-Outschoorn et al., 2010b). Thus, a loss of stromal caveolin-1 was proposed as a biomarker for "The reverse Warburg Effect".

Based on "The Reverse Warburg Effect", the downregulation of caveolin-1 expression reported in breast cancer-associated fibroblasts (Mercier et al., 2008) is the consequence of ROS production induced by cancer cells. This is in contrast to the upregulation of endogenous caveolin-1 expression that occurs during SIPS in cell culture models and *in vivo*. However, downregulation of caveolin-1 in CAFs occurs at the protein level but not at the transcriptional level. In fact, caveolin-1 transcript levels in CAFs are actually increased ~2.4-fold (Mercier et al., 2008), which is consistent with the ~2.0-fold activation of the caveolin-1 promoter after treatment with sublethal concentrations of hydrogen-peroxide that induce premature senescence in fibroblasts (Volonte et al., 2002). These data suggest that a similar signaling pathway links oxidative stress to the activation of the caveolin-1 gene promoter in both CAFs and "normal" fibroblasts. In contrast, in CAFs exists a unique ROS-mediated signaling, which is responsible for the post-transcriptional and/or post-translational downregualtion of caveolin-1 that overtakes the activation of the caveolin-1 promoter induced by oxidative stress. Alternatively, there may be a qualitative difference in the type of ROS that are found in the tumor microenvironment as compared to those that accumulate in "non-tumor" stromal cells with aging, which could explain the different overall effect of oxidative stress on caveolin-1 expression in the two types of stromal fibroblasts.

Together, these data show that the oxidant-induced downregulation of caveolin-1 in "non-senescent" CAFs is protumorigenic. Interestingly, data show that senescent fibroblasts release factors that stimulate the growth of breast cancer cells, in cell culture studies and *in vivo*, in a caveolin-1-dependent manner (Bartholomew et al., 2009). Thus, the oxidant-induced upregulation of caveolin-1 in "senescent" fibroblasts is tumorigenic, which is consistent with data showing that senescent fibroblasts secreting metalloproteinases, growth factors, and inflammatory cytokines may stimulate the proliferation of cells that harbor pre- and/or neoplastic mutations (Linskens et al., 1995; Maier et al., 1990; Millis et al., 1992; West et al., 1989). These two scenarios may not be mutually exclusive. We speculate that senescent stromal fibroblasts, which accumulate overtime through the ROS-mediated upregulation of caveolin-1, may contribute, to a certain extent, to the initiation and/or progression of tumorigenesis together with CAFs in which cancer cell-derived oxidative stress leads to down-regulation of caveolin-1. Further studies are necessary to demonstrate the co-existence of caveolin-1-positive senescent cells and caveolin-1-negative non-senescent CAFs, both of which have protumorigenic properties, within the same tumor microenvironment. Alternatively, the two cell types may be present within the same tumor microenvironment but the timing of their presence may be different, with senescent caveolin-1-positive stromal cells being expressed in the early phases of tumorigenesis, as data show that senescent cells accumulate in benign and preneoplastic hyperproliferative lesions in prostate and liver (reviewed in (Krtolica and Campisi, 2002)).

9. Conclusive remarks

Data suggest that cellular senescence contributes to aging and age-related pathologies. This is a deleterious effect due to accumulation of senescent cells in tissues over time. However, cellular senescence represents a natural tumor suppressor mechanism. In fact, cancer cells need to escape the barrier represented by cellular senescence in order to produce a clinically relevant tumor mass. Thus, a delicate balance exists between the positive effects of cellular senescence on tumor suppression and the negative effects of cellular senescence on aging and age-related diseases. Over the last 5–10 years, there has been mounting evidence that caveolin-1 is a central contributor of the signaling events that lead to senescence of eukaryotic cells in response to external stimuli (Figure 2). Through its ability to regulate

Mdm2, TrxR1 and ATM, caveolin-1 activates p53. The caveolin-1-mediated activation of p53 in combination with the caveolin-1-mediated modulation of EGF-, focal adhesion- and small Rho GTPase-dependent signaling promote cellular senescence. This is a potential beneficial effect if it takes place in cancer cells or cells with potentially carcinogenic lesions in the DNA because it would prevent the uncontrolled cellular proliferation that leads to tumor formation. In contrast, if caveolin-1-mediated premature senescence occurs in non-carcinogenic somatic cells, it represents a detrimental effect that may lead to aging and age-related diseases, including cancer given the ability of senescent cells to stimulate tumorigenesis. In the case of “non-senescent” cancer-associated fibroblasts, it is the downregulation of caveolin-1 expression that has been linked to tumorigenesis. Thus, caveolin-1 represents a signaling molecule whose function may control the fine balance between the positive and negative effects of cellular senescence. Further studies will help us understand as to how exactly this balance is regulated by caveolin-1 and whether targeted caveolin-1-mediated therapeutic interventions can enhance tumor suppression without accelerating aging and age-related phenotypes or slow down the aging process without necessarily promoting tumor initiation and/or progression.

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Highlights

- Oxidative stress upregulates caveolin-1 protein expression
- Caveolin-1 activates the p53/p21$^{Waf1/Cip1}$ pathway
- Caveolin-1 expression is required for stress-induced premature senescence
- Caveolin-1 mediates age-related diseases *in vivo*

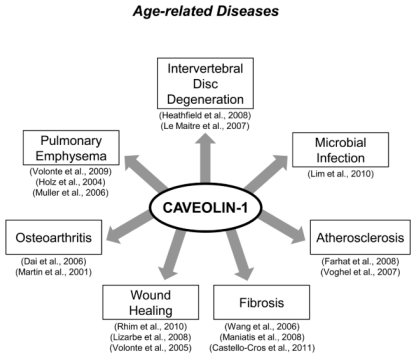

Figure 1. Caveolin-1 and age-related diseases

In vivo studies have shown a critical role of caveolin-1 in SIPS and age-related pathologies, such as cigarette smoking-induced pulmonary emphysema, atherosclerosis, osteoarthritis, microbial infections, human intervertebral disc degeneration, wound healing and fibrosis.

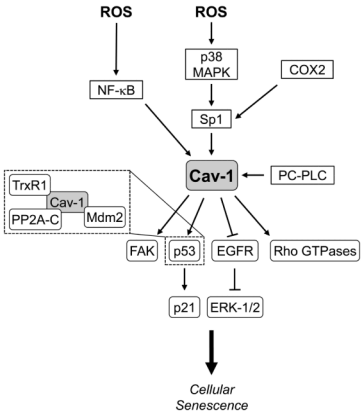

Figure 2. Caveolin-1, a pivotal regulator of cellular senescence

After oxidative stress, the caveolin-1 gene promoter is activated through p38 MAPK-Sp1-dependent and NF-κB-dependent pathways. COX2 and PC-PLC also regulates caveolin-1 expression. Upregulation of caveolin-1 promotes cellular senescence by activating the p53/$p21^{Waf1/Cip1}$, focal adhesion kinase (FAK), and small GTPases pathways and by inhibiting the EGFR/ERK-1/2 pathway. Activation of p53 by caveolin-1 occurs through different mechanisms: 1) interaction of caveolin-1 with Mdm2 prevents the Mdm2-dependent degradation of p53; 2) inhibition of TrxR1 through direct interaction with caveolin-1 activates p53; 3) sequestration of PP2A-C into caveolar membranes activates ATM, which in turns phosphorylates and activates p53. Activation of p53 leads to upregulation of $p21^{Waf1/Cip1}$ and induction of cellular senescence.