Lipids as Regulators of Cellular Senescence

Shruthi Hamsanathan¹ and Aditi U. Gurkar¹,²,³*

¹Aging Institute of UPMC, The University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, ²Division of Geriatric Medicine, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, ³Geriatric Research, Education and Clinical Center, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, PA, United States

Lipids are key macromolecules that perform a multitude of biological functions ranging from maintaining structural integrity of membranes, energy storage, to signaling molecules. Unsurprisingly, variations in lipid composition and its levels can influence the functional and physiological state of the cell and its milieu. Cellular senescence is a permanent state of cell cycle arrest and is a hallmark of the aging process, as well as several age-related pathologies. Senescent cells are often characterized by alterations in morphology, metabolism, chromatin remodeling and exhibit a complex pro-inflammatory secretome (SASP). Recent studies have shown that the regulation of specific lipid species play a critical role in senescence. Indeed, some lipid species even contribute to the low-grade inflammation associated with SASP. Many protein regulators of senescence have been well characterized and are associated with lipid metabolism. However, the link between critical regulators of cellular senescence and senescence-associated lipid changes is yet to be elucidated. Here we systematically review the current knowledge on lipid metabolism and dynamics of cellular lipid content during senescence. We focus on the roles of major players of senescence in regulating lipid metabolism. Finally, we explore the future prospects of lipid research in senescence and its potential to be targeted as senotherapeutics.

Keywords: cellular senescence, lipids, aging, bioactive lipids, senolytics

INTRODUCTION

Senescence is a cell-fate decision that is triggered in response to many different stressors including genotoxic stress, telomere attrition/damage, oncogene activation, and mitochondrial dysfunction (Herranz and Gil, 2018). In contrast to quiescence (cell cycle arrest), cellular senescence is a terminal state of growth arrest, where cells cannot re-enter the cell cycle despite mitogenic growth signals (Pack et al., 2019). Senescent cells resist apoptosis, at least partially due to an upregulation of survival pathways such as the BCL-2 family (Zhu et al., 2015; Yosef et al., 2016). Cellular senescence has been documented to have both beneficial and detrimental roles in maintaining health (He and Sharpless, 2017), and has been linked to embryonic development, wound healing, tumor suppression, as well as metastasis and aging. “Acute” senescence is a programmed cell-fate decision and is usually associated with tissue repair and homeostasis (Krizhanovsky et al., 2008; Jun and Lau, 2010; Rajagopalan and Long, 2012). In contrast, “chronic” senescence is associated with stochastic, persistent macromolecular damage and often associated with disease and aging (van Deursen, 2014). The permanent cell-cycle arrest of senescent cells is accompanied by a senescence associated secretory program (SASP). The SASP consists of pro-inflammatory factors such as cytokines, chemokines and extracellular matrix remodeling factors.
IDENTIFICATION OF SENESCENT CELLS

The field is challenged by the lack of a single universal marker for cellular senescence. Currently, senescent cells are identified based on multiple markers (Figure 1), that allow for distinction between quiescent and senescent cells. The most prominent features of senescent cells include, an enlarged, flat cell morphology with an increase in the cytoplasm-to-nucleus ratio. A recent study suggested that the ratio of DNA to cytoplasm is critical to maintain cell function, and dysregulation of this ratio possibly contributes toward aging (Neurohr et al., 2019). Senescent cells also display an increase in the lysosomal enzyme, senescence-associated-β-galactosidase (SA-β-gal), and thus display increased SA-β-gal activity (Dimri et al., 1995; Hall et al., 2017). Single cell analysis, identified that cells with high SA-β-gal activity also exhibit larger cell size (Biran et al., 2017). It is important to note that SA-β-gal is often associated with senescent cells, but can be observed upon serum starvation or upon confluency in cell culture. Another feature of senescent cells is the accumulation of pigment granules in the lysosomes known as lipofuscin (Evangelou et al., 2017). However, lipofuscin accumulation is observed with age in many cells and organisms, including those that do not typically have other features of cellular senescence, e.g., C. elegans (Pincus et al., 2016). Lack of DNA replication and arrest of the cell cycle usually in G0/G1 phase are features of senescent cells, but do not distinguish between quiescence and senescence.

The two key signaling pathways upregulated for establishment and maintenance of senescence are p53/p21 and p16 (discussed in detail below). The burden of p21- and p16- positive expressing cells increases with age in mammals, however, currently the understanding of what percentage of cells are senescent is incomplete. A recent cross-sectional study in humans, examining three different age groups and multiple tissues, identified that p21- and p16-positive cells increase with age in the skin, pancreas and kidney (Idda et al., 2020). In contrast, p16-positive cells are observed in brain cortex, liver, spleen, and intestine (colon), whereas p21-positive cells increase in the dermis with age. Interestingly, some tissues, such as lung and muscle did not show any changes in these markers. Although a comprehensive study, it is important to note that this study was cross-sectional in design, as well as underlying health conditions may not have been fully examined. Nonetheless, a conclusion to be drawn from this study is that different cells and tissues accumulate different markers of senescence and may display varying burden of senescent cells.

Dynamic chromatin changes are a hallmark of senescent cells. Senescence-associated heterochromatin foci (SAHF) and telomere-associated foci (TAFs) are commonly used as markers for cellular senescence. However, these heterochromatin changes have been associated with senescence caused by nuclear DNA damage or telomere dysfunction, rather than other senescence-inducing stressors (Di Micco et al., 2011). A common chromatin feature in senescent cells is the generation of chromatin fragments that are released into the cytoplasm. The loss of nuclear lamina (Lamin B1) is observed in senescent cells, leading to “leaky” nucleus, and is thought to promote chromatin fragments (CCFs) in the cytoplasm (Di Micco et al., 2011; Dou et al., 2015, 2017). The CCFs activate the cyclic GMP–AMP synthase (cGAS) and the stimulator of interferon genes (STING) pathway (cGAS-STING pathway) and further establish SASP factors (Vizioli et al., 2020), thus reinforcing senescence and affecting neighboring cells.

Last but not least, an integral part of senescent cells is their ability to drive the SASP phenotype. SASP consist of pro-inflammatory cytokines [interleukin (IL)-1α, IL-1β, IL-6, and IL-8], chemokines (CCL2), and extracellular matrix remodeling factors such as matrix metalloproteinases (MMPs), serine/cysteine proteinase inhibitors (SERPINs) such as plasminogen activator inhibitor-1 (PAI-1) and tissue inhibitors of metalloproteinases (TIMPs) (Coppe et al., 2010; Eren et al., 2014). With advances in technology, recent studies have uncovered that different senescence-inducing stressors, as well as different cell types may lead to unique SASP being expressed (Basisty et al., 2020). SASP is thought to be transcriptionally controlled and released into the cytoplasm, as soluble factors or in exosomes (Lehmann et al., 2008; Ozcan et al., 2016; Takahashi et al., 2017), to influence neighboring cells (Ito et al., 2017). Understanding of SASP regulation is incomplete, although, p53, NF-κB, P38 MAPK, NOTCH, mTOR, and mitochondrial NAD+/NADH ratio have recently emerged as modulators of the SASP phenotype (Freund et al., 2011; Herranz et al., 2015; Nacarelli et al., 2019).

In this Review, we first describe the rewiring of lipid metabolism during cellular senescence. This review mostly focuses on cellular senescence observed with aging. We then review the link between major regulators of senescence and their role in lipid metabolism. Lastly, we discuss lipid classes that are altered in senescent cells and how they contribute to the senescence phenotype and outline tools that can help examine the causal role of lipids in driving cellular senescence.

METABOLIC LANDSCAPE OF SENESCENT CELLS

Aging is associated with dysregulated lipid metabolism (Mutlu et al., 2021). Several studies show that lipid composition changes with age in several species, including humans. Particularly, increased ratio of poly- and mono- unsaturated fatty acids have been recently found to be increased with age (Papsdorf and Brunet, 2019). However, whether cellular senescence, a key feature of aging is responsible for these lipid changes has been enigmatic so far. Lipids are an important fuel source that generate energy, as well as create crucial biological intermediates including lipid mediators, second messengers, and ketone bodies. Lipids can act as central metabolites that play a role in cellular signaling, both in an autocrine and paracrine manner, provide cell and organelle structure, and are fundamental for maintaining cellular homeostasis. Recent studies highlight the role of lipids in establishing cell fate decisions, such as cell division, apoptosis and cellular senescence (Ito and Ito, 2016). As described above, hallmarks of cellular senescence consists of increased mass of organelles such as, lysosomes and mitochondria, increased cellular size, loss of nuclear membrane integrity and SASP.
induction of late-stage senescence, and is increased with age in (Fafian-Labora et al., 2019). FASN is upregulated prior to on FASN, during initial establishment of cellular senescence fibroblasts showed an increase in lipid biosynthesis, dependent this theory, mouse hepatic stellate cells and human primary (Kim et al., 2010; Correia-Melo et al., 2016). Consistent with are key hallmarks of senescence, and rely on lipid biosynthesis membranous organelles such as, lysosomes and mitochondria dependent manner. Enlargement of cells and accumulation of senescence is possibly regulated in a context- and stress-Although understudied, the role of FA biosynthesis in cellular acetyl-CoA carboxylase (ACCase) and fatty acid synthase (FAS). of malonyl-CoA to an acyl chain by one of two enzymes: an energy source. Fatty acids are synthesized by the addition to acetylation of histones and other proteins. Indeed, recent data blocks for triglycerides (TGs) and phospholipids, and act as an energy source. Fatty acids are synthesized by the addition of malonyl-CoA to an acyl chain by one of two enzymes: acetyl-CoA carboxylase (ACCase) and fatty acid synthase (FAS). Although understudied, the role of FA biosynthesis in cellular senescence is possibly regulated in a context- and stress-dependent manner. Enlargement of cells and accumulation of membranous organelles such as, lysosomes and mitochondria are key hallmarks of senescence, and rely on lipid biosynthesis (Kim et al., 2010; Correia-Melo et al., 2016). Consistent with this theory, mouse hepatic stellate cells and human primary fibroblasts showed an increase in lipid biosynthesis, dependent on FASN, during initial establishment of cellular senescence (Fafian-Labora et al., 2019). FASN is upregulated prior to induction of late-stage senescence, and is increased with age in mouse liver. Interestingly, pharmacological or genetic inhibition of FASN, reduced p53-induced senescence, as well as, SASP (Borghesan et al., 2019; Fafian-Labora et al., 2019). Whether FASN is required for maintenance of cellular senescence and upregulated in a p53-independent manner is currently unknown. Oncogene-induced senescence (OIS) is a robust mechanism activated by oncogenic signaling due to an activating mutation of an oncogene or an inactivation of a tumor suppressor. Targeted metabolomic and bioenergetic analysis revealed that different modalities of senescence such as OIS and replicative senescence, led to very different metabolite patterns. In this study, Ras-induced OIS elevated levels of long chain free fatty acids (LCFA). Concomitantly, OIS reduced lipid biosynthesis by negatively regulating ACC, a rate limiting step for lipid biosynthesis (Quijano et al., 2012). It is important to note that these contradictory results about the role of lipid biosynthesis in senescence may be due to analyzing a different “stage” of cellular senescence, or different stress modality of senescence (aging versus OIS) or because of differences in cell-type (primary cells versus cancer cells).

Although the role of lipid biosynthesis in cellular senescence may not be straight-forward, FA breakdown has been consistently observed during senescence. A few reports indicate that lipid breakdown particularly through mitochondrial β-oxidation plays a paramount role in cellular senescence. Increased mitochondrial function has long been associated with senescence. Fatty acid oxidation (β-oxidation) is the mitochondrial multi-step process of breaking down a fatty acid into acetyl-CoA units. Long chain fatty acids (LCFA) are activated by acyl-carnitines and imported into the mitochondria for β-oxidation via a rate limiting enzyme carnitine palmitoyltransferase (CPT). Upon completion of β-oxidation, the generated acetyl-CoA can enter the TCA cycle, link to oxidative phosphorylation (OXPHOS) or can lead to acetylation of histones and other proteins. Indeed, recent data suggests that lipids contribute heavily toward histone acetylation and control gene transcriptional programs (McDonnell et al., 2016). During replicative senescence in myoblasts, several acyl-carnitines were increased, suggesting that senescent cells rely
heavily on β-oxidation (Baraibar et al., 2016). Additionally, these senescent myoblasts had increased levels of monoyglycerols and glycerol-3-phosphate, as well as decreased mono- and polynsaturated long chain fatty acids (>18 carbons), whereas medium chain fatty acids remained unaffected. This suggests that senescent cells increase lipid breakdown, however, whether this lipid mobilization and breakdown is used for energy production, gene transcription or generation of SASP (bioactive lipids) is unclear. Interestingly, an increase in CPT function and oxygen consumption rate establishment of the senescence program is also associated with lipids) is unclear. Interestingly, an increase in FASN during production, gene transcription or generation of SASP (bioactive enzymes, diacylglycerol acyltransferase 1 (DGAT1). This study accompanied with the upregulation of the triglyceride synthesis enzyme, diacylglycerol acyltransferase 1 (DGAT1). This study suggests that rather than lipid uptake, TAG biosynthesis may play a crucial role in establishment of senescence (Flor et al., 2017). The caveat though is that in this study the TAG species were not directly measured. It is therefore possible that both uptake and biosynthesis of TAGs may play a role in promoting cellular senescence.

**Cholesterol**

Cholesterol homeostasis is critical to health. It is an important building block for hormones, vitamin D and integral to cell membrane integrity; however, excess cholesterol can have detrimental effects. Few studies have examined the role of cholesterol on cellular senescence. Naked mole rats (NMR) are known for their exceptional longevity, resilience to endogenous and exogenous stressors and cancer resistance. Interestingly, NMR fibroblasts had elevated levels of cholesterol-enriched lipid droplets (LDs), dependent on the Wnt/β-catenin pathway (Chee et al., 2021). Inhibition of cholesterol synthesis using lovastatin, an HMG-CoA reductase inhibitor, promoted senescence-like phenotype in NMR fibroblasts. Of note, only SA β-gal and 8-hydroxy-2'-deoxyguanosine (8-OHdG), a biomarker for DNA damaged by oxidative stress was measured in this study. Furthermore, the Wnt/β-catenin-cholesterol axis seems specific to NMR, as overexpression of β-catenin in mice or rat fibroblasts did not show any elevation in LDs (Chee et al., 2021). On the contrary, lipid profiling of OIS induced by ERBB2 (a member of the epidermal growth factor receptor), revealed increased cholesterol levels accumulated in vacuoles of senescent cells (Cadenas et al., 2012). This study suggests that high cholesterol levels are possibly a feature of senescence, although whether this accumulated cholesterol is a driver of senescence is not fully understood. In contrast, when mouse bone marrow stem cells (BMSCs) were exposed to low dose of cholesterol, it delayed oxidative stress-induced cellular senescence. Indeed, low levels of cholesterol promoted proliferation of BMSCs. Oxidative stress is known to damage macromolecular structures including cellular membranes, and since cholesterol is a major component of cell membranes, exogenous supplementation of cholesterol may help recovery from acute damage (Zhang et al., 2016). Further studies to examine the impact of cholesterol dosage on senescence in vivo is required to ascertain its exact role in the senescence phenotype.

**Phospholipids**

Phospholipids are amphiphilic lipids that play important metabolic and structural roles. In a study looking at ERBB2-induced senescence (OIS), phospholipid with shortened acyl chains and unsaturated acyl chains in phosphatidylglycerol was observed (Cadenas et al., 2012), accompanied by increased membrane fluidity. This study also identified that mitochondrial lipids were altered, specifically, PG(34:1), PG(36:1) (increased) and LPE(18:1), PG(40:7) and PI(36:1) were reduced in senescent cells leading to loss of membrane potential. A comprehensive study compared and analyzed metabolites in replicative senescence, DNA damage-induced senescence and OIS in a human embryonic lung fibroblast (WI-38), using NMR spectroscopy. Interestingly, senescent cells displayed increased glycerophosphorylcholine-to-phosphocholine ratio. Importantly, glycerophosphorylcholine levels were particularly elevated in senescent cells compared to proliferating or quiescent cells, suggesting that this could be a unique feature of senescence (James et al., 2015). Bioactive phospholipids play an important role in “communication” and consist of

**LIPID COMPOSITIONAL CHANGES DURING CELLULAR SENESENCE**

Although several studies show accumulation of lipid droplets (LDs) during cellular senescence, the content of these LDs may be far more critical. Lipids are divided into three groups, triglycerides (TAGs) (utilized for energy), steroids (cholesterol and hormones) and phospholipids (utilized for membrane structures). Here, we summarize the associated changes in composition of these lipids during senescence.

**Triglycerides**

A study to decipher the transcriptomic and lipidomic changes during replicative senescence showed that lipid uptake mediated by CD36 is upregulated in senescent cells (Saitou et al., 2018). This feature is also consistent with DNA damage, oncogenic and chemical stress-induced senescence (Lizardo et al., 2017; Chong et al., 2018). Moreover, there is an enrichment of TAGs containing long- and very long-chain fatty acids, with at least one polyunsaturated fatty acyl (PUFA) chain (Saitou et al., 2018). Another study reported that DNA damage-induced senescence is accompanied with the upregulation of the triglyceride synthesis enzyme, diacylglycerol acyltransferase 1 (DGAT1). This study suggests that rather than lipid uptake, TAG biosynthesis may play a crucial role in establishment of senescence (Flor et al., 2017). The caveat though is that in this study the TAG species were not directly measured. It is therefore possible that both uptake and biosynthesis of TAGs may play a role in promoting cellular senescence.
lysolecithin, ceramides, and sphingomyelin (Horn and Jaiswal, 2019). They can be released as secreted molecules or part of exosomes, and possibly play a role in extracellular matrix formation and release observed during senescence (Tepper et al., 2000; Nurminen et al., 2002; Trajkovic et al., 2008; Bianco et al., 2009; Hirsova et al., 2016). Hydrolysis of phospholipids by phospholipases, such as cPLA2, leads to lysophospholipids. An increase in lysophospholipids has been observed in senescent cells (Buratta et al., 2017; Narzt et al., 2021), and furthermore, lysophospholipids are shown to induce senescence in cholangiocytes (Shimizu et al., 2015). They can also act as a “find me” signal, but impair phagocytosis, possibly leading to inefficient clearance of senescent cells with age (Narzt et al., 2021). Phospholipids also influence the synthesis of eicosanoids that are known inflammatory mediators, thus contributing to the SASP phenotype (discussed in detail below). Thus, phospholipids play a varied role during senescence, including establishment of senescence, paracrine signaling and evasion of senescent cells.

MAJOR LIPID PLAYERS IN SENESCENCE

Oxidized Fatty Acids

One of the major components of complex lipids in mammalian cells are polyunsaturated fatty acids (PUFAs) with at least one bis allelic carbon and chain lengths ranging from 18 and above. PUFAs are precursors for potent metabolites that are involved in numerous pathophysiological events.

One of the most well-studied families are eicosanoids, a class of oxygenated derivatives of arachidonic acid (C20) that include prostaglandins, leukotriens, lipoxins, hydroxy eicosatetraenoic acids, hydroperoxy eicosatetraenoic acids, and epoxy eicosatetraenoic acids. These bioactive lipids are derived enzymatically through the cyclooxygenase pathway, which converts arachidonic acid to thromboxane A2 (TD, prostanoids), 5-LOX (5-LOX), and 12-LOX (12-LOX), which together with other prostaglandin D2-related lipids and PGE2 production and subsequently accelerated the incidence of key senescence features like flat and enlarged cell morphology, SA-β-Gal activity and the cell cycle arrest (Dagouassat et al., 2013). In a study to understand the mechanisms of lung senescence linked with chronic obstructive pulmonary disease (COPD), it was shown that prostaglandin E2 released by pulmonary fibroblasts exerted both autocrine and paracrine effects to induce fibroblast senescence. This was accompanied with inflammation by EP2 and EP4 receptors, COX-2–dependent reactive oxygen species signaling (Dagouassat et al., 2013).

Another primary oxidation product of arachidonic acid is hydroperoxy-eicosatetraenoic acid (hydroperoxyeicosatetraenoic acid, HpETE), generated via lipoxygenase (LOX) activity. Due to its regiospecificity nature, lipoxygenases are classified as arachidonate 5-, 8-, 12-, and 15-lipoxygenase (5-LOX, 8-LOX, 12-LOX, and 15-LOX), which inserts oxygen at carbon 5, 8, 12, or 15 of arachidonic acid peroxidases. The primary oxidation products of HpETE are unstable and reduced further to its corresponding alcohol hydroxy-eicosatetraenoic acid (5-, 8-, 12-, and 15- hydroxy-6-trans,8,11,14-cis-eicosatetraenoic acid, HETE) by glutathione peroxidase. The enzyme 5-LOX can act on 5-HETE to generate an unstable epoxide leukotriene A4 (LTA4), which can serve either as an intracellular intermediate in the synthesis of leukotriene B4/C4 (LTB4 and LTC4). Leukotrienes (LTs) are the second major class of biologically active signaling lipids that plays a key role in inflammation and fibrosis. Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease with elevated senescent cell burden. It was shown that leukotrienes secreted by senescent cells exacerbated IPF by promoting pulmonary fibrosis (Wiley et al., 2019) and kidney fibrosis by unilateral ureteral obstruction in mice (Kim et al., 2016).

Senescence induced irrespective of different modalities (oncogene-, stress-, and radiation-induced) in IMR-90 fibroblasts promoted senescence arrest and SASP through activation of RAS signaling. In mice with drug-induced senescence, a dose of Navitoclax, a senolytic drug (eliminates senescent cells) elevated the levels of prostaglandin in blood and in urine. This study highlights the importance of prostaglandin lipids as biomarkers of senolysis.

The age-related changes in COX-2 are often accompanied by an elevation in the prostaglandin synthesis. COX system is the major pathway catalyzing the conversion of arachidonic acid into prostaglandins, PGG2 and subsequently to PGH2 followed by the production of the bioactive lipids—PGE2, PG12, PGD2, PGF2α—and thromboxane A2 by tissue-specific synthases. An upregulation in COX-2 expression and ensuing PGE2 production was observed during normal and stress-induced senescence of dermal, prostate and lung human fibroblasts. Exogenous supplementation of arachidonic acid enhanced COX-2 activity and PGE2 production and subsequently accelerated the incidence of key senescence features like flat and enlarged cell morphology, SA-β-Gal activity and the cell cycle arrest (Dagouassat et al., 2013). In a study to understand the mechanisms of lung senescence linked with chronic obstructive pulmonary disease (COPD), it was shown that prostaglandin E2 released by pulmonary fibroblasts exerted both autocrine and paracrine effects to induce fibroblast senescence. This was accompanied with inflammation by EP2 and EP4 receptors, COX-2–dependent reactive oxygen species signaling (Dagouassat et al., 2013). Wiley et al. recently showed that senescent cells produced and accumulated 1α,1β-dihomo-15-deoxy-delta-12,14-prostaglandin J2, which together with other prostaglandin D2-related lipids promoted senescence arrest and SASP through activation of RAS signaling. In mice with drug-induced senescence, a dose of Navitoclax, a senolytic drug (eliminates senescent cells) elevated the levels of prostaglandin in blood and in urine. This study highlights the importance of prostaglandin lipids as biomarkers of senolysis.

Another primary oxidation product of arachidonic acid is hydroperoxy-eicosatetraenoic acid (hydroperoxyeicosatetraenoic acid, HpETE), generated via lipoxygenase (LOX) activity. Due to its regiospecificity nature, lipoxygenases are classified as arachidonate 5-, 8-, 12-, and 15-lipoxygenase (5-LOX, 8-LOX, 12-LOX, and 15-LOX), which inserts oxygen at carbon 5, 8, 12, or 15 of arachidonic acid peroxidases. The primary oxidation products of HpETE are unstable and reduced further to its corresponding alcohol hydroxy-eicosatetraenoic acid (5-, 8-, 12-, and 15- hydroxy-6-trans,8,11,14-cis-eicosatetraenoic acid, HETE) by glutathione peroxidase. The enzyme 5-LOX can act on 5-HETE to generate an unstable epoxide leukotriene A4 (LTA4), which can serve either as an intracellular intermediate in the synthesis of leukotriene B4/C4 (LTB4 and LTC4). Leukotrienes (LTs) are the second major class of biologically active signaling lipids that plays a key role in inflammation and fibrosis. Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease with elevated senescent cell burden. It was shown that leukotrienes secreted by senescent cells exacerbated IPF by promoting pulmonary fibrosis (Wiley et al., 2019) and kidney fibrosis by unilateral ureteral obstruction in mice (Kim et al., 2016).
acute kidney injury and drive renal pathogenesis in response to chemotherapy-induced senescence (Rubinstein and Dvash, 2018; Wiley, 2020). In line with these findings, leukotrienes increasingly released from senescent cells, irrespective of the senescence-inducer, and appear to function in parallel to SASP factors.

Besides lipoxygenases and cyclooxygenases, the third class of enzymes involved in eicosanoid synthesis are epoxygenases or cytochrome P450 (CYP) enzymes. Cytochrome P450 epoxygenases (CYP2C and CYP2J) synthesize epoxides, such as epoxygenosatrienoic acid (EETs) in four different regioisomers (5, 6-, 8, 9-, 11, 12-, and 14,15-) that are recognized as specialized pro-resolving mediators (Alkayed et al., 1996; Zhang et al., 2007; Li et al., 2012). EETs have a wide range of protective actions such as anti-inflammatory, anti-apoptotic, vasodilatory and pro-angiogenic (Node et al., 1999; Iliff et al., 2009). The levels of EETs are often determined through production of dihydroxyeicosatrienoic acid (DHET) isoforms via soluble epoxide hydrolase (sEH) (Morisseau and Hammock, 2013). Gene deletion of soluble epoxide hydrolase was shown to improve blood flow and reduce infarct size following cerebral ischemia in reproductively senescent female mice (Zuloga et al., 2014). 14,15-EET inhibited rat mesenteric arterial endothelial senescence, down-regulated p53 expression in aged endothelial cells and improved the impaired endothelium-dependent vasodilatation in aged rats through activation of mTORC2/Akt signaling pathway (Yang et al., 2014). Injection of 11,12-EET accelerated wound healing, tissue repair and reduced production of proinflammatory factors TNFα, IL-6, MMP and IL-1β in type 2 diabetic models of B6.VLepob/J (leptin-deficient, ob/ob) mice. In another study, both forms of EETs 11,12 and 14,15 epoxygenosatrienoic acid rescued deteriorated wound healing in ischemic conditions (Sommer et al., 2019). Orally active subset of 14,15-EET analogs, termed EET-A, EET-B, and EET-C22 reduced cardiac and renal injury in spontaneous and angiotensin hypertension as well as promoted recovery after Ischemia/Reperfusion Injury by reducing contractile dysfunction (Campbell et al., 2017). Although several studies have highlighted the deleterious impact of cellular senescence in numerous chronic diseases, it is also recognized for its beneficial role in tumor suppression, wound healing and tissue regeneration. These studies highlight the contribution of CYP generated pro-resolvin lipid mediators in wound healing.

Oxidized Phospholipids
Polysaturated fatty acyl containing phospholipids are prone to lipid peroxidation and form oxidized phospholipids (OxPLs) that play a significant role in apoptosis and inflammation. OxPLs are generated enzymatically through lipoxygenases or non-enzymatic attack through reactive oxygen species. However, irrespective of the mode, identical primary oxidation products (i.e., peroxyl radicals and hydroperoxides) are produced initially that subsequently undergo further oxidation in a stochastic manner and release a heterogenous mixture of bioactive OxPL species. In general, lipid peroxidation and levels of OxPLs increase with age. OxPLs generated via cytoplasmic hydroxyl radicals exacerbated cellular senescence in Toll-like receptor 4-knockout (TLR4-/-) OKD48- and IDOL-Tg mouse models (Sakai et al., 2019). Inhibition of TLR2 with oxidized-1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphorylcholine (OxPAPC), a well-studied oxidized product of a common phospholipid in mammalian cell membranes, 1-palmitoyl-2-arachidonyl-sn-phosphatidylyceroline (PAPC) significantly reduced IL-1α and IL-1β mRNA induction in oncogene induced senescence of IMR90 cells. In another study targeting OxPLs by transgenic overexpression of E06-svFv, a single chain variable fragment that binds to phosphatidyl choline head group of OxPL attenuated age-associated trabecular bone loss in both female and male mice (Palmieri et al., 2021). Similar E06-svFv transgene mechanisms to inactivate OxPLs have been studied with age-associated diseases such as atherosclerosis, osteoarthritis (Sun et al., 2020) and macular degeneration (Handa et al., 2015) suggesting neutralizing OxPLs as a promising therapeutic target for some of the age-associated diseases. Cardiolipins, major phospholipids in mitochondria are extremely prone to lipid oxidation. With mitochondria being the critical organelle handling oxidative stress, oxidation of cardiolipin can lead to organelle dysfunction and generate lipid peroxides further exacerbating oxidative stress and promoting senescence. Knock out of ALCAT-1, an enzyme that promotes cardiolipin peroxidation protected against onset of cellular senescence and preserved mitochondrial function by reducing sensitivity to lipid oxidation.

Greenberg et al. (2008) proposed the “lipid whisker” hypothesis as a novel feature of membrane architecture in senescent or apoptotic cells. These cells are distinguished by the presence of protruding “whiskers” as a result of phospholipid oxidation via lipid peroxidation or oxidative stress. The oxPL whiskers such as oxidized phosphatidylserine contribute to pattern recognition for common receptors like CD36 that play a major role in engulfment and phagocytosis of senescent cells (Podrez et al., 2002; Greenberg et al., 2006, 2008).

Sphingolipids
Sphingolipids are a class of complex phospholipids with a hydrophobic core consisting of an amino alcohol, sphingosine and a long-chain fatty acid chain. Bioactive forms this class such as sphingosine, sphingosine-1-phosphate, ceramide, ceramide-1-phosphate, dihydroceramide are known to modulate a plethora of cellular functions such as cell migration, growth regulation, adhesion, apoptosis, senescence and inflammatory responses (Hannun and Obeid, 2018).

Several studies have highlighted the role of sphingolipids in both development and aging (Giusto et al., 1992; Lightle et al., 2000; Cutler and Mattson, 2001; Hannun and Obeid, 2018). For example, aging induces accumulation of sphingosine and ceramides in liver and brain tissues and alterations in sphingolipid metabolism increases the risk and progression of age-related disease (Giusto et al., 1992; Lightle et al., 2000). A systemic study on sphingolipid metabolic enzymes in kidney, liver and brain tissues of day-1 to 720-day-old rats revealed a significant increase in activities of the sphingolipid catalytic enzymes (SMase and ceramidases) (Sacket et al., 2009). Impairment of ceramide and sphingolipid synthesis genes in
yeast, worms and flies extended lifespan (Cutler and Mattson, 2001; Rao et al., 2007; Yi et al., 2016).

In senescent human dermal fibroblasts (HDF), ceramide levels and a sphingomyelinase activity were markedly elevated. Exogenous ceramide induced senescent phenotype in young HDF at concentrations that mimics endogenous ceramide levels in senescent cells and recapitulated molecular changes of senescence, suggesting ceramides act as mediators of senescence (Venable et al., 1995). Of note, in therapy-induced senescence, exogenous addition of sphingomyelin increased ceramide levels that induced apoptosis and decreased senescence. This is possibly explained by ceramide levels—no inhibition of cell cycle progression at low ceramide levels, induction of senescence at moderate levels, and initiation of apoptosis at high levels (Modrak et al., 2009). In another study, deficiencies in ceramide transfer protein (CERT) in primary mouse embryonic fibroblasts led to senescence and dysregulated sphingolipid metabolism by increasing hexosylceramides production (Rao et al., 2007). Increased hexoceramides such as glucosylceramide led to age-related impairments in CD4(+) T cell function and immunosenescence (Molano et al., 2012). Several studies have suggested that sphingolipid metabolism as effectors or modulators of the p53 tumor suppressor pathway, particularly sphingomyelinase and sphingosine kinase I (SK1), which are directly regulated by p53, contributing to ceramide-induced senescence in cells (Dbaibo et al., 1998; Oskouian et al., 2006; Heffernan-Stroud and Obeid, 2011). For example, the expression of sphingosine kinase I (SK1), a downstream target of p53, was significantly elevated in p53-knockout mice that developed thymic lymphoma, and p53-deficient mice lacking SK1 were protected from thymic lymphoma. Mechanistic studies revealed that p53 tumor suppression caused by loss of SK1 was mediated by increased sphingosine and ceramides, resulting in tumor senescence. Non-canonical sphingolipids such as deoxyceramides has been shown to be depleted during tumor-induced senescence and increasing the levels of 1-deoxyceramides reduced the senescence phenotype in human colorectal cancer cells. The imbalance in deoxyceramide levels can affect sphingolipid signaling and alter membrane remodeling (Müller et al., 2020). Despite the fact that several evidences point to the multiple roles of bioactive sphingolipids in aging, these intriguing findings warrant more research into the functional role of sphingolipids in senescence.

**Lysophospholipids**

Lysophospholipids are multifunctional lipid mediators and are formed from hydrolyzed phospholipids with either an alkyl or acyl chain (Rivera and Chun, 2008). The lysophospholipids (LPLs) are broadly categorized as lysoglycerophospholipids and lysosphingolipids. The common ones in circulation are lysophosphatidylcholine (LPC), lysophosphatic acid (LPA), lysophosphatidylserine (LPS), sphingosine, sphingosine-1-phosphate (S1P), and sphingosylphosphorylcholine (SPC) that are derived from corresponding phospholipids. Among the LPLs, lysophosphatidylcholine is the most abundant class (Ojala et al., 2007) and activates multiple signaling pathways that are involved in oxidative stress and inflammatory responses (Kakisaka et al., 2012; Bansal et al., 2016). They are also major secretory components of extracellular vesicles, which has recently gained a lot of attention as key players within the secretome of senescent cells (Urbanelli et al., 2016; Buratta et al., 2017). For example, biochemical characterization of extracellular vesicles released by fibroblasts subjected to H-Ras induced senescence indicated a significant enrichment in LPCs species (16:0; 16:1; 18:1; 18:2; 20:4, and 26:0). Both, replicative- and stress-induced-senescent dermal fibroblasts showed elevated levels of lysophosphatidylcholines. The LPC exhibited SASP activity by eliciting chemokine release in non-senescent fibroblasts and obstructed TLR2–6/CD36 signaling in macrophages (Narzt et al., 2021). Cholangiocyte senescence in biliary tract cancer has been linked to an increase in LPC levels and the resulting cytotoxicity. LPCs induced upregulation of components of SASP interleukin-8 (IL-8), IL-6, transforming growth factor-β and PAI-1, as well as p21 and SA-β-gal activity in MMNK-1 human cholangiocyte cells.

Studies have also shown association between aging and lysophosphatidic acid (LPA) signaling. For instance, alterations in LPA1 receptor was linked to the presence of depression and cognitive deficits in the elderly population (Moreno-Fernandez et al., 2018). Age-dependent changes in cAMP profiles were induced by LPA as noted in young and senescent human fibroblasts (Jang et al., 2006). LPA were detected at significantly higher concentrations in the cerebral cortex synaptosomes of aged rats (Pasquare et al., 2009). Knockdown of LPA3 led to cell senescence in mesenchymal stromal cells (Kanehira et al., 2017). Another finding showed that LPA regulates ROS levels and cell senescence through LPA3 to alleviate cell aging in Hutchinson–Gilford progeria syndrome (Chen et al., 2020). Together these studies reveal a key role of lysophospholipid signaling and its wide spread effects in the process of aging and senescence. Figure 2 illustrates the key lipid players involved in senescence.

**MAJOR MOLECULAR PLAYERS OF CELLULAR SENESCENCE AND THEIR ROLE IN LIPOID REGULATION**

**p16**

Cellular senescence is initiated and maintained through two critical pathways: p16^{ink4a}/Rb and/or p53/p21_cip1. It is important to note that both, p16 and p53, are well known tumor suppressors. p16 inhibits cyclin dependent kinases, CDK4 and CDK6, thus maintaining Rb in a hypophosphorylated form and blocking cell cycle progression (Figure 3). Expression of p16 is a key factor for maintaining long-term senescence (Serrano et al., 1997; Yamakoshi et al., 2009). A recent study isolated high expressing p16-positive cells, specifically macrophages, and showed that these cells exhibit several other markers of senescence, including SA-β-gal, reduced proliferation and accompanying SASP (Liu et al., 2019). This suggests that high expression of p16 is indeed associated with cellular senescence. Additionally, several single nucleotide polymorphisms (SNPs) have been identified in the CDKN2a/b locus (encoding the
FIGURE 2 | Major lipid species involved in senescence. Species illustrated in red increase with senescence, whereas species in orange and green regulate and inhibit it, respectively.

p16INK4a, ARF, and p15INK4b transcripts) and associated with multiple age-related pathologies (Jeck et al., 2012; Fortney et al., 2015). Furthermore, p16 expression is largely undetectable in young mice, Krishnamurthy et al. (2004), Liu et al. (2009) but is strongly associated with aging in multiple mouse tissues (Burd et al., 2013). Similarly, other “drivers” that accelerate aging features, for example high fat diet, drives p16 expression through epigenetic modulation of its coding region (Zhang et al., 2018). Consistent with p16 being a major player in cellular senescence, genetic ablation of p16-positive cells, using the INK-ATTAC (Baker et al., 2011) and p16-3MR mice (Demaria et al., 2014), reduced senescent cell burden and improved healthspan, both in a progeria model, as well as naturally aged WT animals. Of note, preventing the accumulation of p19ARF-positive cells, another tumor suppressor that regulates p53 stability did not delay or prevent age-related pathologies (Baker et al., 2008), suggesting that p16 is crucial for maintenance of senescence, at least in mice models.

In humans, peripheral blood T lymphocytes exhibit increased expression of p16INK4a with age, tobacco smoking and physical inactivity. Similarly, p16-positive senescent T cells increase with age in mice (Yousefzadeh et al., 2021). In addition to aging, senescent T cells have been isolated from a number of tumors including lung and breast cancer (Meloni et al., 2006; Gruber et al., 2008; Urbaniak-Kujda et al., 2009). These senescent T cells from the tumor microenvironment seem to be dysfunctional and have reduced antitumor activity (Liu et al., 2018; Zhao et al., 2020). Interestingly, such senescent T cells with increased p16 expression display unbalanced lipid metabolism, leading to accumulation of lipid droplets (Liu et al., 2021), consistent with senescent cells in other tissues. Inhibition of the group IVA phospholipase A2, reprogrammed metabolism and prevented T cell senescence, suggesting that unbalanced lipid metabolism could be a key driver of T cell senescence (Liu et al., 2021). However, whether p16 directly controls lipid metabolism is still unknown in this model. One recent study did identify a direct link between p16 expression and lipid metabolism. During fasting, inhibition of p16 in primary hepatocytes enhanced activation of PPARα, a transcription factor with a major role in lipid metabolism, and increased fatty acid oxidation (Deleye et al., 2020; Figure 3). Consistent with this, p16 overexpression reduced mitochondrial activity and fatty acid oxidation, and led to accumulation of lipid droplets both in vitro and in vivo. However, p16 is known to have roles outside of senescence and these studies did not analyze cellular senescence in this fasting model. Of note, several studies (described above) suggest that elevated lipid β-oxidation is observed in senescent cells. Therefore, further studies exploring if p16 controls lipid catabolism during senescence will uncover insights into how p16 maintains long-term senescence.

p53

p53 is one of the most well-studied tumor suppressor, and is activated in response to various stressors including DNA damage, telomere attrition, mitochondrial, oxidative or oncogenic stress. Post-translational modification of p53, including phosphorylation, acetylation, sumoylation, ubiquitination and neddylation, regulate its activity. Upon acute stress, p53 is activated and can modulate DNA repair and quiescence (Vousden and Prives, 2009; Kasteri et al., 2018). However, chronic activation of p53 promotes cellular senescence (Sharpless and Depinho, 2006; Salama et al., 2014). p53 indirectly
FIGURE 3 | The role of major players of senescence in lipid metabolism. P16INK4a, p53, and p21 are major cell cycle regulators that control cellular senescence. INK4a/ARF encodes both p16 and ARF. MDM2 is an E3 ligase that ubiquitinates and leads to degradation of cellular senescence. ARF can inhibit MDM2 and therefore stabilize p53. P21 is a bona fide target of p53 and is partially responsible for cell cycle arrest and cellular senescence. P16 inhibits cyclin dependent kinases (CDK) thus maintaining Rb in a hypophosphorylated state and preventing E2F transcription factor activity. On the right are modulators of lipid metabolism that are regulated by p16, p53, and p21 (possibly regulated by p16).

downregulates the expression of several genes required for cell cycle progression. Although the role of p53 in regulating the cell cycle is well-understood, recent studies indicate that p53 can also regulate metabolism and in particular lipid metabolism.

p53 enhances fatty acid oxidation and oxidative phosphorylation (OXPHOS), while inhibiting fatty acid synthesis. The role of p53 in suppressing lipid synthesis is prominent in the p53 knock out mouse models that exhibit obesity (Wang S. J. et al., 2016). Interestingly, induction of cellular senescence increases oxygen consumption and inhibits fatty acid synthesis, suggesting that p53 may play a pivotal role in rewiring the metabolic circuitry of senescent cells (Quijano et al., 2012). Inhibition of fatty acid synthesis by p53 is predominantly through repression of the master regulator of fatty acid synthesis, SREBP1 (Yahagi et al., 2003). SREBPs control the expression of multiple lipogenic enzymes, including acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), and fatty acid synthase (FASN) (Yahagi et al., 2003; Eberle et al., 2004). These observations stem from a model of obese (ob/ob) mice, that displayed elevated p53 and a concomitant downregulation of SREBP-1 and its targets, possibly by reducing promoter activity. Indeed, p53 deletion in the ob/ob mice partially rescues SREBP-1 expression (Yahagi et al., 2003).

Carnitine palmitoyltransferase 1A and 1C (CPT1A, CPT1C), the rate limiting enzyme for fatty acid oxidation and aid in the transport of fatty acids into the mitochondria are transcriptionally regulated by p53 (Sanchez-Macedo et al., 2013). Carnitine O-octanoyltransferase (CROT) another enzyme that facilitates export of fatty acids from the peroxisomes has also been identified as a p53 target (Goldstein et al., 2012). Once exported from the peroxisomes these fatty acids can undergo mitochondrial β-oxidation. Similarly, Acad11 that catalyzes the first step of mitochondrial fatty acid oxidation, is a transcriptional target of p53 (Jiang et al., 2015). DNA damage with doxorubicin, an agent that induces double strand breaks and activates p53, upregulated Acad11 expression in a p53-dependent manner (He et al., 2011; Jiang et al., 2015). Malonyl-CoA decarboxylase (MLYCD) is a mitochondrial enzyme that converts malonyl-CoA to acetyl-CoA and a critical regulator of fatty acid oxidation. In a recent study in mice exhibiting ribosomal stress, MLYCD transcription was controlled through p53 binding to its promoter and intron regions, and reduced lipid accumulation in the liver (Liu et al., 2014). Another bonafide p53 target, Lipin1 has three p53 binding sites in intron 1, and is important for adipose tissue development. DNA damage, particularly double strand breaks (DSBs) by γ-irradiation, that activates p53 leads to increased Lipin1 expression in several tissues including spleen and thymus (Assaily et al., 2011). Recent data in mouse myoblast C2C12 cells, shows that upon glucose starvation p53 upregulates Lipin 1 and fatty acid oxidation (Assaily et al., 2011). Additionally, Lipin1 has also been shown to interact with PGC-1α, another p53 target, to promote fatty acid oxidation (Finck et al., 2006; Sen et al., 2011). Clearly, activated wild-type p53 does seem to play a role in lipid metabolism, particularly fatty acid oxidation. However, whether chronic p53 activation that is known to promote cellular senescence, leads to similar changes has not yet been fully elucidated. Fatty acid oxidation is linked to OXPHOS, and provides reduced equivalents to the OXPHOS pathway. p53 has several targets that play a role in OXPHOS, including cytochrome c oxidase 2 (SCO2) (Matoba et al., 2006).
and the mitochondrial encoded cytochrome c oxidase 1 (MT-CO1) (Okamura et al., 1999). p53 is also shown to translocate into the mitochondria and can interact with mitochondrial DNA polymerase γ (Achanta et al., 2005), control mitochondrial biogenesis through PGC1α, regulate mitochondrial DNA copy number and mitochondrial mass through p53-controlled ribonucleotide reductase (p53R2) (Bourdon et al., 2007) and is also involved in clearance of dysfunctional mitochondria by mitophagy through mitochondria-eating protein (MiecA) (Kitamura et al., 2011).

Interestingly, short-chain dehydrogenase reductase (DHRS3) that is localized to lipid droplets has also been identified as a target of p53 (Beilstein et al., 2016). There are two p53 responsible elements in the DHRS3 promoter, and several reports show that activated p53 promotes buildup of lipid droplets concomitant with an increase in DHRS3 (Kirschner et al., 2010; Deisenroth et al., 2011). In addition to FAO, OXPHOS and lipid droplet dynamics, p53 is also involved in cholesterol homeostasis. Caveolin 1 is a structural protein that binds to cholesterol. In an in vitro study, in human dermal fibroblasts, caveolin 1 was induced upon overexpression of p53 (Bist et al., 2000). This led to reduced intracellular cholesterol, suggesting the possible role of p53 in cholesterol efflux. The HMG-CoA reductase pathway is important for cholesterol synthesis and several enzymes in this pathway are p53 targets including 3′-hydroxy-3′-methylglutaryl-coenzyme A reductase, MVA kinase, farnesyl diphosphate synthase and farnesyl diphosphate farnesyl transferase 1 (Laezza et al., 2015). However, there are opposing reports on whether p53 activates or represses the HMG-CoA reductase pathway. Both studies use WT p53 expressing cell lines, however, one study uses astrocytes and glioblastoma cell lines whereas the other uses mouse embryonic fibroblasts, SK-HEP-1 and HCT116 cells (Laezza et al., 2015; Moon et al., 2019; Figure 3). Currently the role of HMG-CoA reductase pathway in cellular senescence is not clear, although a few reports suggest that inhibiting this pathway in pre-malignant cells promotes cellular senescence and inhibits tumorigenesis.

p21
A bona fide transcriptional target of p53 is p21$^{\text{WAF/CIP1}}$, a 21 kDa protein encoded by the CDKN1A gene (el-Deiry et al., 1993). p21 interacts with cyclin dependent kinases (CDKs), thus maintaining RB in a hypophosphorylated state and inhibiting cell cycle progression (Harper et al., 1993; Chen et al., 1996). Since, p21 binds several cyclin/CDK complexes, including CDK1, 2, 4 and 6, it can promote arrest at any stage of the cell cycle. In contrast p16 specifically binds to inactive CDK4 and CDK6, thus arresting cells in G0/G1 phase (Harper et al., 1993; Pavletich, 1999). p21 can also bind proliferating cell nuclear antigen (PCNA) (Waga et al., 1994) and inhibit the cell cycle. It is important to note that p21 can be activated in a p53-independent manner (Aliouat-Denis et al., 2005; Abbas and Dutta, 2009). As mentioned above, p16 expression is required to maintain a senescent state. In contrast, p21 is crucial for initiation of senescence (Noda et al., 1994; Hernandez-Segura et al., 2017). Indeed, mice lacking p21$^{\text{WAF/CIP1}}$ showed defects in embryonic senescence leading to developmental defects (Munoz-Espin et al., 2013; Storer et al., 2013). Of note, embryonic senescence is a transient program thought to be beneficial and is resolved in a timely manner. Furthermore, several reports show that p21 expression does not persist in senescent cells (Stein et al., 1999; Sharpless and Sherr, 2015).

Role of p21 in lipid metabolism is not well understood. p21 does have an apparent role in adipocyte maintenance, however, outside of adipogenic effects not much is known about p21 in regulating lipid metabolism. There are some studies that report p21 as a pro-adipogenic factor. Knockdown or loss of p21 inhibited adipocyte differentiation (Inoue et al., 2008). Consistent with this, phosphorylation of p21 by MPK-38 led to nuclear translocation and increased association with peroxisome proliferator-activated receptor γ (PPARγ), thus inhibiting the role of PPARγ in adipogenesis. Furthermore, in this study expression of p21 rescued the metabolic phenotypes observed. Contradicting these studies, loss of p21 showed an increase in adipocyte hyperplasia (Naaz et al., 2004). In this study loss of p21 led to spontaneous adipose conversion and adipocyte hyperplasia in mice. However, effects in the study of Inoue et al. were observed in the terminal differentiation phase of the adipogenic program, whereas the anti-adipogenic effects were evident in the earlier determination phase of adipogenesis. Interestingly, p21 was identified as a target of SREBP-1a and SREBP-2 binding sites exist in the p21 promoter (Inoue et al., 2005). Furthermore, SREBP-1a led to p21 expression and cell cycle inhibition, under conditions of lipid deprivation. Consistent with this observation, SREBP null mice had reduced expression of p21 (Figure 3). It will be of great interest to examine whether expression of p21 leads to differential lipid changes during “acute” versus “chronic” senescence. Although, p16, p53, and p21 are key molecular players in cellular senescence their exact role in modulating lipid metabolism, reprogramming lipid composition and generation of bioactive lipid species is not well explored.

**Potential Role of Lipids as Therapeutics in Targeting Senescence**

Cellular senescence is a defining feature of aging, as well as a contributor to chronic non-healing wounds and general tissue aging pathology. Several key bioactive lipids such as cytochrome P450 (CYP)-derived epoxyeicosatrienoic acids (EETs), leukoterines, lipoxins described above are known to play a significant role in tissue repair. In fact, EETs have been shown as a viable angiogenic therapeutic strategy for its ability to accelerate wound epithelization (Sander et al., 2013). Long term inhibition of PGE2 degradation significantly reduced pulmonary fibrosis lesions in mouse model of bleomycin-induced lung senescence. In contrast, profibrotic leukotriene synthesis is elevated in IPF. Although PGE2 inhibition holds great promise as a stand-alone treatment or in combination with currently approved therapies for idiopathic pulmonary fibrosis, modulating eicosanoid metabolism in context of senescence can open up therapeutic avenues and provide mechanistic clues into tissue aging. Although the above studies have highlighted the
beneficial role of senescent cells in wound healing, it is still a paradox as to how these senescent cells also impair wound healing in aging. A temporal lipidome analysis of senescent cells from different tissues would provide insights into lipid changes that occur in senescent cells of aged tissues, as well as allow for the development of tailored senescence-targeting therapeutics.

TOOLS TO IDENTIFY FUNCTIONAL LIPIDS AND CURRENT CHALLENGES

The ubiquitous and structurally diverse nature of lipids molecules and its varied abundance across cells and tissues contributes to the complexity in the process of lipid identification. There are various techniques available for studying individual lipids and the lipidome, each with its own set of constraints. Understanding the benefits and limitations of these approaches is therefore crucial in identifying lipids within a biological model. With the emergence of lipidomics, there has been several advancements in analytical techniques such as soft ionization methods, high resolution mass spectrometry, tandem mass spectrometry, MS imaging and development of spectral libraries and lipid database such as LIPIDMAPS. This has led to not only identifying novel lipids but also unravel mechanisms responsible for pathophysiological conditions, biomarkers for early diagnosis and drug targeting (Quehenberger et al., 2010; Wang M. et al., 2016). Advances in high-resolution lipidomics platforms have made it possible to investigate lipidome changes associated with aging and age-associated diseases (Wong et al., 2019). For example, both targeted and untargeted lipidomics approaches provided insights into phospholipid remodeling in senescent cells, led to the identification of 15d-PGJ2 as a biomarker of senolysis and elevated ceramide C16:0 levels as prognostic marker for functional decline (Wennberg et al., 2018; Millner and Atilla-Gokcumen, 2020; Wiley et al., 2021). Despite advancements made in this field, the complexity in terms of chemistry, diversity, and abundances necessitates the continued pursuit of technical innovation. For example, identifying certain isomers of eicosanoids, a variety of sphingolipids, phospholipid intermediates are still challenging to be quantified accurately. Developing the informatics tools or libraries to interpret a multitude of lipid species and large sets of lipidomics data has been challenging. Nevertheless, a lot of progress has been made toward fine tuning of high-resolution mass spectrometry and precise identification of lipid structures. Multi-omic data integration approaches, dynamic lipidomics to assay turnover kinetics, single cell lipidomics has generated a lot of interest and holds promise in advancing the field forward.

UNANSWERED QUESTIONS IN THE FIELD

With advances in technology, we have unraveled that lipids do play a role in cellular senescence. However, we are left with several unanswered and interesting questions: Do different stages of cellular senescence (e.g., initiation versus late senescence) have different lipid compositions? If so is it causal in initiation or maintenance of senescence? While the lipids discussed in this review have been linked to senescence, more research is needed to establish cause or consequence effect. In addition to this, the link between major senescent players- p53, p21, or p16, and lipid alterations is still to be uncovered. Importantly, it will be interesting to understand whether lipids could act as biomarkers for senescence and/or senolysis, hence making intervention possible in the near future.

Cellular senescence, in summary is a cell-fate process associated with several age-related pathologies including frailty, Alzheimer’s disease, Parkinson disease, atherosclerosis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and osteoarthritis (Schafer et al., 2017; Chinta et al., 2018; Sagiv et al., 2018). Indeed, the National Institutes of Health (NIH) has recently started a new initiative, The Common Fund’s Cellular Senescence Network (SenNet) Program, to better understand the key hallmarks of cellular senescence and map the burden of senescent cells in human. This further highlights the critical need of understanding cellular senescence. Additionally, directed removal of senescent cells or associated SASP improves health considerably, at least in animal models (Zhu et al., 2015; Jeon et al., 2017; Bussian et al., 2018; Guerrero et al., 2019; Zhang et al., 2019). Further understanding the role of lipids in cellular senescence will open new therapeutic approaches for several age-related diseases.

AUTHOR CONTRIBUTIONS

SH and AUG reviewed the literature, authored the review, contributed to the article, and approved the submitted version.

FUNDING

This work was supported by NIH grants R00AG049126 and U54AG075931 (AUG).

ACKNOWLEDGMENTS

We thank Aakriti Kallianpur for help with the illustrations and Tamil Anthymuthu for critical discussions on the manuscript.

REFERENCES

Abbas, T., and Dutta, A. (2009). p21 in cancer: intricate networks and multiple activities. Nat. Rev. Cancer 9, 400–414. doi: 10.1038/nrc2657
Achanta, G., Sasaki, R., Feng, L., Carew, J. S., Lu, W., Pelciano, H., et al. (2005). Novel role of p53 in maintaining mitochondrial genetic stability through interaction with DNA Pol gamma. EMBO J. 24, 3482–3492. doi: 10.1038/sj.
emboj,7600819
Aliouat-Denis, C. M., Dendouga, N., Van denWyngaert, I., Goehlmann, H., Steller, U., van deWeyer, I., et al. (2005). p53-independent regulation of p21Waf1/Cip1 expression and senescence by Chk2. Mol. Cancer Res. 3, 627–634. doi: 10.1158/ 1541-7786.MCR-05-0121
Alkayed, N. J., Narayanam, J., Gerebmedhin, D., Medhora, M., Roman, R. J., and Harder, D. R. (1996). Molecular characterization of an arachidonic acid epoxygenase in rat brain astrocytes. Stroke 27, 971–979. doi: 10.1161/01.str.27.5.971

Assali, W., Rubinger, D. A., Wheaton, K., Lin, Y., Ma, W., Xuan, W., et al. (2011). ROS-mediated p53 induction of Lpin1 regulates fatty acid oxidation in response to nutritional stress. Mol. Cell 44, 491–501. doi: 10.1016/j.molcel.2011.08.038

Badawi, A. F., Liu, Y., Eldeen, M. B., Morrow, W., Razak, Z. R., Maradeo, M., et al. (2001). Age-associated changes in the expression pattern of cyclooxygenase-2 and related apoptotic markers in the cancer susceptible region of rat prostate. Carcinogenesis 22:1650.

Badawi, A. F., Liu, Y., Eldeen, M. B., Morrow, W., Razak, Z. R., Maradeo, M., et al. (2004). Age-associated changes in the expression pattern of cyclooxygenase-2 and related apoptotic markers in the cancer susceptible region of rat prostate. Carcinogenesis 25, 1681–1688. doi: 10.1093/carcin/bgh176

BaeK, S., Kim, J. W., Lee, J. H., Kwon, H. J., Kim, N. D., Kang, H. S., et al. (2001). Age-related increase of brain cyclooxygenase activity and dietary modulation of oxidative status. J. Gerontol. A Biol. Sci. Med. Sci. 56, B246–B241. doi: 10.1093/gerona/56.10.b426

Baker, D. J., Perez-Terzic, C., Jin, F., Pitel, K. S., Niederlander, N. J., Jeganathan, K., et al. (2008). Opposing roles for p16ink4a and p19Arf in senescence and aging caused by BubR1 insufficiency. P Natl. Acad. Sci. 10.1038/ncb1744

Baker, D. J., Wyshshake, T., Tchkonia, T., LeBrasseur, N. K., Childs, B. G., van deSluis, B., et al. (2011). Clearance of p16ink4a-positive senescent cell delays aging-associated disorders. Nature 479, 232–236. doi: 10.1038/nature10600

Bansal, P., Gaur, S. N., and Arora, N. (2016). Lysophosphatidylcholine plays critical role in allergic airway disease manifestation. Sci. Rep. 6:27430. doi: 10.1038/srep27430

Baraibar, M. A., Hyzewicz, J., Rogowska-Wrzesinska, A., Bulûta, A. L., Prip-Buus, C., Butler-Browne, G., et al. (2016). Impaired energy metabolism of senescent cells. Exp. Cell Res. 352, 172–179. doi: 10.1016/j.yexcr.2015.09.018

Bianco, F., Perrotta, C., Novellino, L., Francolini, M., Riganti, L., Menna, E., et al. (2016). Characteristics and functions of lipid droplets and associated proteins in enterocytes. Exp. Cell Res. 340, 172–179. doi: 10.1016/j.yexcr.2015.09.018

Bourdon, A., Minai, L., Serre, V., Jais, J. P., Sarzi, E., Aubert, S., et al. (2020). Beta-catenin-promoted cholesterol metabolism protects against cellular senescence in naked mole-rat cells. Aging Cell 19:e13064. doi: 10.1111/ace.13064

Bussian, T. J., Aziz, A., Meyer, C. F., Swenson, B. L., van Deursen, J. M., and Baker, D. J. (2018). A p16(INK4a)-luciferase model. Cell 175, 825–836. doi: 10.1016/j.cell.2018.12.010

Cadenas, C., Vosbeck, S., Hein, E. M., Hellwig, B., Langer, A., Hayen, H., et al. (2012). Glycerophospholipid profile in oncogene-induced senescence. Biochim. Biophys. Acta 1821, 1256–1268. doi: 10.1016/j.bbalip.2011.11.008

Chintala, S. J., Woods, G., Demaria, M., Rane, A., Zou, Y., McQuade, A., et al. (2018). Cellular senescence is induced by the environmental neurotoxin paraquat and contributes to neuropathology linked to Parkinson’s disease. Cell Rep. 22, 930–940. doi: 10.1016/j.celrep.2017.12.092

Choi, Y. J., Kim, H. S., Lee, J., Chung, J., Lee, J. S., Choi, J. S., et al. (2014). Down-regulation of oxidative stress and COX-2 and iNOS expressions by dimethyl lipoateamide in aged rat kidney. Arch. Pharm. Res. 37, 1032–1038. doi: 10.1007/s12272-014-0332-6

Chong, M., Yin, T., Chen, R., Xiang, H., Yuan, L., Ding, Y., et al. (2018). CD36 initiates the secretory phenotype during the establishment of cellular senescence. EMBO Rep. 19:e45274. doi: 10.15252/embr.201745274

Chung, H. Y., Kim, H. J., Shim, K. H., and Kim, K. W. (1999). Dietary modulation of prostanooid synthesis in the aging process: role of cyclooxygenase-2. Mech. Ageing Dev. 111, 97–106. doi: 10.1016/S0047-6374(98)00061-5

Coppe, J. P., Patil, C. K., Rodier, F., Krtolica, A., Beausejour, C. M., Parrinello, S., et al. (2010). A human-like senescence-associated secretory phenotype is conserved in mouse cells dependent on physiological oxygen. PLoS One 5:e9188. doi: 10.1371/journal.pone.0009188

Correia-Melo, C., Marques, F. D., Anderson, R., Hewitt, G., Hewitt, R., Cole, J., et al. (2016). Mitochondria are required for pre-aging features of the senescent phenotype. EMBO J. 35, 724–742. doi: 10.15252/embj.201592862

Cox, L. S., and Redman, C. (2017). The role of cellular senescence in the ageing of the placenta. Placenta 52, 139–145. doi: 10.1016/j.placenta.2017.01.116

Cutler, R. G., and Mattson, M. P. (2001). Sphingomyelin and ceramide as regulators of development and lifespan. Mech. Ageing Dev. 122, 895–908. doi: 10.1016/S0047-6374(01)00246-9

Daguussaat, M., Gagliolo, J. M., Chrusciel, S., Bourin, M. C., Duprez, C., Caramelle, P., et al. (2013). The cyclooxygenase-2-prostaglandin E2 pathway maintains senescence of chronic obstructive pulmonary disease fibroblasts. Am. J. Respir. Crit. Care Med. 187, 703–714. doi: 10.1164/rccm.201208-1361OC

Dbaibo, G. S., Pushkareva, M. Y., Rachid, R. A., Alter, N., Smyth, M. J., Obeid, L. M., et al. (1998). p53-dependent ceramide response to genotoxic stress. J. Clin. Invest. 102, 329–339. doi: 10.1172/JCI11880

Deisenroth, C., Itahana, Y., Tollini, L., Jin, A., and Zhang, Y. (2011). p53-Inducible DHRS5 is an endoplasmic reticulum protein associated with lipid droplet accumulation. J. Biol. Chem. 286, 28833–28836. doi: 10.1074/jbc.M111.24227

Deleye, Y., Cotte, A. K., Hannou, S. A., Hennuyer, N., Bernard, L., Derudas, B., et al. (2020). CDKN2A/p16INK4a suppresses hepatic fatty acid oxidation through the AMPKalpha2-SIRT1-PPARalpha signaling pathway. J. Biol. Chem. 295, 17310–17322. doi: 10.1074/jbc.A120.212543

Demaria, M., Ohtani, N., Youssef, S. A., Rodier, F., Toussaint, W., Mitchell, J. R., et al. (2014). An essential role for senescent cells in optimal wound healing through secretion of PGDF-αA. Dev. Cell 31, 722–733. doi: 10.1016/j.devcel.2014.11.012

Di Micco, R., Sulli, G., Dobrevea, M., Lioniotes, M., Botrugno, O. A., Gargiulo, G., et al. (2011). Interplay between oncogene-induced DNA damage response and heterochromatin in senescence and cancer. Nat. Cell Biol. 13, 292–302. doi: 10.1038/ncli12170

Frontiers in Physiology | www.frontiersin.org 12 March 2022 | Volume 13 | Article 796850

Role of Lipids in Senescence
Dimitri, G. P., Lee, X., Basile, G., Acosta, M., Scott, G., Roskelley, C., et al. (1995). A biomarker that identifies senescent human cells in culture and in aging skin in vivo. Proc. Natl. Acad. Sci. U.S.A. 92, 9363–9367. doi: 10.1073/pnas.92.20.9363

Dou, Z., Ghosh, K., Viziali, M. G., Zhu, J., Sen, P., Wangensteen, K. J., et al. (2017). Cyclophosphamide chromatin triggers inflammation in senescence and cancer. Nature 550, 402–406. doi: 10.1038/nature24050

Dou, Z., Xu, C., Donahue, G., Shimi, T., Pan, J. A., Zhu, J., et al. (2015). Autophagy mediates degradation of nuclear lamina. Nature 527, 105–109. doi: 10.1038/nature15548

Eberle, D., Hegarty, B., Bossard, P., Ferre, P., and Foufelle, F. (2004). SREBP transcription factors: master regulators of lipid homeostasis. Biochimie 86, 839–848. doi: 10.1016/j.biochi.2004.09.018

el-Deiry, W. S., Tokino, T., Velculescu, V. E., Levy, D. B., Parsons, R., Trent, J. M., et al. (1993). WAF1, a potential mediator of p53 tumor suppression. Cell 75, 817–825. doi: 10.1016/0092-8674(93)90500-p

Eren, M., Boe, A. E., Murphy, S. B., Place, A. T., Nagpal, V., Morales-Nebreda, L., et al. (2014). PAI-1-regulated extracellular proteolysis governs senescence and survival in Klotho mice. Proc. Natl. Acad. Sci. U.S.A. 111, 7090–7095. doi: 10.1073/pnas.1321942111

Evangelou, K., Lougias, N., Rizo, S. V., Kotsinas, A., Kletas, D., Munoz-Espin, D., et al. (2017). Universal biomarker assay to detect senescent cells in biological specimens. Aging Cell 16, 192–197. doi: 10.1111/acel.12545

Fafian-Labora, J., Carpinero-Fernandez, P., Jordan, S. J. D., Shihk-Bahaei, T., Abdullah, S. M., Malhenthiran, M., et al. (2019). FASN activity is important for the initial stages of the induction of senescence. Cell Death Dis. 10, 318. doi: 10.1038/s41419-019-1550-0

Finck, B. N., Gropler, M. C., Chen, Z., Leone, T. C., Croce, M. A., Harris, T. E., et al. (2006). Lipin 1 is an inducible amplifier of the hepatic PGC-1alpha/PPARalpha regulatory pathway. Cell Metab. 4, 199–210. doi: 10.1016/j.cmet.2006.08.005

Flor, A. C., Wolfgeher, D., Wu, D., and Kron, S. J. (2017). A signature of enhanced lipid metabolism, lipid peroxidation and aldehyde stress in therapy-induced senescence. Cell Death Discov. 3, 170375. doi: 10.1038/cddiscovery.2017.75

Fortney, K., Dobriban, E., Garagnani, P., Pirazzini, C., Monti, D., Mari, D., et al. (2015). Genome-wide scan identified by age-related disease identifies loci for exceptional human longevity. PLoS Genet. 11:e1005728. doi: 10.1371/journal.pgen.1005728

Freund, A., Patil, C. K., and Campisi, J. (2011). p38MAPK is a novel DNA damage response-independent regulator of the senescence-associated secretory phenotype. EMBO J. 30, 1536–1548. doi: 10.1038/emboj.2011.69

Giusto, N. M., Roque, M. E., and Ilincheta de Boschero, M. G. (1992). Effects of Flor, A. C., Wolfgeher, D., Wu, D., and Kron, S. J. (2017). A signature of enhanced lipid metabolism, lipid peroxidation and aldehyde stress in therapy-induced senescence. Cell Death Dis. 3, 170375. doi: 10.1038/cddiscovery.2017.75

Fortney, K., Dobriban, E., Garagnani, P., Pirazzini, C., Monti, D., Mari, D., et al. (2015). Genome-wide scan identified by age-related disease identifies loci for exceptional human longevity. PLoS Genet. 11:e1005728. doi: 10.1371/journal.pgen.1005728

Freund, A., Patil, C. K., and Campisi, J. (2011). p38MAPK is a novel DNA damage response-independent regulator of the senescence-associated secretory phenotype. EMBO J. 30, 1536–1548. doi: 10.1038/emboj.2011.69

Giusto, N. M., Roque, M. E., and Ilincheta de Boschero, M. G. (1992). Effects of aging on the content, composition and synthesis of sphingomyelin in the central nervous system. Lipids 27, 835–839. doi: 10.1007/BF02555859

Goldstein, I., Ezra, O., Rivlin, N., Mokhadas, A., Madar, S., Goldfinger, N., et al. (2012). p53, a novel regulator of lipid metabolism pathways. J. Hepatol. 56, 656–662. doi: 10.1016/j.jhep.2011.08.022

Greenberg, M. E., Li, X. M., Gugiu, B. G., Gu, X., Qin, J., Salomon, R. G., et al. (2008). The lipid whisker model of the structure of oxidized cell membranes. J. Biol. Chem. 283, 2385–2396. doi: 10.1074/jbc.M707348200

Greenberg, M. E., Sun, M., Zhang, R., Febbraio, M., Silverstein, R., and Hazen, S. L. (2006). Oxidized phosphatidylserine-CD36 interactions play an essential role in macrophage-dependent phagocytosis of apoptotic cells. J. Exp. Med. 203, 2613–2625. doi: 10.1084/jem.20060070

Gruber, I. V., Youshi, S. E., Durr-Storrer, S., Wallwiener, D., Solomayer, E. F., and Fehm, T. (2008). Down-regulation of CD28, TCR-zeta (zeta) and up-regulation of FAS in peripheral cytotoxic T-cells of primary breast cancer patients. Anticancer Res. 28, 779–784.

Guerrero, A., Herranz, N., Sun, B., Wagner, V., Gallage, S., Guiho, R., et al. (2019). Cardiac glycosides are broad-spectrum senolytics. Nat. Metab. 1, 1074–1088. doi: 10.1038/s42255-019-0122-z

Hall, B. M., Balan, V., Giebberman, A. S., Strom, E., Krasnov, P., Virtuoso, L. P., et al. (2017). p16(Ink4a) and senescence-associated beta-galactosidase can be induced in macrophages as part of a reversible response to physiological stimuli. Aging (Albany NY) 9, 1867–1884. doi: 10.18622/aging.101268

Handa, J. T., Tagami, M., Ebrahimi, K., Leibundgut, G., Janiak, A., Witztum, J. L., et al. (2015). Liprotein(A) with an intact lysine binding site protects the retina from an age-related macular degeneration phenotype in mice (an american ophthalmological society thesis). Trans. Am. Ophthalmal. Soc. 113:T5.
The retinal Kitamura, N., Nakamura, Y., Miyamoto, Y., Miyamoto, T., Kabu, K., Yoshida, M., Kasteri, J., Das, D., Zhong, X., Persaud, L., Francis, A., Muharam, H., et al. (2019). Role of the high-affinity leukotriene B4 receptor signaling in fibrosis after unilateral ureteral obstruction in mice. *PloS One* 14:e0202842. doi: 10.1371/journal.pone.0202842

Kanehira, M., Fujitawa, T., Nakajima, S., Okitsu, Y., Onishi, Y., Fukuhara, N., et al. (2017). An lysophosphatidic acid receptors 1 and 3 axis governs senescence of mesenchymal stromal cells and promotes growth and vascularization of multiple myeloma. *Cell Stem Cell* 35, 739–753. doi: 10.1016/j.stem.2017.07.011

Kang, K. B., Van Der Zyppe, A., Iannazzo, L., and Majewski, H. (2006). Age-related changes in monocyte and platelet cyclooxygenase expression in healthy male humans and rats. *Transl. Res.* 148, 289–294. doi: 10.1016/j.trsl.2006.06.004

Kasteri, J., Das, D., Zhong, X., Persaud, L., Francis, A., Muharam, H., et al. (2018). Translation control by p53. *Cancers (Basel)* 10:133. doi: 10.3390/cancers10050133

Kim, J. W., Baek, B. S., Kim, Y. K., Herlihy, J. T., Ikeno, Y., Yu, B. P., et al. (2001). Gene expression of cyclooxygenase in the aging heart. *J. Gerontol. A Biol. Sci. Med. Sci.* 56, B350–B355. doi: 10.1093/gerona/56.8.b350

Kim, J., Vaish, V., Feng, M., Field, K., Chatzistamou, I., and Shim, M. (2016). Transgenic expression of cyclooxygenase-2 (COX2) causes premature aging phenotypes in mice. *Aging (Albany NY)* 8, 2392–2406. doi: 10.18632/aging.101060

Kim, Y. M., Shin, H. T., Seo, Y. H., Byun, H. O., Yoon, S. H., Lee, I. K., et al. (2010). Sterol regulatory element-binding protein (SREBP)-1-mediated lipogenesis is involved in cell senescence. *J. Biol. Chem.* 285, 29069–29077. doi: 10.1074/jbc.M110.210386

Kirschner, R. D., Rother, K., Muller, G. A., and Engelk, K. (2010). The retinal dehydrogenase/reductase retSDR1/DHRS3 gene is activated by p53 and p63 but by not mutants derived from tumors or ECC/ADULT malformation syndromes. *Cell Cycle* 9, 2177–2188. doi: 10.4161/cc.9.16.11844

Kitamura, N., Nakamura, Y., Miyamoto, Y., Miyamoto, T., Kabu, K., Yoshida, M., et al. (2011). Mieap, a p53-inducible protein, controls mitochondrial quality by repairing or eliminating unhealthy mitochondria. *PloS One* 6:e16060. doi: 10.1371/journal.pone.0016060

Krishnamurry, J., Torrice, C., Ramsey, M. R., Kovalev, G. I., Al-Regaiey, K., Su, L., Kirschner, R. D., Rother, K., Muller, G. A., and Engeland, K. (2010). The retinal...
Song, W., Zhang, Y., Wang, J., Ma, T., Hao, L., and Wang, K. (2018). Antagonism of cysteiny1 leukotriene receptor 1 (cysLT1R) by montelukast suppresses cell senescence of chondrocytes. Cytokine 103, 83–89. doi: 10.1016/j.cyt.2017.12.021

Stein, G. H., Drumlinger, L. F., Soulard, A., and Duling, V. (1999). Differential roles for cyclin-dependent kinase inhibitors p21 and p16 in the mechanisms of senescence and differentiation in human fibroblasts. Mol. Cell. Biol. 19, 2109–2117. doi: 10.1128/MCB.19.3.2109

Storer, M., Mas, A., Robert-Moreno, A., Pecoraro, M., Ortelis, M. C., Giacomino, V. Di, et al. (2013). Senescence is a developmental mechanism that contributes to embryonic growth and patterning. Cell 155, 1119–1130.

Sun, X., Seidman, J. S., Zhao, P., Troutman, T. D., Spann, N. J., Que, X., et al. (2020). Neutralization of oxidized phospholipids ameliorates non-alcoholic steatohepatitis. Cell Metab. 31, 189–206.e8. doi: 10.1016/j.cmet.2019.10.014

Surowiak, P., Gansukh, T., Donzé, P., Halon, A., and Rybak, Z. (2014). Increase in cytochrome-c (COX-2) expression in keratinocytes and dermal fibroblasts in photoaged skin. J. Cosmet. Dermatol. 13, 195–201. doi: 10.1111/jocd.12103

Takahashi, A., Okada, R., Nagao, K., Kawamata, Y., Hanyu, A., Yoshimoto, S., et al. (2017). Exosomes maintain cellular homeostasis by excreting harmful DNA from cells. Nat. Cell. 8:15287.

Tepper, A. D., Ruurs, P., Wiedmer, T., Sins, P. J., Borst, J., and van Blitterswijk, W. J. (2000). Sphingomyelin hydrolysis to ceramide during the execution phase of apoptosis results from phospholipid scrambling and alters cell-surface morphology. J. Cell Sci. 150, 155–164. doi: 10.1042/jcs.150.1.155

Trąjkoń, K., Hsu, C., Chiantia, S., Rajendran, L., Wieland, F., et al. (2008). Ceramide triggers budding of exosome vesicles into multivesicular endosomes. Science 319, 1244–1247. doi: 10.1126/science.1153124

Tung, B. T., Rodriguez-Bies, E., Talero, E., Gamero-Estevez, E., Motilva, V., Navas, P., et al. (2017). Anti-inflammatory effect of resveratrol in old mice liver. Exp. Gerontol. 64, 1–7. doi: 10.1016/j.exger.2015.02.004

Urbanielli, L., Buratta, S., Sagini, K., Tancini, B., and Emiliani, C. (2016). Extracellular vesicles as new players in cellular senescence. Int. J. Mol. Sci. 17:1408. doi: 10.3390/ijms17091408

Urbaniak-Kujda, D., Kapelko-Slowik, K., Wolowiec, D., Dybko, J., Halon, A., Jarzbiw, B., et al. (2009). Increased percentage of CD8+CD28- suppressor lymphocytes in peripheral blood and skin infiltrates correlates with advanced disease in patients with cutaneous T-cell lymphomas. Postepy Hig. Med. Dosw. (Online) 63, 355–359.

van Deursen, J. M. (2014). The role of senescent cells in ageing. Nature 509, 439–446.

Venable, M. E., Lee, J. Y., Smyth, M. J., Bielawska, A., and Obeid, L. M. (1995). Role of ceramide in cellular senescence. J. Biol. Chem. 270, 30701–30708. doi: 10.1074/jbc.270.51.30701

Vizioli, M. G., Liu, T., Miller, K. N., Robertson, N. A., Gilroy, K., Lagnado, A. B., et al. (2020). Mitochondria-to-nucleus retrograde signaling drives formation of cytoplasmic chromatin and inflammation in senescence. Genes Dev. 34, 428–445. doi: 10.1101/gad.331272.119

Vousden, K. H., and Prives, C. (2009). Blinded by the light: the growing complexity of p53. Nat. Rev. Cancer 9, 155–168. doi: 10.1038/nrc2564

Wang, S. J., Li, D., Ou, Y., Jiang, L., Chen, Y., Zhao, Y., et al. (2016). Acetylation of 14,15-EET on endothelial senescence through activation of mTOR complex 2/Akt signaling pathways. Int. J. Biochem. Cell Biol. 50, 93–100. doi: 10.1016/j.biocel.2014.02.020

Yi, J. K., Xu, R., Jeong, M., Mileva, I., Truman, J. P., Lin, C. L., et al. (2016). Ageing-related elevation of sphingobase shortens yeast chronological life span by compromising mitochondrial function. Oncotarget 7, 21124–21144. doi: 10.18632/oncotarget.8195

Yosef, R., Pilpel, N., Tokarsky-Amiel, R., Biran, A., Ovadya, Y., Cohen, S., et al. (2016). Directed elimination of senescent cells by inhibition of BCL-W and BCL-XL. Nat. Commun. 7:11190. doi: 10.1038/ncomms11190

Yousefzadeh, M. J., Flores, R. R., Zhu, Y., Schmiechen, Z. C., Brooks, W. R., Trussoni, C. E., et al. (2021). An aged immune system drives senescence and ageing of solid organs. Nature 594, 100–105. doi: 10.1038/s41586-021-03547-7

Zhang, M., Du, Y., Lu, R., Shu, Y., Zhao, W., Li, Z., et al. (2016). Cholesterol retards senescence in bone marrow mesenchymal stem cells by modulating autophagy and ROS/p53/p21(Cip1/Waf1) pathway. Oxid. Med. Cell Longev. 2016;7524308. doi: 10.1155/2016/7524308

Zhang, P., Kishimoto, Y., Grammatikakis, I., Gottimukkala, K., Cutler, R. G., Zhang, S., et al. (2019). Senolytic therapy alleviates Abeta-oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model. Nat. Neurosci. 22, 719–728. doi: 10.1038/s41593-019-0372-9

Zhang, W., Koerner, I. P., Noppens, R., Grafe, M., Tsai, H. J., Morisseau, C., et al. (2007). Soluble epoxide hydrolase: a novel therapeutic target in stroke. J. Cereb. Blood Flow Metab. 27, 1931–1940. doi: 10.1038/sj.jcbfm.9600494

Zhang, X., Xu, G. B., Zhou, D., and Pan, Y. X. (2018). High-fat diet modifies expression of hepatic cellular senescence gene p16(INK4a) through chromatin modifications in adult male rats. Genes Nutr. 13:6. doi: 10.1186/s12263-018-0593-5

Zhao, Y., Shao, Q., and Peng, G. (2020). Exhaustion and senescence: two crucial dysfunctional states of T cells in the tumor microenvironment. Cell Mol. Immunol. 17, 27–35. doi: 10.1038/s41423-019-0344-8

Zhu, Y., Tchkonia, T., Pirtskhalava, T., Gower, A. C., Ding, H., Giorgadze, N., et al. (2014). Senolytic effect of resveratrol in old mice liver. J. Biol. Chem. 289, 2109–2117. doi: 10.1074/jbc.M113.521441

Zhou, Y., Chkonia, T., Pirtskhalava, T., Gower, A. C., Ding, H., Giorgadze, N., et al. (2015). The Achilles’ heel of senescent cells: from transcriptome to senolytic drugs. Aging Cell 14, 644–658. doi: 10.1111/acel.12344

Zuloaga, K. L., Zhang, W., Rosee, N. E., and Alkayed, N. J. (2014). Soluble epoxide hydrolase gene deletion improves blood flow and reduces infarct size after cerebral ischemia in reproducibly senescent female mice. Front. Pharmacol. 5:290. doi: 10.3389/fphar.2014.00290

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Hamsanathan and Gurkar. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY).