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The impact of ageing on lipid-mediated regulation of adult stem cell behavior and tissue homeostasis

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Abstract

Adult stem cells sustain tissue homeostasis throughout life and provide an important reservoir of cells capable of tissue repair in response to stress and tissue damage. Age-related changes to stem cells and/or the specialized niches that house them have been shown to negatively impact stem cell maintenance and activity. In addition, metabolic inputs have surfaced as another crucial layer in the control of stem cell behavior (Chandel et al., 2016; Folmes and Terzic, 2016; Ito and Suda, 2014; Mana et al., 2017; Shyh-Chang and Ng, 2017). Here, we will present a brief review of how lipid metabolism influences adult stem cell behavior under homeostatic conditions and speculate on how changes in lipid metabolism may impact stem cell aging. This review considers the future of lipid metabolism research in stem cells, with the long-term goal of identifying mechanisms that could be targeted to counter or slow the age-related decline in stem cell function.

Keywords

lipid; metabolism; fatty acids; stem cells; niche

The role of lipid metabolism in adult stem cell behavior

Lipids have been shown to participate in regulating various aspects of cellular behavior, including intracellular signaling, energy generation and membrane composition (Houten and Wanders, 2010; van Meer and de Kroon, 2011; Wymann and Schneiter, 2008) (Figure 1). In addition, lipids can alter gene expression through the regulation of transcription factor activity (Barrera et al., 2008; Bernal et al., 2015; Boonsong et al., 2007; Gu et al., 2019; Lecomte et al., 2010), changes to the epigenome (McDonnell et al., 2016), or through direct

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binding to DNA and chromatin (Silva et al., 2017; Zhdanov et al., 2016) (Figure 2). Therefore, it is not surprising that lipid catabolism and anabolism have both been shown to influence the behavior of adult stem cells. We recently reviewed, in detail, potential mechanisms by which lipids could influence stem cell behavior, highlights of which are summarized below (Clémot et al., 2020) (Figure 1).

Fatty acid oxidation (FAO)

One critical, cellular energy-generating process, which occurs in the mitochondrial matrix, is the breakdown of fatty acids (FAs), through the process of fatty acid oxidation (FAO) (Figure 2). Recent studies have contributed to an emerging model in which FAO plays a pivotal role in the maintenance of adult stem cells. For instance, in hematopoietic stem cells (HSCs), FAO is required for stem cell maintenance by controlling the critical cell fate choice between stem cell self-renewal and the onset of differentiation. Genetic or pharmacological inhibition of FAO led to stem cell loss through differentiation (Ito et al., 2012). Mitochondrial activity was shown to be important for maintaining FAO and the appropriate ratio of stem and differentiating daughter cells through asymmetric cell division, as disruption in Pink1/PARKIN-mediated mitophagy resulted in stem cell loss (Ito et al., 2016). In a similar manner, active mitochondria capable of importing lipids for oxidation are required to prevent male germline stem cell (GSC) loss through differentiation in *Drosophila melanogaster* (Sênos Demarco et al., 2019).

FAO was also shown to be important for promoting maintenance of murine embryonic neural stem cells (NSCs) (Xie et al., 2016), while in adult neural stem/progenitor cells (NSPCs), FAO is required to maintain stem cells in a quiescent state (Knobloch et al., 2017; Stoll et al., 2015). Indeed, inhibition of FAO or activation of lipogenesis in adult NSPCs stimulated excess stem cell proliferation and eventual depletion of the stem cell pool (Knobloch et al., 2017; Stoll et al., 2015). Similarly, quiescent muscle satellite cells preferentially use FAO and switch to glycolysis upon differentiation (Ryall et al., 2015). In contrast, dietary changes that raise FAO rates correlated with increased intestinal stem cell (ISC) number and function (Beyaz et al., 2016; Chen et al., 2019; Singh et al., 2016). Taken together, data indicate that FAO can influence the maintenance of several types of tissue stem cells via multiple mechanisms (Figure 1). Moving forward, it will be important to elucidate how FAO is regulated in different stem and niche support cell populations over time, for example by characterizing the variation in mitochondrial pools in active versus quiescent stem cell populations, as well as the pathways that positively or negatively regulate the expression of FAO-related genes. Future studies should also determine whether specific FAO-associated metabolites are utilized for regulating stem cell behavior (e.g. ATP for energetic demands or acetyl groups for modification of histones) and evaluate whether a decline in these byproducts contributes to altered stem cell behavior as a consequence of aging.

Lipogenesis

Cells can generate lipids through *de novo* lipogenesis, using acetyl-CoA as a building block for new FAs (Kersten, 2001). These lipids can be further modified through the action of enzymes, such as elongases, to diversify the lipid pool (Jump, 2009). Alternatively, lipids

can be imported into the cell through the activity of fatty acid binding proteins (FABPs) and transporters (Figure 2). Regardless of whether the lipids are generated *de novo* or imported into the cell from the environment, intracellular lipids appear to stimulate stem cell proliferation. For example, in contrast to the role of FAO in stem cells, *de novo* lipogenesis in NSPCs stimulates neurogenesis (Knobloch et al., 2013). A decrease in the activity of either fatty acid synthase (FASN) or acetyl-CoA carboxylase (ACC) led to a decrease in FA synthesis and an arrest in NSPC proliferation (Knobloch et al., 2013). In addition, lipid elongation and/or modification has been shown to influence ISC behavior (Wang et al., 2018a). In mice, Lysophosphaticylcholine acyltransferase 3 (Lpcat3) activity is required to prevent ISC hyperproliferation, while increased cholesterol levels can promote ISC proliferation (Wang et al., 2018a). Hence, as a trend, while FAO generally promotes quiescence and maintains adequate stem cell numbers, lipogenesis and the buildup of complex lipids promote stem cell activation and/or differentiation (Figure 1). In the future, lipid profiling in adult stem cells and during differentiation will be beneficial to understanding how changes in specific lipid classes and lipid modifying enzymes can influence stem cell behavior *in vivo*.

Stem cell maintenance mechanisms influenced by lipids

Both intrinsic and extrinsic factors are involved in regulating maintenance, survival, proliferation and differentiation capacity of stem cells. Stem cells reside in highly specialized microenvironments, also called “niches”, that provide structural support, nutrients, and/or signals related to the control of stem cell behavior. In addition, cell-intrinsic mechanisms, such as those regulating asymmetric cell division, can be employed to ensure proper tissue homeostasis (Voog and Jones, 2010).

Lipids can influence stem cell-niche communication. Indeed, stem cells can respond to lipid-based signals from adjacent cells or from the circulation. For example, HSCs are regulated by the eicosanoid lipid prostaglandin E2 (PGE2), which is secreted by osteoblasts in the bone marrow (Domingues et al., 2017; Goessling et al., 2009; Hoggatt et al., 2009; Reya et al., 2003), and by sphingosine-1-phosphate (S1P), both of which influence homing to the bone marrow (Ogle et al., 2017). In the NSC niche, the accumulation of lipid droplets (LDs) in glial cells adjacent to NSCs is observed in neurodegenerative diseases and under some stress conditions, such as hypoxia and mitochondrial damage (Bailey et al., 2015; Hamilton et al., 2015; Liu et al., 2017, 2015). Although the accumulation of LDs in the niche plays a protective role to maintain NSCs in the *Drosophila* brain under hypoxia (Bailey et al., 2015), it seems to play an adverse role and promote NSC loss and neurodegeneration in a mouse model of Alzheimer’s disease (Hamilton et al., 2015). In addition, niche support cells themselves can respond to changes in lipids in the environment. For example, in the *Drosophila* ovary, niche cells can sense changes in dietary cholesterol, resulting in the release of the signaling molecule Hedgehog (Hh), which is important for the activation and proliferation of follicle stem cells (FSCs) (Hartman et al., 2013). Furthermore, the differentiation and maintenance of Paneth cells, a primary component of the ISC niche in the small intestine, rely upon secreted phospholipase A2-derived lipids (Schewe et al., 2016), which affects ISC maintenance in a non-autonomous manner.

As stem cells rely on mechanisms such as cell polarity and asymmetric division in order to specify renewal of stem cell identity and maintain the stem cell pool upon division, membrane lipids can also play an important role in regulating stem cell behavior. One class of membrane lipids that appears to be important for regulating stem cell fate decisions are the phosphatidylinositols (PIs). In *Caenorhabditis elegans* seam cells, which act as progenitor cells for the developing epithelia, mutations in phospholipid-modifying enzymes that disrupt the composition and localization of PI to the plasma membrane impair trafficking of polarity-related proteins, which ultimately disrupts spindle orientation and asymmetric cell division (Kanamori et al., 2008). Similarly, in *Drosophila* larval neural progenitor cells, enzymes that bind to and regulate PIs are required for the asymmetric distribution of cell fate determinants (Koe et al., 2018), and in mouse epidermal stem cells, asymmetric division relies on PI-dependent kinase 1 (PDK1) and apically-enriched PIP3 (Dainichi et al., 2016). In addition to PIs, other lipid classes may also influence cell polarity. For instance, lipids can be covalently linked to proteins important for cell polarity and asymmetric division through N-terminal myristoylation (Benetka et al., 2008). In addition to the establishment of cell polarity, other mechanisms involving membrane lipids are important for regulating stem cell behavior. For example, the clustering of lipid rafts at specific domains in the plasma membrane can influence signaling pathways important for HSC and NSC behavior (Deng et al., 2019; Hermetet et al., 2019; Yamazaki et al., 2006).

Given the roles of FAO and lipogenesis in controlling stem cell behavior described above, it will be interesting to determine through which mechanism(s) these metabolic processes act to control stem cell behavior. For instance, *de novo* lipogenesis could fundamentally change the lipid pool in differentiating cells, which might activate or inhibit intracellular signaling by interfering with lipid rafts or secondary messengers (Figure 1; Figure 2). Metabolomic analyses in adult stem cell populations will be highly beneficial for further understanding which specific lipid-derived metabolite(s) contribute to stem cell maintenance, and which of those metabolites, if any, change during differentiation and with age.

Age-related changes in lipid metabolism and the decline in stem cell function

Changes in lipid homeostasis are observed as organisms age. For instance, there is a trend toward increased fat storage, including in tissues that normally would not have fat deposits (Kuk et al., 2009). In addition, changes are observed in lipid membrane composition that impact membrane fluidity in some cell types, and an increase in the proportion of unsaturated phospholipids correlates with increased lipid peroxidation and intracellular damage (Gonzalez-Covarrubias, 2013; Papsdorf and Brunet, 2018). Furthermore, lipid metabolites that play a role in signaling pathways, such as ceramides (in apoptosis) and SP1 (in survival and proliferation), have also been observed to change proportionally with age (Montoliu et al., 2014; Papsdorf and Brunet, 2018). For example, ceramides have been shown to increase with age, and have been associated with shorter lifespans in *C. elegans*, while decreased levels of SP1 are associated with age-related diseases (Montoliu et al., 2014; Papsdorf and Brunet, 2018). Importantly, age-related changes among lipid species appear to be tissue-specific (Papsdorf and Brunet, 2018).

Given the important role that lipid metabolism plays in controlling stem cell homeostasis in young tissues (Figure 2), it is likely that age-related disruptions in lipid homeostasis contribute to the decline in stem cell function. However, as lipidomics studies of relatively pure stem cell populations are largely unavailable, it is difficult to predict which specific age-related changes in lipid homeostasis might impact stem cell maintenance and differentiation.

As mitochondrial function and autophagy both change with age and are tightly linked to lipid homeostasis, we speculate in the next sections about how age-related changes in mitochondrial function and autophagy could alter lipid homeostasis and stem cell function. In addition, recent evidence linking alterations in lipid metabolism to modifications in the epigenome may also represent a way in which adult stem cell function may be impacted as a result of lifelong exposure to multiple changes in lipid levels.

Mitochondrial function

As noted above, recent studies in model organisms have begun to address the mechanisms through which mitochondrial metabolism, and to some extent lipid imbalance, influence stem cell behavior. In *Drosophila* male GSCs, active mitochondria are important to prevent the accumulation of LDs and stem cell loss due to differentiation, which appear to result, at least in part, from ectopic activation of the Target of Rapamycin (TOR) pathway (Sênos Demarco et al., 2019). It remains to be determined whether this mechanism contributes to loss of GSCs in aged animals (Boyle et al., 2007). In addition, overexpression of the *Drosophila* homolog of the mitochondrial biogenesis factor *PGC1α, Spargel,* in ISCs and daughter enteroblasts (EBs) delayed the age-related onset of stem cell dysfunction by enhancing OXPHOS efficiency and reducing ROS (Rera et al., 2011); similar results were found with the enhancement of mitochondrial complex I activity by overexpressing the yeast alternative NADH dehydrogenase (NDI1) in ISCs/EBs (Hur et al., 2013). Moreover, both Pink1 and Parkin are required for promoting ISC proliferation throughout life, perhaps through stimulation of mitophagy and maintenance of a healthy pool of mitochondria (Koehler et al., 2017). Mitochondrial function is also important for mammalian ISCs, as fasting resulted in stimulation of FAO in old, murine ISCs, which led to increased proliferation, as assayed by organoid formation capacity (Mihaylova et al., 2018). Importantly, FAO is required for long-term maintenance of ISCs *in vivo*, as measured by quantifying Lgr5+ cells and assaying organoid formation *in vitro* in CPT1a knock-out mice (Mihaylova et al., 2018). Given the importance of sustained mitochondrial function for optimal ISC behavior in both systems, it would be interesting to test whether the enhancement of mitochondrial activity in *Drosophila* ISCs was beneficial due to sustained FAO rates.

Together, these studies suggest that FAO must be preserved in aged stem cells to keep the balance of intracellular lipids in check and that any decrease in FAO could change lipid composition and/or lipid-derived metabolite pools that contribute to the age-related decline in stem cell function. As decreased mitochondrial activity and turnover are commonly observed features in old stem cells (Ho et al., 2017; Mohrin et al., 2015; Oh et al., 2014;

Trifunovic et al., 2004), it will be important to determine whether enhancing mitochondrial activity will be a feasible approach to prevent age-related changes in lipid homeostasis.

Autophagy

Another strategy utilized by cells to control lipid homeostasis is through autophagy, either directly, through lipophagy, or indirectly through the turnover of cellular components responsible for the metabolism of lipids, such as mitochondria (Zhang et al., 2018). A number of studies have shown that a decline in autophagic activity in stem cells is often observed with age (Ho et al., 2017; Kaushik and Cuervo, 2018), and the maintenance of active autophagy prevents age-related stem cell dysfunction (García-Prat et al., 2016; Ho et al., 2017). Indeed, reduced levels of autophagy in aged muscle stem cells leads to a decrease in regenerative potential and contributes to muscle atrophy (García-Prat et al., 2016). In HSCs from aged animals, a decline in autophagy leads to the accumulation of mitochondria which, in turn, contributes to an 'activated' metabolic state that correlates with the myeloid differentiation bias characteristic of aged HSCs (Geiger et al., 2013; Ho et al., 2017). Conversely, when autophagy is active, mitochondria are routinely cleared leading to reduced oxidative metabolism and preservation of HSC function over time (Ho et al., 2017). Hence, it is possible that decreased autophagy in stem cells from aged individuals could result in a lipid imbalance by either increasing FAO, if an abnormal number of mitochondria are present, or decreased FAO if the mitochondria are present but dysfunctional.

Several recent reports have linked changes in autophagy, altered lipid levels, and loss of stem cell behavior more directly (Sênos Demarco et al., 2020; Wang et al., 2019). In young *Drosophila* testes, autophagy is required in somatic cyst stem cells (CySCs) to prevent the accumulation of neutral lipids, which contributes to the loss of CySCs due to differentiation; the GSCs that are surrounded by CySCs depleted for autophagy-related genes (Atgs) are also lost in a non-autonomous manner (Sênos Demarco et al., 2020). However, it is not clear whether the increase of lipids in this model is due to a decrease in mitophagy, lipophagy, or another mechanism. In addition, it is unclear how this requirement might change in testes from aged animals. Elucidating how changes in lipid composition and homeostasis impact stem cell behavior and the mechanisms that drive lipid imbalance in stem cells will prove useful for the development of new interventions that could be used in the context of regenerative medicine and to counter the loss of stem cell function in aged animals and number over time.

Epigenome

Recently, studies have revealed how alterations in lipid metabolism can influence the state of the epigenome (reviewed in Papsdorf and Brunet, 2018) (Figure 2). Both histone and nucleotide modifications, including methylation and acetylation, are thought to provide cellular "memory" and identity by reinforcing a specific profile of gene expression. Moreover, changes in chromatin modifications (called "marks") have been observed with age, and the prevention of these alterations can often extend animal lifespan (Benayoun et al., 2015; Pal and Tyler, 2016; Sen et al., 2016). Chromatin marks can be derived from lipid sources (Berger and Sassone-Corsi, 2016; Etchegaray and Mostoslavsky, 2016). For instance, the majority of the acetyl-CoA utilized by histone acetyltransferases to add acetyl

groups onto lysines in histones is thought to be derived from lipid sources (McDonnell et al., 2016), and histone acylation utilizes the direct addition of short-chain FAs to histones when more than two carbon-based FA groups are used (Sabari et al., 2017) (Figure 2). Of note, short-chain FAs derived from the microbiota have been shown to contribute to histone modifications in mouse intestinal epithelial cells (Fellows et al., 2018), opening up the possibility that ISCs could also be regulated by this mechanism.

Another way lipid metabolism can influence the epigenome is through chromatin methylation. S-adenosylmethionine (SAM) is a common precursor to both histone and DNA methylation and phospholipids, as it is required for the generation of phosphatidylcholines (PCs) through the methylation of phosphatidylethanolamines (PEs) (Bremer and Greenberg, 1961; Ye et al., 2017). As such, the increase or decrease in phospholipid generation can impact the availability of SAM for the generation of methylation marks in the chromatin (Ye et al., 2017) (Figure 2). SAM levels have been shown to affect stem cell behavior, at least in part, through chromatin methylation (Nishikawa et al., 2015; Obata et al., 2018; Tsogtbaatar et al., 2020; Uribe-Etxebarria et al., 2020). Because age-related changes to SAM concentration have been observed in rats (Stramentinoli et al., 1977), and SAM availability has been shown to affect longevity (Lee et al., 2016), it is tempting to speculate that changes in lipid metabolism that affect cellular SAM levels would also impact animal physiology and lifespan, perhaps also by regulating stem cell maintenance and activity.

In addition, lipids can impact signaling pathways that themselves modify the chromatin state (Figure 2). For instance, lipid-derived prostaglandins and lipopolysaccharides can modulate epigenetic marks (De Santa et al., 2009; Wymann and Schneiter, 2008). Moreover, G protein-coupled receptor (GPCR) signaling can be affected by lipid-derived ligands, membrane fluidity and composition, and by lipid-derived post-translational modifications (Escribá et al., 2007; Im, 2013; Wymann and Schneiter, 2008). Interestingly, GPCR signaling can potentially affect the epigenome, as was shown in the case of a lysophosphatidic acid receptor regulating histone deacetylases function (Ishdorj et al., 2008). Since GPCR signaling has been implicated in the regulation of multiple types of adult stem cells (reviewed in Doze and Perez, 2013), age-related changes in lipid homeostasis could potentially affect stem cells through changes in GPCR activity. Hence, an emerging and exciting hypothesis is that age-related changes in lipid-derived metabolites could influence stem cell maintenance or activity through the epigenetic regulation of gene expression.

Lipid metabolism and ageing-related diseases

A link between FA/lipid profiles and human and model organism longevity has been reported in several studies (Atzmon et al., 2004; Barzilai et al., 2001; Vaarhorst et al., 2011), and many age-related disorders are accompanied by a change in lipid homeostasis. For example, metabolic reprogramming (Hanahan and Weinberg, 2011) and dysregulation of lipid metabolism are common features of cancer initiation and progression (Beloribi-Djefaflia et al., 2016; Cruz et al., 2020; Sledzinski et al., 2019; Tirinato et al., 2017; Yi et al., 2018), which has an increased incidence with increasing age. Hence, it is possible that age-related changes in lipid homeostasis contribute to the transformation of tissue stem cells into tumor-initiating cells or endow cancer cells with stem cell traits, leading to the formation of

the so-called “cancer stem cells”. A comprehensive discussion of this topic is beyond the scope of this review, but serves as one example of how age-related changes in lipid mediated regulation of stem cell behavior could contribute to disease. Here, we will focus on how changes in lipid homeostasis occurring in other types of age-onset disorders, such as neurodegeneration and metabolic disorders, may impact tissue stem cells and, in turn, how this could contribute to the pathophysiology of disease.

Neurodegeneration

NSC activity decreases with age (Hamilton et al., 2013) and is dysregulated in neurodegenerative disorders (Lazarov et al., 2010), many of which show increased incidence with age (Hou et al., 2019). Interestingly, alterations in lipid metabolism have been shown to occur in both patient biopsies and in several models of neurodegeneration (Alzheimer, 1907; Hamilton et al., 2015; Hussain et al., 2013; Podtelezhnikov et al., 2011; Tanzi, 2012). For instance, it has been known since the first diagnoses that lipids aberrantly accumulate in brains of Alzheimer’s disease (AD) patients (Alzheimer, 1907). Recently, it was shown that LDs containing oleic acid accumulate in the forebrain and correlate with a decrease in NSC proliferation (Hamilton et al., 2015). Strikingly, in a mouse model of Alzheimer’s disease where NSCs proliferate less, the pharmacological inhibition of oleic acid production rescues the proliferative capacity of these stem cells (Hamilton et al., 2015). Though it is currently unknown if lipid accumulation precedes any other changes that occur in human AD patients, there is evidence that lipids accumulate in microglia in non-diseased aged brains (Marschallinger et al., 2020). LD accumulation in these cells prevented phagocytic activity, increased ROS generation and dramatically increased the pro-inflammatory response in the brain, likely contributing to age-related neurodegeneration (Marschallinger et al., 2020). It is tempting to speculate that the microglial LDs in this scenario would also be rich in oleic acid, sharing a common feature with the AD model. Whether aged NSCs in non-AD models, including wild type animals and other neurodegeneration models, positively respond to the inhibition of oleic acid production has not yet been tested.

Interestingly, omega-3 FA supplementation has been shown to suppress the age-related decrease in neurogenesis seen in old rats (Dyall et al., 2010). With age, retinoic acid receptor (RAR), retinoid X receptor (RXR), and PPAR levels decline in the rat forebrain, negatively impacting learning and memory. However, dietary eicosapentaenoic acid and docosahexaenoic acid, both of which are ligands for RXRs and PPARs, were able to reverse the age-associated decline in these receptors and positively affect neurogenesis (Dyall et al., 2010). Together, these studies suggest that specific lipid species may contribute to the integrity of the NSC niche. Hence, future studies should profile lipids in young and old NSC and glial populations for the elucidation of the specific contribution of different lipids to NSC behavior.

Diabetes and metabolic syndrome

Metabolism-related disorders can impact lipid composition in tissues and organs. For instance, the composition and abundance of sphingomyelin and triacylglycerides have been shown to participate in the incidence of insulin resistance and obesity (Pietiläinen et al., 2007; Rhee et al., 2011; Suhre et al., 2010). In general, dyslipidemias are thought to

contribute to the incidence of age-related disease, as interventions that attempt to restore lipid balance are associated with increased health and fitness (Crimmins and Finch, 2012). For example, the monounsaturated fatty acid (MUFA) to polyunsaturated fatty acid (PUFA) ratio likely contributes to organismal health, at least in part, by regulating the degree of oxidative damage (Gonzalez-Covarrubias, 2013). While saturated and MUFAs are resistant to ROS-induced peroxidation, PUFAs are significantly more damaged by these insults, leading to additional oxidation and damage to other cellular components and organelles (Hulbert, 2003; Muller et al., 2007). Although lipid composition and deposition are significantly altered in age-related metabolic disorders such as type 2 diabetes, the impact of these "extra" lipids in resident stem cell populations and the corresponding niches is currently underexplored. Nevertheless, a few studies have suggested that type 2 diabetes may impact the behavior of hematopoietic and mesenchymal stem cells (MSCs) (Deng et al., 2018; Fadini et al., 2017).

Dietary interventions and stem cell aging

Different types of dietary interventions have been shown to affect aging, at least in part, through effects on adult stem cells. These interventions are often accompanied by changes in lipid homeostasis. As dietary lipids likely contribute to healthy aging (Abbott et al., 2012; Puca et al., 2008), below we discuss the relationships between diet-induced changes in lipid balance and age-related changes in stem cell function.

Caloric restriction

Typically defined as a 20–40% reduction in caloric intake, caloric restriction (CR) is well-known to extend lifespan and delay the onset of age-related disorders (Fontana and Partridge, 2015; Puca et al., 2008). CR influences lipid homeostasis through different pathways (de Diego et al., 2019; Puca et al., 2008). As CR delays age-related changes in DNA methylation in mammals, it was shown to affect the expression of lipid metabolism genes, leading to increased lipolysis and shorter FA chain lengths (Hahn et al., 2017). CR also leads to a decrease in total serum cholesterol and other lipid factors related to higher risk for age-related atherosclerosis (Fontana et al., 2004) and to changes in membrane lipid profiles that are associated with decreased peroxidability (Puca et al., 2008). Furthermore, CR elevates nitric oxide levels, which stimulates mitochondrial biogenesis and enhances FAO and lipolysis (Nisoli et al., 2005). Altogether, CR leads to a reduction of fat accumulation, which participates in the observed extension of lifespan.

In parallel, CR appears to delay the age-related decline in tissue homeostasis, as it generally improves stem cell maintenance and function (Mana et al., 2017). In the mouse small intestine, CR stimulates ISC self-renewal and function, promoting the ability of isolated crypts to form organoids *in vitro* and increasing the regeneration of crypts after damage *in vivo* (Igarashi and Guarente, 2016; Yilmaz et al., 2012). This effect is mediated non-autonomously through downregulation of mechanistic Target of Rapamycin (mTOR) signaling in the adjacent Paneth cells. Interestingly, short-term fasting, which also has pro-longevity and regenerative effects, intrinsically improves ISC function in young and aged mice, and this effect is dependent upon induction of FAO (Mihaylova et al., 2018). In the

hematopoietic system, CR promotes HSC quiescence, thereby preventing loss due to hyper-proliferation with age, in a mechanism involving a decrease in Insulin/Insulin-like growth factor I signaling (IIS) (Tang et al., 2016). Interestingly, CR also attenuates the age-related decline in GSCs in *Drosophila* testes (Mair et al., 2010) and ovaries (Hsu and Drummond-Barbosa, 2009), at least in part through mechanisms involving reduced IIS in the niche (Hsu and Drummond-Barbosa, 2009). Finally, CR was also shown to enhance the function of muscle satellite cells, which was correlated with an increase in the number of mitochondria (Cerletti et al., 2012). In addition, the transcriptome of satellite cells follows a circadian rhythm that is altered aging (Solanas et al., 2017). Amongst the genes that exhibit an oscillatory pattern are lipid metabolism genes, whose expression no longer appears to peak during the day in aged stem cells. Interestingly, CR prevents this age-related change in the circadian patterns of gene expression (Solanas et al., 2017).

Although the contribution of changes in lipid homeostasis to the positive effects of CR on adult stem cells is not clearly established, we speculate that they are likely to play a significant role. Indeed, the mTOR and IIS pathways are known to regulate lipid homeostasis in response to nutrient availability (Caron et al., 2015; Lamming and Sabatini, 2013). Downregulation of these pathways in HSCs or in intestinal and ovarian niche support cells could decrease lipid accumulation and contribute to improved stem cell function. Similarly, increased mitochondrial biogenesis in satellite cells could lead to increased or more efficient FAO, which is correlated with stem cell maintenance.

High fat diet

High fat diet (HFD) in animal models has been used to better understand the interplays between Western diets, which contain excess saturated fats, and the development of obesity and metabolic disorders in humans (Wang and Liao, 2012). Importantly, HFD accelerates the development of many age-related pathologies (López-Otín et al., 2013).

In contrast to CR, a systemic excess of lipids resulting from HFD negatively impacts stem cells (Mana et al., 2017) and appears to mimic at least some aspects of the age-related decline in stem cell function. In the mouse intestine, HFD reversibly increases the number and self-renewal capacity of ISCs, at the expense of differentiation (Beyaz et al., 2016; Mah et al., 2014) and this increase in proliferation was suggested to contribute to ISC-derived cancers (Beyaz et al., 2016). The effect of HFD on ISCs seems to be largely mediated by an increase in lipids, as these could be reproduced by treatment with FAs *in vitro* (Beyaz et al., 2016). In addition, excess dietary cholesterol has a similar effect on ISCs (Wang et al., 2018b). In the bone marrow, HFD-treated MSCs show a bias in differentiation toward the adipogenic fate at the expense of osteogenesis (Ambrosi et al., 2017), similar to what is observed during aging. HFD also increases the number and function of HSCs and skews differentiation toward the myeloid lineage at the expense of the lymphoid lineage, which also occurs with age and is believed to contribute to inflammation and metabolic disease (Singer et al., 2014; Adler et al., 2014; Hermetet et al., 2019; Luo et al., 2015; Van Den Berg et al., 2016). Furthermore, the increased consumption of saturated fats is thought to contribute to neurodegenerative diseases, long-term memory loss and cognitive impairment (Park et al., 2010). In agreement, HFD leads to a decrease in NSCs in mice by altering

proliferation and function (Li et al., 2012; Ogrodnik et al., 2019; Park et al., 2010) through a mechanism that seems to involve increased lipid peroxidation (Park et al., 2010) and signaling originating from an abnormal accumulation of lipid-enriched senescent cells in the NSC niche (Ogrodnik et al., 2019).

Although the effects of HFD on adult stem cells have been investigated primarily in the intestine, the hematopoietic system and the nervous system because of well-known effects of obesity on these tissues, HFD was also shown to negatively affect stem cells of the lung (Hegab et al., 2018) and prevent satellite cell activation and muscle regeneration (Fu et al., 2016). However, in these systems, it is unclear whether and how changes in lipid homeostasis are directly involved in the effects observed on stem cells. In the lung, HFD might influence stem cells via an indirect mechanism, as supplementation of a regular diet with a lipid mix or individual lipids had no obvious effects (Hegab et al., 2018).

Ketogenic diet

A ketogenic diet (KD) consists of high fat, moderate protein and low-carbohydrate uptake, resulting in an elevation of circulating ketone bodies, compounds produced during the metabolism of fats. KD has been associated with extended longevity in mice (Newman et al., 2017; Roberts et al., 2017) and has neuroprotective effects that are potentially beneficial against age-related neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases (Balietti et al., 2010; Gano et al., 2014). However, the impact of KD on adult stem cells and whether this could contribute to its beneficial effects remains mostly unexplored. Interestingly, a recent study demonstrated that a KD enhances ISC number and function (Cheng et al., 2019). This is mediated by an increase in the ketone body beta-hydroxybutyrate, which acts as a signaling molecule inhibiting class 1 histone deacetylases and resulting in enhanced Notch signaling. However, in this case, the increase in FAs provided in the diet does not directly affect the behavior of the ISCs. Rather they fuel FAO in order to provide acetyl-CoA as a substrate for ketogenesis, in presence of low carbohydrates.

Altogether, these findings imply that dietary interventions leading to systemic excess of lipids, such as HFD, could contribute to age-related decline in stem cell function, whereas those leading to decreased lipid storage positively affect stem cells and extend lifespan. Of note, specific dietary lipids may contribute to healthy aging depending on their specific distribution and levels throughout the body (Abbott et al., 2012; Puca et al., 2008). For instance, omega-3 FAs appear to increase neurogenesis (Dyall et al., 2010; Kang et al., 2014; Lo Van et al., 2019; Nascimento et al., 2016), suggesting that diet could be used to rescue neuronal loss in diseases and aging.

Conclusions

Lipids can affect the behavior of stem cells by impacting energy reserves, plasma membrane composition, secondary messenger signaling, and changes to gene expression, among others (Figure 2). Whether or not these lipid-impacted cellular features change with age and how they could affect adult stem cell behavior remain to be fully elucidated. Given that stem cells rely on different mechanisms to maintain proper lipid metabolism, including FAO,

mitochondrial quality control and the downregulation of pro-lipid anabolism programs, it will be interesting to see whether changes to lipid metabolism are associated with and/or caused by dysfunctional mitochondria or cellular quality control mechanisms (Figure 1). It is highly likely that fatty acids serve as an important energy source for adult stem cells and/or that FAO can supply stem cells with extra energy under challenging conditions, such as during starvation. As such, age-related decreases in FAO levels could negatively impact stem cell maintenance and activity. Future studies will shed light on whether lipid imbalance can also be directly linked to age-onset disorders, including but not limited to neurodegenerative diseases, metabolic syndrome and cancer. If so, targeting lipid homeostasis may be a viable approach to treat age-related disease.

The composition of the lipid pools in young versus old stem cell populations remain elusive, as is the careful characterization and comparison of lipid species in stem cells and differentiated progeny. A major breakthrough in the field will come in the form of lipidomics and metabolomics analyses in purified adult stem cell populations and supporting niche cells. Having a framework upon which more direct hypotheses can be proposed and tested will be extremely beneficial for a more detailed understanding of how age-related changes in lipid metabolism affect adult stem cells and surrounding niche components.

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Highlights

- Lipids can impact intracellular signaling, energy generation, and gene expression
- Mechanisms that maintain lipid homeostasis impact stem cell behavior
- Comprehensive lipidomics studies in young and old adult stem cell pools have yet to be performed
- Targeting lipid homeostasis may be a viable approach to treat age-related disease

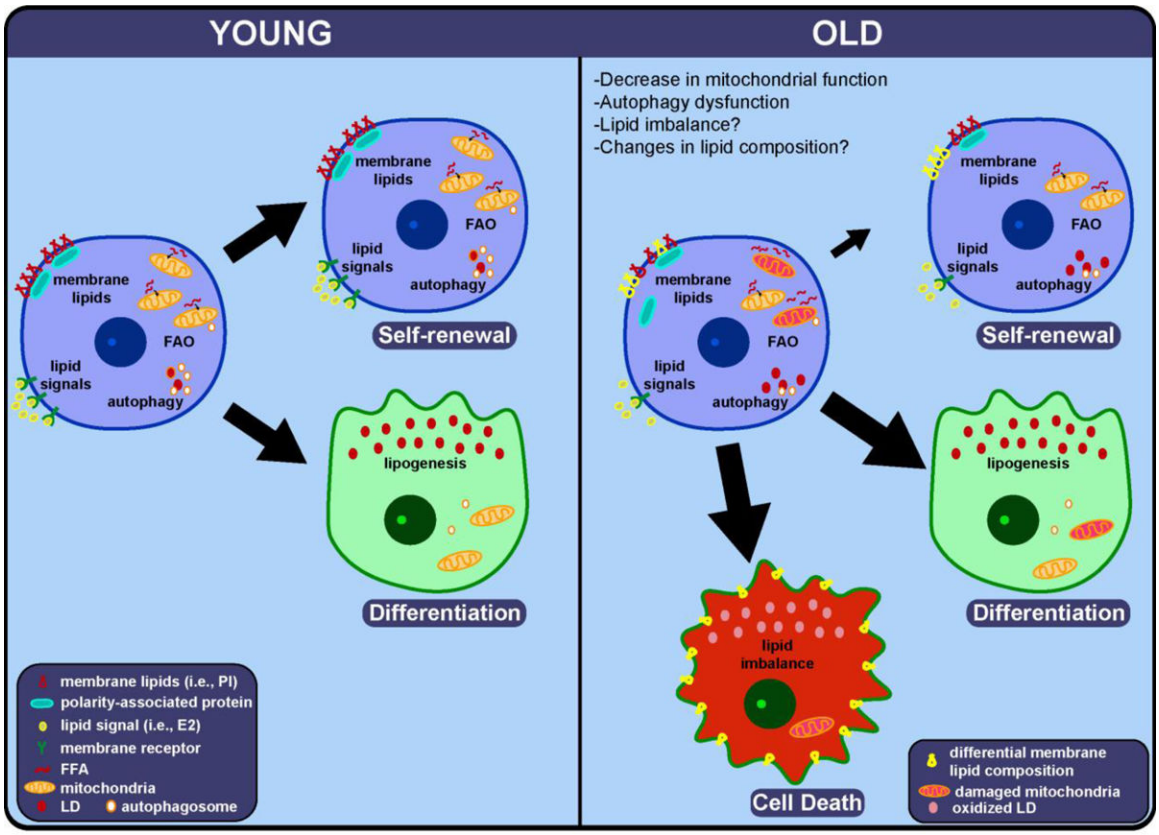

Figure 1- Ways in which an imbalance in lipid metabolism may contribute to age-related changes in stem cell function:

FAO is one mechanism utilized for the maintenance of several stem cell populations, including HSCs, ISCs, NSPCs and GSCs. Meanwhile, *de novo* lipogenesis is often associated with stem cell activation and differentiation, such as in NSPCs. Quality control mechanisms, including autophagy, are also required for the maintenance and activity of stem cells and are likely to contribute to intracellular lipid levels through mitophagy and lipophagy. Specific lipid species, such as PIs, also contribute to stem cell self-renewal by establishing cell polarity and contributing to asymmetric divisions. Moreover, lipid and lipid-derived metabolites also contribute to intracellular signals that govern stem cell behavior. Aging can result in decreased mitochondrial function and autophagy in stem cells, leading to the onset of age-related stem cell malfunction, including, but not limited to, differentiation biases and cell death. As both of these cellular processes contribute to lipid homeostasis, it is likely that changes in both will lead to alterations in lipid species, which in turn, may impact stem cell self-renewal, differentiation, and survival.

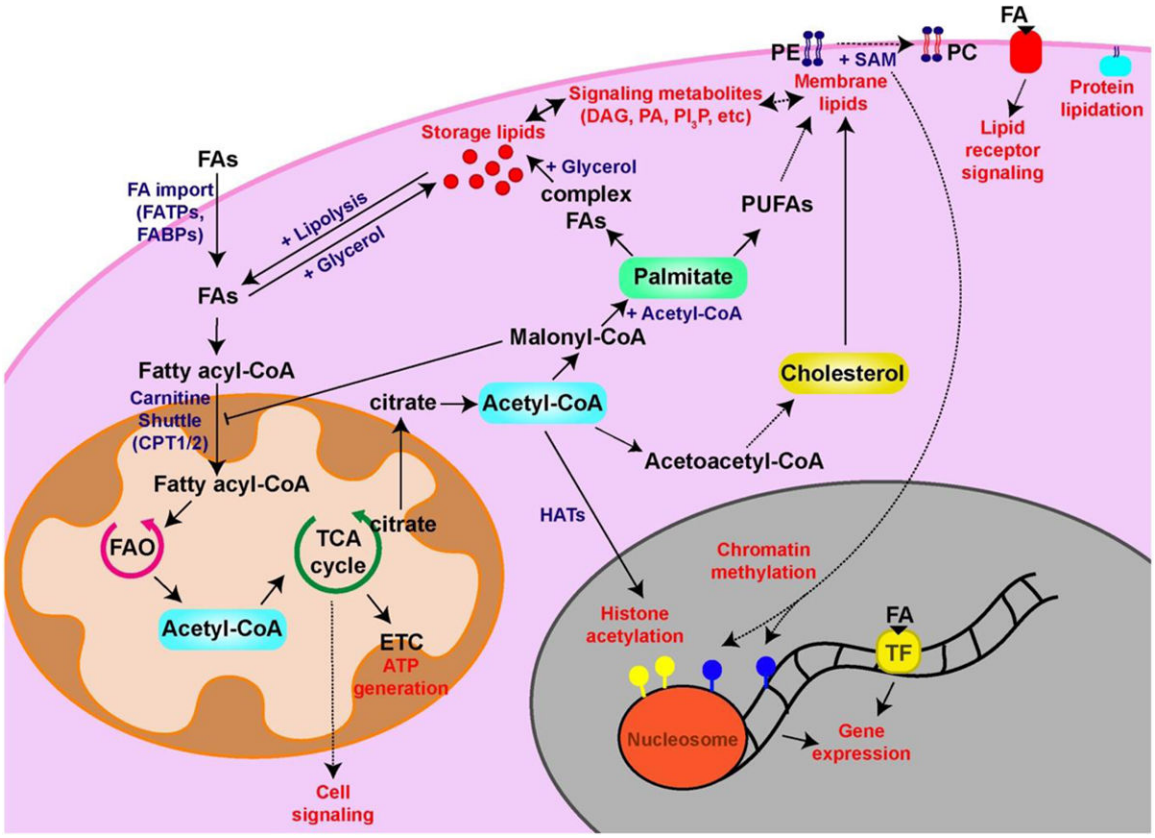

Figure 2. Lipid metabolism contributes to numerous cellular processes.

Fatty acids (FAs) are incorporated into the cell through FA transport proteins (FATPs) and FA binding proteins (FABPs). Once inside the cell, FAs can be converted into neutral lipids (with the addition of FAs into a glycerol backbone) and stored into lipid droplets. Alternatively, FAs can be conjugated with Coenzyme A (CoA) and incorporated into the mitochondria through the action of the carnitine shuttle (including CPT1 and CPT2) for FA oxidation (FAO). As a result of FAO, acetyl-CoA molecules are produced, which then enters the tricarboxylic acid cycle (TCA) for full reduction and the generation of metabolites that can 1) contribute to energy generation in the form of ATP through the electron transport chain (ETC), 2) contribute to the generation of metabolites that participate in cell signaling (e.g., α-KG), and 3) contribute to the generation of pools of citrate, which can be exported into the cytoplasm and converted back into acetyl-CoA. Cytoplasmic pools of acetyl-CoA can contribute to lipogenesis (through the generation of complex FAs, polyunsaturated FAs – PUFAs – and cholesterol), which can ultimately contribute to the generation of neutral storage lipids, membrane lipids and signaling metabolites. In addition, acetyl-CoA can also be utilized as a source for histone acetylation through the action of histone acetyl-transferases (HATs). As s-adenosylmethionine (SAM) acts as a substrate for the methylation of phosphatidylethanolamine (PE) into phosphatidylcholine (PC), lipid metabolism can also influence chromatin methylation through the regulation of SAM levels. Asides from lipid-controlled epigenetic modifications, FAs can also control gene expression through the direct binding to transcription factors (TFs) that are normally membrane-bound or cytoplasmic, but that translocate into the nucleus upon FA binding. Finally, FAs can also act as ligands for

membrane receptors, and lipid moieties can be used to post-transcriptionally modify proteins for membrane localization.