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REVIEW

Lipid metabolism in focus: how the build-up and breakdown of lipids affects stem cells

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ABSTRACT

Cellular metabolism has recently emerged as a key regulator of stem cell behavior. Various studies have suggested that metabolic regulatory mechanisms are conserved in different stem cell niches, suggesting a common level of stem cell regulation across tissues. Although the balance between glycolysis and oxidative phosphorylation has been shown to be distinct in stem cells and their differentiated progeny, much less is known about lipid metabolism in stem cell regulation. In this Review, we focus on how stem cells are affected by two major lipid metabolic pathways: the build-up of lipids, called *de novo* lipogenesis, and the breakdown of lipids, called fatty acid beta-oxidation. We cover the recent literature on hematopoietic stem cells, intestinal stem cells, neural stem/progenitor cells and cancer stem cells, where these two lipid pathways have been studied in more depth.

KEY WORDS: Lipid metabolism, *De novo* lipogenesis, Fatty acid beta-oxidation, Neural stem/progenitor cells, Hematopoietic stem cells, Intestinal stem cells, Cancer stem cells

Introduction

Stem cells are not only crucial during development, they also fulfill fundamental roles in tissue maintenance and regeneration throughout adulthood. These somatic stem cells are multipotent and give rise to lineage-specific progeny. For example, hematopoietic stem cells (HSCs) constantly replenish the blood system and failure to do so results in severe disease (Calvi and Link, 2015). Similarly, stem cells of the intestine (ISCs) regenerate the intestinal surface roughly every 5 days (Gehart and Clevers, 2019). Although the function of these two stem cell types is well-defined, the role of other somatic stem cells are just being discovered. Neural stem/progenitor cells (NSPCs) generate new neurons until old age (Bond et al., 2015; Kempermann et al., 2018), a process which is thought to contribute to learning and memory. Dysfunctional neurogenesis has been correlated with neurodegenerative diseases (Toda et al., 2019). Although the proper function of somatic stem cells is crucial for homeostasis, another type of stem cell has detrimental effects: many cancer types are thought to harbor cancer stem cells (CSCs), which contribute to cancer relapse and metastasis (Nassar and Blanpain, 2016). Thus, understanding their properties is important for the development of specific cancer therapies aimed at eradicating CSCs.

Understanding the regulation of stem cells is thus highly relevant for health and disease. Somatic stem cells reside in specific niches and have distinct gene transcription signatures. However, the emergence of a common metabolic stem cell profile suggests that, at least on a metabolic level, stem cells across niches might be more similar than previously anticipated. Several recent reviews outline their general metabolic signature (Ito and Ito, 2018; Ly et al., 2020; Shapira and Christofk, 2020; Zhang et al., 2018). Despite the acknowledged importance of metabolism for stem cell regulation, relatively little is known about lipid metabolism in stem cells.

Lipids are a diverse group of organic compounds that play roles in energy storage, membrane production and signaling. Thus, lipid metabolism comprises a large variety of pathways, including elongation, desaturation and modification of lipids into various lipid classes. For a comprehensive resource on lipids, we refer the reader to the LIPID MAPS Consortium (http://www.lipidmaps.org). Furthermore, two recent reviews by Jones and colleagues have covered lipid-mediated regulation of stem cell behavior and stem cell aging, providing a good overview of the vast relevance of lipids in this context (Clémot et al., 2020; Demarco et al., 2020).

In this Review, we focus on two major lipid metabolic pathways and how they influence stem cell behavior: the build-up of lipids in the cytosol, called *de novo* lipogenesis (DNL), and the breakdown of lipids in the mitochondria, called fatty acid beta-oxidation (FAO). Both pathways are explained in detail in Box 1. FAO also partially occurs in peroxisomes (Islinger et al., 2018), but as peroxisomes have various other functions besides FAO, it is beyond the scope of this Review to cover their role in stem cell regulation.

We here discuss selected recent literature on how DNL and FAO affect HSCs, ISCs, NSPCs and CSCs. Because this research field is just emerging, not all aspects of these two lipid metabolic pathways have been studied to the same extent in these different stem cell types. Thus, we not only highlight similarities and differences, but also show the existing knowledge gaps.

Hematopoiesis and hematopoietic stem cells

HSCs arise from the aorta-gonad-mesonephros of endothelium during development. They then migrate into the fetal liver, where they expand before migrating to their final niche, the bone marrow (BM). HSCs repopulate the blood cell pool, giving rise to either myeloid or lymphoid progeny (Crane et al., 2017). HSCs are broadly used to treat various diseases, such as leukemia, lymphoma and immune disorders by BM transplantation (Bazinet and Popradi, 2019). However, their low number within the BM limits their therapeutic potential.

Given the importance for clinical applications, many studies have addressed the requirements for HSCs to remain quiescent or proliferative; the contribution of metabolism to this regulation has been recently summarized in several reviews (Huang et al., 2019; Ito, 2018; Ly et al., 2020; Nakamura-Ishizu et al., 2020). Interestingly, the BM is very rich in adipocytes; adipocyte-HSC interactions could also involve lipid metabolic interactions, which

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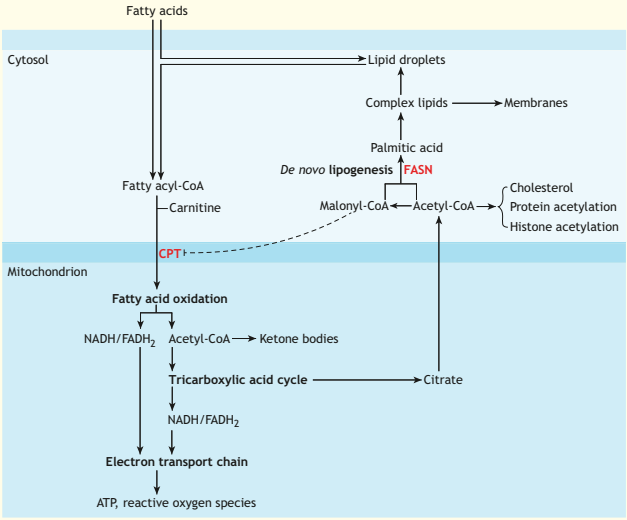
Box 1. The build-up and breakdown of lipids



Build-up by *de novo* lipogenesis (DNL)

Fatty acid synthase (FASN, shown in red), a multi-enzyme protein, catalyzes the synthesis of palmitic acid from acetyl-CoA and malonyl-CoA in a process called DNL. Palmitic acid is further modified and can be used for membranes, stored in lipid droplets (LDs) or used for fatty acid beta-oxidation (FAO).

Breakdown by FAO

The cell receives lipids either from the periphery as fatty acids or can extract them from LDs. Fatty acids are processed in the cytosol to become fatty acyl-CoAs. Fatty acyl-CoAs are transported into the mitochondria via carnitine palmitoyl transferase enzymes (CPT, shown in red), such as CPT1A, in a carnitine-dependent manner. Once in the mitochondria, fatty acyl-CoAs are oxidized through FAO, generating NADH, $FADH_2$ and acetyl-CoAs. These products can be directly used for oxidative phosphorylation (OXPHOS) in the electron transport chain, or indirectly in the case of acetyl-CoA via the tricarboxylic acid (TCA) cycle. The electron transport chain then generates ATP and reactive oxygen species (ROS). Acetyl-CoA can also be used to form ketone bodies or be transported back out in the cytosol via citrate. Cytosolic acetyl-CoA can be transformed to malonyl-CoA and used for DNL, and be used for several other cellular processes, such as production of cholesterol or protein and histone acetylation. Notably, FAO also partially occurs in peroxisomes (not shown).

have been discussed elsewhere (Lee et al., 2018). Although several studies have directly addressed the role of FAO, less is known about the role of DNL in HSCs.

FAO is important for HSC maintenance

In mammals, HSCs balance self-renewal and differentiation to maintain blood production: asymmetric HSC division produces one multipotent and one lineage-committed daughter cell. Symmetric division, however, produces two committed daughter cells. Symmetric divisions can eventually lead to HSC pool exhaustion. Quiescent HSCs have relatively low mitochondrial activity and are thought to rely primarily on glycolysis (Nakamura-Ishizu et al., 2020). However, at least in mice, quiescent HSCs also utilize FAO to maintain their stem cell pool. Ito and colleagues (Ito et al., 2012) have identified the signaling cascade regulating FAO in HSCs, which is initiated by the nuclear receptor peroxisome proliferator-activated receptor-delta (PPARδ), a transcription factor regulating genes involved in fatty acid uptake, transport and FAO (Liu et al., 2018). PPARδ ablation or FAO inhibition in HSCs favors symmetric division and commitment, thus negatively affecting HSC maintenance and leading to exhaustion. Conversely, PPARδ activators, which increase FAO, improve HSC function by promoting asymmetric division (Ito et al., 2012). The level of FAO activation is also important, because largely increasing FAO levels through deletion of the transcriptional repressor Hairy enhancer of split 1 (Hes1) in mice leads to exhaustion of the HSC pool under transplant stress (Ma et al., 2020). Further support for an important role for FAO in HSCs comes from proteomics analyses of enriched mitochondria from mouse HSC-like progenitors and their differentiated progeny. These analyses have shown that carnitine palmitoyltransferase 1a (CPT1A), which is necessary for FAO (Box 1), decreases during HSC differentiation and indicates that FAO is required for maintenance of multipotent HSCs (Billing et al., 2017).

Taken together, these studies suggest that there is an ‘optimal’ level of FAO for mouse HSC maintenance and that manipulating this level has negative consequences for HSCs (Fig. 1A). Yet, the detailed mechanism behind FAO-dependent regulation of mouse HSCs remains to be determined.

FAO in *Drosophila* hemocytes

FAO genes are also highly expressed in hemocyte progenitors, the *Drosophila* equivalent to mammalian HSCs (Tiwari et al., 2020). However, FAO seems to play a different role in these HSCs. Rather than promoting HSC self-renewal, as shown in mouse HSCs (Ito et al., 2012), FAO in *Drosophila* hemocyte progenitors is essential for proper differentiation (Tiwari et al., 2020). Genetic ablation of *withered*, the *Drosophila* ortholog of *Cpt1*, by RNAi or by pharmacological inhibition reduces the generation of differentiated progeny and increases progenitor proliferation. Upregulation of FAO by either genetic or pharmacological means has the opposite effect (Tiwari et al., 2020). Whether these different effects of FAO in mouse and *Drosophila* HSCs are species specific, or whether the developmental stage (adult in mouse versus larval stage in *Drosophila*) are contributing to the differences is unknown.

Protein acetylation

The main product of FAO, acetyl-CoA (Box 1), can be used in the tricarboxylic acid (TCA) cycle for further oxidation, but acetyl-CoA is also important for protein acetylation, especially for histones. In fact, it has been shown that up to 90% of acetyl-CoA used for histone acetylation can come from FAO (McDonnell et al., 2016). Indeed, reduced histone acetylation in the *Drosophila* hemocyte progenitors has been shown upon FAO inhibition. The supplementation of acetate, which can be converted to acetyl-CoA, can rescue the lack of differentiation caused by FAO inhibition. This suggests that FAO-derived acetyl-CoA regulates proliferation and differentiation of *Drosophila* hemocyte progenitors at an epigenetic level (Tiwari et al., 2020). The extent to which this mechanism is similar in mammalian HSCs remains to be determined. FAO-mediated epigenetic alterations have been shown in other mammalian cell types; for example, *Cpt1a* knock down in mouse and human lymphatic endothelial cells strongly reduces histone acetylation and directly affects lymphatic differentiation (Wong et al., 2017).

Reactive oxygen species

In addition to FAO-mediated epigenetic regulation, reactive oxygen species (ROS) might also contribute to the FAO-related HSC

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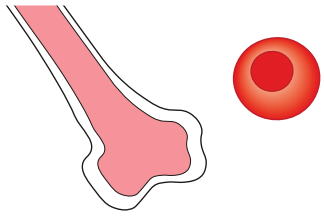
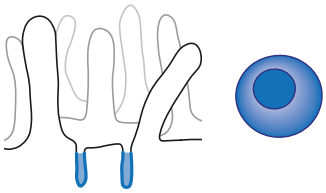
A Hematopoietic stem cells



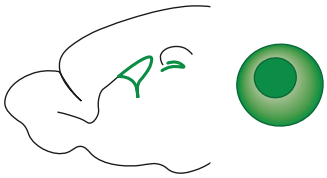
Manipulation	Consequences
↑FAO	- Exhaustion of the HSC pool (mouse) - Increased differentiated progeny (*Drosophila*) - Decreased number of HSC progenitors (*Drosophila*)
⊣ FAO	- Exhaustion of the HSC pool (mouse) - Increased differentiated progeny (*Drosophila*) - Decreased number of HSC progenitors (*Drosophila*)
FAO/DNL	- Quiescence/proliferation (mouse and human) - Altered cell fate (mouse)

B Intestinal stem cells



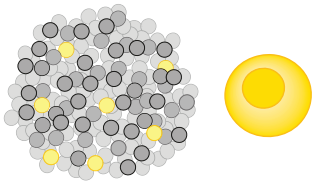
Manipulation	Consequences
High fat diet	- Increased FAO (mouse) - Enhanced ISC organoid formation *in vitro* (mouse) - Enhanced tumor-forming capacity (mouse)
Caloric restriction	- Increased FAO (mouse) - Enhanced ISC organoid formation *in vitro* (mouse)

C Neural stem/progenitor cells



Manipulation	Consequences
⊣ FAO	- Impaired NSPC maintenance (mouse) - Reduced NSPC proliferation (mouse)
FAO/DNL	- Quiescence/proliferation (mouse)
⊣ DNL	- Reduced NSPC proliferation (mouse, human) - Reduced neurogenesis (mouse)

D Cancer stem cells



Manipulation	Consequences
⊣ FAO	- Reduced tumor growth (mouse, human) - Increased susceptibility to treatment (mouse, human)
⊣ DNL	- Reduced viability (human) - Decreased invasiveness (human xenograft)

E Common pattern?

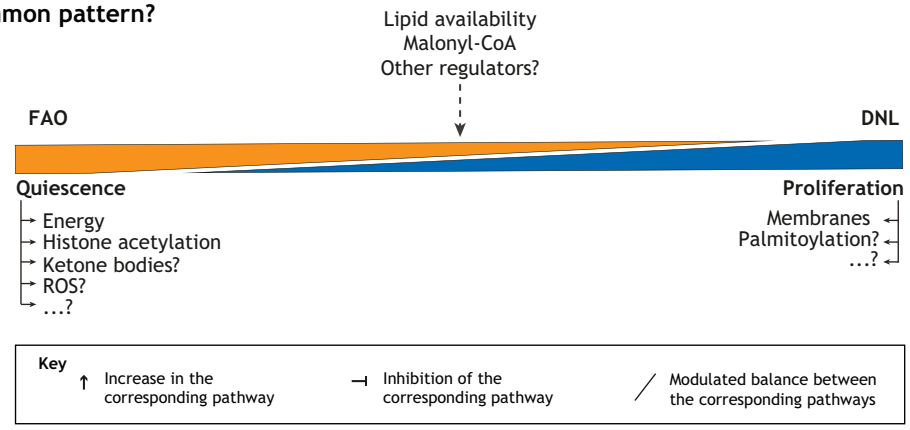


Fig. 1. Summary of the key effects upon manipulation of build-up and breakdown of lipids in the discussed stem cell populations. (A) Both activation and inhibition of fatty acid beta-oxidation (FAO) has a strong effect on the homeostasis of HSCs, and manipulating the balance between FAO and *de novo* lipogenesis (DNL) affects the balance between a quiescent and proliferative state. (B) Diet strongly influences ISCs; both a high fat diet and caloric restriction affect the regulation of ISCs. (C) Inhibition of both FAO or DNL impairs NSPC maintenance and reduces NSPC proliferation. Modulation of the balance of FAO and DNL regulates the balance between a quiescent and proliferative state, just as in HSCs. (D) Both inhibition of FAO and of DNL have a negative effect on CSCs, and thus could be targets for cancer treatments. (E) Schematic demonstrating a potential common pattern in the balance and effects of FAO and DNL in stem cell function. Overall, FAO appears to be important for stem cell quiescence, whereas DNL has a role in stem cell proliferation.

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regulation. In mitochondria, ROS are generated as a by-product of oxidative phosphorylation at various sites in the electron transport chain (ETC). FAO generates NADH/FADH2 and acetyl-CoA (Box 1), which can be used in the ETC for energy production, making ROS a natural by-product of FAO. Increased FAO activity thus leads to increased ROS production, although it is debated if ROS production is higher with FAO than with other substrate oxidation (Quijano et al., 2016; Schönfeld et al., 2010; Seifert et al., 2010). However, ROS production and ROS levels do not have to be in a linear relationship, as cells have several defense systems and antioxidants to reduce ROS (Snezhkina et al., 2019). NADPH, for instance, plays an important role in these antioxidant mechanisms (Ju et al., 2020). FAO can also indirectly contribute to the production of NADPH, and some studies even suggest a ROS-protective action of FAO (Ju et al., 2020). This increase or decrease in net ROS changes due to increased FAO could be cell type dependent. Interestingly, ROS levels seem to be important for the activation of quiescent HSCs and ROS levels correlate with HSC potency: HSCs with low ROS perform better upon transplantation compared with HSCs with high ROS. Furthermore, activated HSCs and their progenies show higher ROS levels compared with quiescent HSCs (Huang et al., 2019). In *Drosophila* hemocyte progenitors, ablation of FAO even increases ROS levels (Tiwari et al., 2020), indicating a ROS-protective action of FAO in these cells. Given the complex interplay between FAO-mediated ROS production and FAO-mediated ROS protection, further studies are required to understand how much FAO contributes to ROS level alterations in HSCs.

Modulation of lipid metabolism influences HSC behavior

The activity of lipid metabolism in HSCs not only depends on the cellular state but is also influenced by the medium composition and culture conditions. Kobayashi and colleagues addressed gene expression differences of freshly isolated mouse HSCs compared with *in vitro* cultured HSCs and found significant upregulation of genes involved in DNL in cultured HSCs, depending on the amount of external fatty acids provided. High amounts of fatty acids in the medium extended the *in vivo*-like quiescent state *in vitro* for up to 1 month (Kobayashi et al., 2019). Under these conditions, DNL gene expression was closer to the *in vivo* situation. Whether these fatty acids were used by the HSCs for FAO or whether a quiescent HSC state was due to suppression of DNL genes remains to be determined. As cytokine and oxygen concentration were lowered at the same time, other pathways besides lipid metabolism are likely to also be influenced. Thus, linking the quiescent state of these HSCs *in vitro* only to changes in FAO and DNL is not possible. However, this study nicely illustrates the importance of medium composition and culture conditions and highlights a significant part played by lipids.

In line with this concept, we have recently shown that malonyl-CoA affects HSCs (Giger et al., 2020). Malonyl-CoA is the endogenous inhibitor of CPT1A and at the same time, a key substrate for FASN (Box 1). This dual function of malonyl-CoA balances the two lipid pathways: high concentrations of malonyl-CoA favor DNL while suppressing FAO, whereas low concentrations of malonyl-CoA have the opposite effect. The addition of this single metabolite to a classical HSC culture medium is sufficient to increase mouse and human HSC numbers *in vitro*. Furthermore, mouse HSCs grown in this condition have an enhanced lymphoid repopulation capacity upon transplantation *in vivo* (Giger et al., 2020). With aging, HSCs display a myeloid bias and fewer lymphoid cells are produced, which can lead to reduced immune functions (Kovtonyuk et al., 2016). Addition of malonyl-CoA even partially reverts the myeloid bias in aged mouse HSCs *in vitro*, suggesting that modulation of lipid metabolism in HSCs can also affect fate (Giger et al., 2020). As malonyl-CoA has a dual function on DNL and FAO, it is difficult to say which of the two pathways is responsible for the observed effects without further experiments. But this study illustrates that modulating the balance between these two pathways is sufficient to alter HSC behavior (Giger et al., 2020) (Fig. 1A).

Other lipids, not directly related to FAO, have also been shown to regulate HSCs (Bansal et al., 2018). Taken together, these studies open up an interesting new avenue to enhance the current clinical approaches by modulating HSCs through metabolite and/or lipid treatments prior to HSC transplantation.

Intestinal stem cells

The intestine is an organ responsible for food digestion and nutrient absorption. The major lipid uptake from the diet occurs in the small intestine, where bile acids emulsify the lipids and lipases digest them for cellular uptake (Ciaula et al., 2017). The epithelium of the intestine consists of two main regions: the villi, with a high turnover of differentiated cells responsible for nutrient absorption, and the crypt of Lieberkühn containing ISCs responsible for constantly replenishing the cells of the villi (Clevers, 2013). The ISCs reside in the bottom of the crypt together with Paneth cells, where they either self-renew or give rise to progenitor cells. The progenitor cells enter the trans-amplifying zone for further proliferation before final differentiation. ISCs can be defined with several markers, with the leucine-rich repeat-containing G protein-coupled receptor 5 (Lgr5) being the most widely used (Barker et al., 2007; Clevers, 2013). ISCs with high Lgr5 expression are highly proliferative, cells with lower Lgr5 are more quiescent (Basak et al., 2014). Besides specific signaling pathways and epigenetic modifications, recent studies have shown that cell metabolism plays a crucial role in the regulation of ISCs (Alonso and Yilmaz, 2018; Baulies et al., 2020). Advances in intestinal organoid culture systems (Kretzschmar and Clevers, 2016) have further contributed to a better understanding of the metabolic regulation of ISCs. However, to date, most studies in ISCs have focused on altered diets and FAO. Thus, not much is known about the role of DNL in ISCs.

FAO plays an important role in the maintenance of ISCs

Caloric restriction has several effects on the organism and is thought to be beneficial for tissue regeneration. To mimic this, Mihaylova and colleagues applied a short-term fasting (24 h) in adult mice and assessed ISC potency using intestinal organoids. Although numbers of ISCs or progenitors are unchanged with this fasting paradigm, the capacity of ISCs to form organoids is enhanced (Mihaylova et al., 2018). These changes are accompanied by an increase in PPARδ/CPT1A-mediated FAO. In addition, treatment with a PPARδ agonist alone improves organoid formation, and both fasting and PPARδ agonist treatment result in increased levels of *Cpt1a* mRNA in mouse ISCs. Furthermore, the CPT1A inhibitor etomoxir abrogates the enhanced organoid-forming effects of fasting on ISCs, whereas *Cpt1a* knockout decreases the number of $Lgr5^{+}$ ISCs in the long-term (after 3 months) and reduces their organoid-forming capacity (Mihaylova et al., 2018). Interestingly, 24 h fasting significantly elevates the levels of palmitate in the blood, which can be used to produce FAO-derived energy (Mihaylova et al., 2018) and might explain the increased FAO in ISCs.

These data suggest that, as in HSCs, FAO is required for ISC maintenance and FAO ablation leads to impaired ISC function.

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Furthermore, genomic and metabolic analyses have shown that the transcription factor PR-domain containing 16 (PRDM16) controls FAO in the crypts (Stine et al., 2019). In mice, PRDM16 expression is enriched in the upper part of the intestine along with several proteins involved in FAO, such as CPT1A and PPARs. Both the deletion of PRMD16 and the inhibition of FAO result in diminished epithelial differentiation, impaired maintenance and atrophy in the upper intestine (Stine et al., 2019). Further evidence linking FAO to ISC maintenance comes from a recent study about the role of the hepatocyte nuclear factor 4 (HNF4), a transcription factor that regulates FAO genes. Chen and colleagues have demonstrated that a double knockout of *Hnf4a* and *Hnf4g* in the mouse intestinal epithelium results in decreased expression of genes involved in FAO, decreased FAO activity, a decrease in metabolites of the TCA cycle and subsequently ISC loss (Chen et al., 2020). Interestingly, genes involved in DNL are upregulated in the intestine of these double knockout mice (Chen et al., 2020). Intestinal organoids derived from these mice have more committed progenitor cells at the expense of ISCs, suggesting that a shift away from FAO towards increased DNL might promote progenitor generation, but results in long-term loss of ISCs.

As discussed above, the main FAO product acetyl-CoA has many functions (Box 1). An alternative source of acetyl-CoA, namely acetate and dichloroacetate, can rescue organoids from *Hnf4* double knockout mice and increase ISC renewal *in vitro* (Chen et al., 2020). This shows that, similar to the study in *Drosophila* HSCs (Tiwari et al., 2020), acetyl-CoA levels are crucial for proper stem cell function (Fig. 1A,B). Whether FAO-derived acetyl-CoA can also alter histone acetylation in ISCs remains to be determined.

Whereas the studies described above directly identify FAO-related ISC regulation, a recent study by Schell and colleagues has provided indirect evidence for the importance of FAO for ISCs in *Drosophila* (Schell et al., 2017). The mitochondrial pyruvate carrier protein 1 (MPC1) transports pyruvate into the mitochondria to fuel the TCA cycle. If blocked, a cell must either increase glycolysis or oxidize other substrates, such as fatty acids or glutamine (Box 1). Loss of the *Drosophila* ortholog of MPC1 causes overgrowth of the intestinal epithelium, and mice lacking MPC1 only in the $Lgr5^+$ cells exhibit increased ISC number and proliferation in the crypts. Interestingly, *Mpc1* knockout leads to increased FAO (Schell et al., 2017), which might link the observed ISC enhancement with the studies discussed above.

Taken together, there is clear evidence that FAO plays an important role for ISC function (Fig. 1B). However, the detailed mechanism of how increased FAO regulates ISCs remain to be determined. FAO-derived energy might only be one explanation. For example, ketone body production (a downstream product of FAO; Box 1) has also been linked to ISC homeostasis (Beyaz et al., 2016; Mihaylova et al., 2018). *Hmgcs2*, which encodes the rate-limiting enzyme in ketone body production, is highly expressed in $Lgr5^+$ ISCs. Loss of *Hmgcs2* in either the entire mouse intestine or specifically in $Lgr5^+$ ISCs depletes the levels of beta-hydroxybutyrate (βOHB), the most abundant ketone body in mammals, and skews ISC differentiation towards secretory cell fates. This phenotype can be rescued by supplying exogenous βOHB, showing that ketone bodies are important for ISC homeostasis (Cheng et al., 2019). However, *Cpt1a* and *Hmgcs2* knockdown do not have entirely overlapping effects on ISCs. Thus, they might act partly through independent mechanisms, which might be explained by βOHB also acting as a signaling metabolite that facilitates Notch signaling, a pathway involved in regulating stemness and differentiation (Cheng et al., 2019). Another possible explanation could be a differential effect on the available acetyl-CoA pool: increased CPT1A activity leads to an increase in acetyl-CoA, whereas Hmgcs2 activity will reduce the acetyl-CoA pool, as ketone body production uses acetyl-CoA. Thus, in theory, knocking down these two enzymes should have the opposite effect on the acetyl-CoA pool, which might explain why *Cpt1a* or *Hmgcs2* knockdown have different phenotypes, for instance by differentially affecting histone acetylation.

The effect of increased exogenous fatty acid levels on ISC function

A diet rich in saturated lipids is dominant in ‘western’ countries and associated with obesity and other health issues (Blüher, 2019). Owing to their position, ISCs are in close contact with dietary lipids, thus their function might be directly influenced. Beyaz and colleagues have recently studied how high-fat diet (HFD) affects ISC function: the number and proliferation of ISCs and progenitor cells is increased in HFD-fed mice, whereas Paneth cells are reduced (Beyaz et al., 2016). Furthermore, ISCs become less niche dependent, which also manifests in an increased *in vitro* capability to form intestinal organoids. The same effect is observed when providing fatty acids to the culture medium of intestinal organoids derived from animals fed a normal diet (Beyaz et al., 2016). Interestingly, HFD activates PPARδ signaling, similar to short-term fasting (Mihaylova et al., 2018). Although these two paradigms appear quite different at a first glance, they both increase the levels of circulating lipids, which might explain why both upregulate PPARδ (and subsequently FAO). Treating cells with an agonist of PPARδ increases ISC proliferation and their independence from Paneth cells. However, acute ablation of *Ppard* has no notable effect on ISCs alone, but it does block the enhancing effect of fatty acids and the PPARδ agonist (Beyaz et al., 2016). Thus, PPARδ seems to be important, but not crucial, for ISC proliferation. Whether or not other PPAR family members can compensate for the lack of PPARδ in *Ppard* knockout ISCs remains to be determined. Interestingly, HFD also increases the tumorigenic potential of ISCs and progenitor cells, further substantiating the importance of controlled stem cell proliferation to avoid tumor formation (Beyaz et al., 2016).

The studies discussed show that ISCs react to altered lipid levels in the diet. However, the paradigms used involve relatively drastic changes in nutrient composition. Thus, it will be interesting to know whether subtler, but long-term differences in the lipid composition of a diet is able to impact ISC maintenance. Such knowledge might allow for specifically tailored diets under certain disease conditions to improve stem cell health.

Neurogenesis and neural stem/progenitor cells

The majority of neurons are generated from NSPCs during embryonic development (Taverna et al., 2014). However, neurogenesis continues throughout adulthood and plays an important role in learning and memory formation (Christian et al., 2014; Obernier and Alvarez-Buylla, 2019). In rodents, adult neurogenesis is best studied in the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricles (Bond et al., 2015). More recently, adult neurogenesis has also been demonstrated in the hypothalamus (Yoo and Blackshaw, 2018). Cellular metabolism has emerged as a key contributor to NSPC behavior (Knobloch and Jessberger, 2017), and lipid metabolism plays a particular role in their regulation (Hamilton and Fernandes, 2017; Knobloch, 2017), as outlined below. Here, we largely focus on the role of DNL and FAO in adult NSPCs, but highlight similar mechanisms in embryonic neurogenesis where known.

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NSPCs rely on DNL for proliferation

Several years ago, we showed that the build-up of lipids from carbohydrates is crucial for proliferating adult mouse NSPCs and that FASN (Box 1) is greatly enriched in the DG and SVZ in the adult mouse brain (Knobloch et al., 2013). FASN is highly expressed in proliferating NSPCs and is downregulated upon differentiation. Furthermore, pharmacological and genetic inhibition of FASN *in vitro* results in reduced proliferation of mouse NSPCs. This effect is also seen *in vivo*, where inducible conditional knockout of *Fasn* in nestin-positive NSPCs of adult mice reduces neurogenesis in both the SVZ and DG.

We further identified thyroid hormone-responsive protein (Thrsp or Spot14) as a novel quiescence marker for NSCPs. Spot14 reduces FASN activity by reducing the levels of its substrate malonyl-CoA (Box 1), thus leading to decreased DNL. Knockdown of Spot14 led to NSPC activation (Knobloch et al., 2013).

The importance of FASN for proliferating NSPCs has been confirmed in a voluntary running study in mice, which is known to increase NSPC proliferation in the hippocampus (Chorna et al., 2013). *Fasn* mRNA and palmitic acid (the main product of FASN) increased upon exercise (Chorna et al., 2013; Cooper et al., 2018). Furthermore, exercise-induced proliferation is prevented upon chronic inhibition of FASN, confirming its importance for NSPC proliferation. FASN also seems to be important in human NSPCs: individuals homozygous for a variant of *FASN* (FASN-R1819W) present intellectual disability (Najmabadi et al., 2011). Interestingly, when this *FASN* variant is introduced into cultured human NSPCs *in vitro*, proliferation is decreased. Furthermore, knock-in mice homozygous for FASN-R1819W display impaired hippocampal NSPC activity and cognitive defects (Bowers et al., 2020).

It is not fully understood why proliferating NSPCs need DNL, but radioactive tracing of the newly generated lipids suggests that the majority of them are used for membrane production (Knobloch et al., 2013). Cell division requires the generation of new membranes; thus, it makes sense that membrane production is important in proliferating NSPCs. Neurons, the progeny of NSPCs, have complex shapes with long axons and many dendrites. Thus, NSPCs might require especially large amounts of lipids on their way to become newborn neurons. Although the lipid need for membrane production during neurogenesis seems evident, it remains unclear whether these lipids have to be produced *de novo* or the dependency on DNL is due to a lack of access to circulating lipids in the neurogenic niches.

FAO is important for NSPC maintenance and proliferation

Although glucose is considered the main fuel for the brain, it has been known for decades that astrocytes perform FAO as well, at least *in vitro* (Edmond et al., 1987). The overall functional importance of FAO in the brain *in vivo* is still under debate (Schoenfeld and Reiser, 2013). Some of the proposed reasons why the brain does not favor FAO over glucose are a potential risk of increased ROS production causing oxidative damage, and a slower rate of ATP production from lipids compared with glucose or lactate owing to limited enzymatic capacity for FAO (Schoenfeld and Reiser, 2013). Whether these reasons are mainly important for neurons or also hold true for astrocytes remains to be determined. NSPCs share many features with astrocytes and the FAO machinery is also present in NSPCs. *In vivo*, NSPCs use FAO as an alternative energy source and FAO inhibition in adult SVZ NSPCs results in decreased proliferation, which nicely illustrates that not all brain cells equally depend on glucose (Stoll et al., 2015).

Even though FAO inhibition reduces proliferation of adult NSPCs (Knobloch et al., 2017; Stoll et al., 2015), FAO seems to be even more important for quiescent NSPCs. Quiescent NSPCs have higher levels of CPT1A-dependent FAO, compared with proliferating NSPCs (Knobloch et al., 2017). Pharmacological and genetic inhibition of CPT1A, both *in vitro* and *in vivo*, leads to severely impaired NSPC function with increased cell death and decreased neurogenesis (Knobloch et al., 2017). These findings are similar to what has been observed in HSCs and ISCs. This seemingly common regulation of stem cell maintenance through FAO is especially interesting and deserves further exploration. However, to directly compare the downstream mechanisms of FAO-mediated stem cell maintenance, studies conducted in the three stem cell types in parallel would be most meaningful. The specialized expertise required for working with each stem cell type makes such study designs challenging.

Strikingly, manipulations of the levels of malonyl-CoA, inhibiting FAO and promoting DNL, are sufficient to alter NSPC activity. Its addition to the culture medium prevents induction of quiescence and triggers quiescent NSPCs to re-enter the cell cycle (Knobloch et al., 2017). As mentioned, we have recently proven that malonyl-CoA acts similarly in mouse and human HSCs (Giger et al., 2020), further underlining the shared metabolic mechanisms that seem to control stem cell activity.

FAO is also important for embryonic NSPCs. Short hairpin RNA (shRNA)-mediated knockdown of *Cpt1a* leads to a disorganized ventricular/subventricular zone, reduced proliferation at the apical surface and increased cell death (Knobloch et al., 2017). Furthermore, Xie and colleagues have shown that deficiencies in biosynthesis of carnitine, a micronutrient necessary for CPT1A to import fatty acid chains into the mitochondria (Bankaitis and Xie, 2019), negatively affects embryonic NSPCs (Xie et al., 2017). Supporting this, deficiencies in trimethyllysine hydroxylase (TMLHE), used in the first step of carnitine synthesis, lead to impaired embryonic neurogenesis, and inhibition of CPT1A recapitulates the impairment in neurogenesis caused by TMLHE (Xie et al., 2017).

Increased exogenous fatty acid levels affect neurogenesis

The source of lipids used for FAO in NSPCs remains unclear. Besides *de novo* build-up, cells can take up exogenous fatty acids from the environment. The effect of exogenous lipids on stem cells has been explored in the context of HSCs and ISCs, as described above, and has also been studied in the context of neurogenesis. Several studies have used an HFD feeding paradigm and addressed the effects on juvenile or adult neurogenesis in rodents (Boitard et al., 2012; Hwang et al., 2008; Lee et al., 2012; Lindqvist et al., 2006; Tozuka et al., 2009). However, the results of these studies vary considerably depending on the animal's sex, genetic background, age and the neurogenic brain region, which suggests a complex effect of HFD on neurogenesis. For example, male rats exposed to HFD for 4 weeks have reduced hippocampal neurogenesis without signs of obesity. In contrast, female rats exposed to the same conditions gain weight, but do not show altered neurogenesis. In mice, HFD feeding results in reduced NSPC proliferation and neurogenesis in a strain-specific manner (Hwang et al., 2008). Furthermore, neurogenesis seems to be more vulnerable in younger mice (Boitard et al., 2012). HFD-induced maternal obesity during pregnancy also negatively affects neurogenesis in the offspring (Tozuka et al., 2009). Taken together, these studies suggest that, in general, increased exogenous fatty acid levels negatively impact neurogenesis. Interestingly, HFD increased neurogenesis in the

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Box 2. Are lipid droplets a hub for the build-up and breakdown of lipids in neural stem/progenitor cells?

Free fatty acids are toxic, so cells sequester them into more complex lipids or store them as triacylglycerides in lipid droplets (LDs) until further use (Jarc and Petan, 2019). LDs are at the perfect interface between DNL and FAO, providing a safe storage place for newly synthetized lipids, as well as a reservoir for lipids to be used by FAO. However, the role of LDs in neural stem/progenitor cells (NSPCs) is poorly understood. A study by Bailey and colleagues in *Drosophila* has suggested that LDs play an antioxidant role in the NSPC niche (Bailey et al., 2015). They have shown that LDs are formed in the glial cells of the stem cell niche during oxidative stress. Storage of lipids, especially polyunsaturated fatty acids (PUFAs), in LDs protects these PUFAs from oxidation by reactive oxygen species (ROS). This mechanism allows glia to support proliferating NSPCs, even under oxidative stress conditions (Bailey et al., 2015). A similar protective role of glial LDs has been seen in neuron-glia interactions. In *Drosophila*, ROS and neuronal mitochondrial dysfunction lead to accumulation of LDs in glia (Liu et al., 2015). Further studies have suggested that this increase in glial LDs is due to ROS-induced lipid synthesis in neurons (Liu et al., 2017), which are subsequently transferred to glia via fatty acid transportation proteins and apolipoproteins (Liu et al., 2017). Similarly, mice with hyperactive neurons release excess fatty acids in lipid particles associated with apolipoprotein E; astrocytes endocytose these particles and store the lipids in LDs, which is suggested to protect neurons from fatty acid-induced toxicity. Astrocytes containing LDs upregulate detoxification genes, and use LD-stored fatty acids for mitochondrial FAO (Ioannou et al., 2019). However, it remains to be determined whether LDs can exert the same function within NSPCs alone.

hypothalamus (Lee et al., 2012), a brain structure known to regulate fasting and feeding behavior (Morton et al., 2006). This suggests that increased fatty acid levels are not necessarily negatively impacting NSPCs directly but rather have differential effects depending on where the NSPCs reside.

As diet alterations change many other physiological parameters, it is difficult to prove a direct effect of exogenous fatty acids on NSPC behavior. *In vitro* culture of SVZ-derived NSPCs as neurospheres have shown that sphere formation is reduced without increased apoptosis in the presence of a high dose of oleic acid (OA) (Hamilton et al., 2015). To test this in an *in vivo* setting, Hamilton and colleagues used osmotic mini pumps to infuse OA intracerebroventricularly in adult wild-type mice. Despite a large increase in lipid droplets (LDs) in the ependymal layer, which is part of the NSPC niche, this treatment did not have any effect on SVZ neurogenesis. Proliferating progenitors can be depleted in the SVZ using Ara-C, an antimitotic agent, to subsequently induce NSPCs to repopulate the niche. When Ara-C is infused together with OA, such activation of quiescent NSPCs is diminished, suggesting that OA influences activation of quiescent NSPCs (Hamilton et al., 2015). Interestingly, an increase of LDs in the ependymal cells, together with impaired neurogenesis in the SVZ, has been observed in a mouse model of Alzheimer's disease (Hamilton et al., 2015), suggesting that niche lipid metabolism influences NSPC activity. Whether or not these LDs are influencing FAO or DNL in NSPCs remains to be determined. In addition, some studies suggest a close interplay between build-up and breakdown of lipids and LDs in neuron-glia interactions (Box 2). It will be interesting to see if such interactions are also present between NSPCs and their progeny.

Taken together, these studies on NSPCs show that both DNL and FAO can directly influence NSPC maintenance, proliferation and differentiation (Fig. 1C), although the underlying mechanisms are not yet resolved. The influence of exogenous lipids on NSPCs, however, seems to be more difficult to categorize. Compared with ISCs, where HFD directly increases ISC proliferation and stem cell potential, the effects of HFD on NSPCs are less clear. Whether this is due to cell-intrinsic differences between ISCs and NSPCs remains to be explored. The location of these two stem cell types and their differential exposure to circulating lipids might also contribute to these differences.

Lipid metabolism in cancer and cancer stem cells

Because of their life-threatening risk, cancer cells have been extensively studied in the past few decades. Metabolic alterations in cancer cells towards aerobic glycolysis were initially proposed by Otto Warburg and are known as the 'Warburg effect' (Heiden et al., 2009). Several additional metabolic changes have since been described as hallmarks for cancer cells and targets for novel therapeutic approaches (Pavlova and Thompson, 2016). A particular subtype of cancer cells with stem cell-like properties, called CSCs, are found in various tumors (Nassar and Blanpain, 2016). Like somatic stem cells, CSCs are also a rare population of cells and share common stem cell features such as self-renewal and differentiation abilities. Despite their low frequency (0.001 to 0.1% of tumor cells), CSCs are believed to be tumor- and metastasis-initiating, responsible for therapy resistance and the reason for tumor relapses (Nassar and Blanpain, 2016; Steinbichler et al., 2018). Several recent publications, discussed below, have shown that CSCs alter their lipid profile. These changes have been proposed to make them more resistant to treatment and allow them to metastasize, thus emphasizing the need to explore these metabolic features to increase therapeutic benefits. Other changes in lipid metabolism, not discussed here, have been recently reviewed by Yi and colleagues (2018).

Enhanced FAO activity is crucial for certain CSCs

Similar to the importance of FAO in various stem cells described above, several studies have recently established that FAO is crucial for certain CSCs. CPT1A and CPT2 expression is enhanced in radiation-resistant CSCs in breast cancer (Han et al., 2019). Moreover, an increase in FAO-associated genes is observed in human glioblastoma cells and in mouse NSPCs that have been oncogenically transformed into glioblastoma (Lin et al., 2017). Likewise, FAO genes are activated in tumor-initiating stem-like cells (TICs) in hepatocellular carcinoma (Chen et al., 2016).

Targeting FAO in these CSCs shows promising results, reducing tumor growth and making the tumors more susceptible to anti-tumor treatments. For example, etomoxir and CRISPR-mediated *CPT1A/2* gene deletion enhanced the susceptibility of breast CSCs to radiation (Han et al., 2019). FAO inhibition also drastically reduces breast cancer growth, both in mouse breast cancer models and in a human-derived xenograft model (Camarda et al., 2016; Wang et al., 2018). Etomoxir, in combination with either a selective small molecule with pro-apoptotic properties or with Ara-C, also leads to reduced proliferation of leukemia cells *in vitro* and in a leukemia mouse model *in vivo* (Samudio et al., 2010). In hepatocellular carcinoma, etomoxir alone is sufficient to reduce TIC sphere formation and render them more susceptible to chemotherapy (Chen et al., 2016). Oncogenically modified NSPCs, transplanted into the brains of wild-type mice, also react to etomoxir treatment *in vivo*, showing significantly reduced tumor growth (Lin et al., 2017).

Why FAO is important for CSCs and why it is upregulated is not yet entirely clear. The parallels between the role of FAO in CSCs

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and healthy stem cells are intriguing and indicate a general function for stem cell maintenance. If high levels of FAO render CSCs more quiescent-like, as seems to be the case for HSCs and NSPCs, this could explain the high resistance of CSCs to chemotherapy, which targets proliferative cells. If upon FAO inhibition CSCs start proliferating, they could be more susceptible to these therapies.

CSCs upregulate fatty acid uptake and DNL

To perform FAO, cells need fatty acids, which can be taken up either from the surrounding environment or produced *de novo* (Box 1). A change in fatty acid uptake has recently been shown in oral squamous cell carcinomas. Overexpression of CD36, which is involved in extracellular fatty acid importation, increases metastatic potential, whereas its downregulation reduces metastasis formation. Targeting CD36 using antibodies leads to a modest, but significant, metastasis remission *in vivo* (Pascual et al., 2017).

Once inside the cells, transportation of fatty acids to the mitochondria has also been shown to be crucial for CSC maintenance. Acyl-CoA-binding protein (ACBP; also known as DBI), which acts as an intracellular transporter of fatty acyl-CoAs, is highly expressed in glioblastoma and its silencing reduces proliferation in glioma stem-like cell culture *in vitro*, as well as in human xenografts *in vivo* (Duman et al., 2019). Mutations in *ACBP*, which reduce the affinity to acyl-CoA, result in reduced glioblastoma proliferation *in vitro* and *in vivo*. Similar effects have been observed either upon *CPT1A* knockdown or by using etomoxir, suggesting that ACBP-mediated fatty acids transport sustains FAO and is crucial for glioblastoma proliferation (Duman et al., 2019).

De novo production of fatty acids also seems to be crucial for CSCs, similar to NSPCs. Pharmacological inhibition of FASN decreases cell viability, sphere formation and invasiveness of glioma stem cells, whereas the viability of their differentiated progeny is not impaired (Yasumoto et al., 2016). Several other proteins involved in fatty acid synthesis have been found to be important for CSCs, as recently discussed by Li and collaborators (Li et al., 2020). Whether these newly synthesized lipids are used for membrane synthesis or are eventually consumed in FAO remains to be determined.

LD accumulation correlates with CSC stemness

In line with an increase in fatty acid uptake and DNL, LD accumulation seems to correlate with aggressiveness and stemness of several CSCs. For example, breast cancer-derived cell lines that have the most LDs are enriched in CSC stemness markers (Hershey et al., 2019). Moreover, when grown as mammospheres, LD-enriched cell lines have a higher number of CSCs compared with cell lines with fewer LDs. Decreasing DNL and reducing LD accumulation by inhibiting conversion of acetyl-CoA to malonyl-CoA leads to decreased growth (Hershey et al., 2019). As discussed in Box 2, LDs might protect NSPCs and neurons from fatty acid toxicity and oxidative stress. Thus, they could have a similar effect in CSCs. Indeed, Cheng and colleagues have found that synthesis of LDs is crucial for glioblastoma: pharmacological and genetic inhibition of LD synthesis led to increase ROS levels followed by increased tumor cell death *in vitro* and *in vivo* (Cheng et al., 2020). Inhibition of LD synthesis was accompanied by a strong increase in FAO, which might be the underlying cause of the increased ROS.

Taken together, these different lipid metabolic changes observed in CSCs provide promising novel therapeutic avenues, as recently summarized (Visweswaran et al., 2020). However, whether to target FAO, DNL or LD formation might depend on the tumor origin of the CSCs (Fig. 1D).

Open questions

The general importance of the build-up and breakdown of lipids in HSCs, ISCs, NSPCs and CSCs is evident and remarkably similar in many aspects (summarized in Fig. 1E). However, there are still many remaining open questions.

How do these two pathways control stem cell activity mechanistically?

The difficulties in answering the mechanistic question lie in the versatile functions of lipids: they can serve as an energy source, energy storage and membrane building blocks, as well as being involved in ketone body and hormone production. Lipids can act as signaling molecules, required for the post-translational modification of proteins and also contribute to histone acetylation (Fig. 2). This

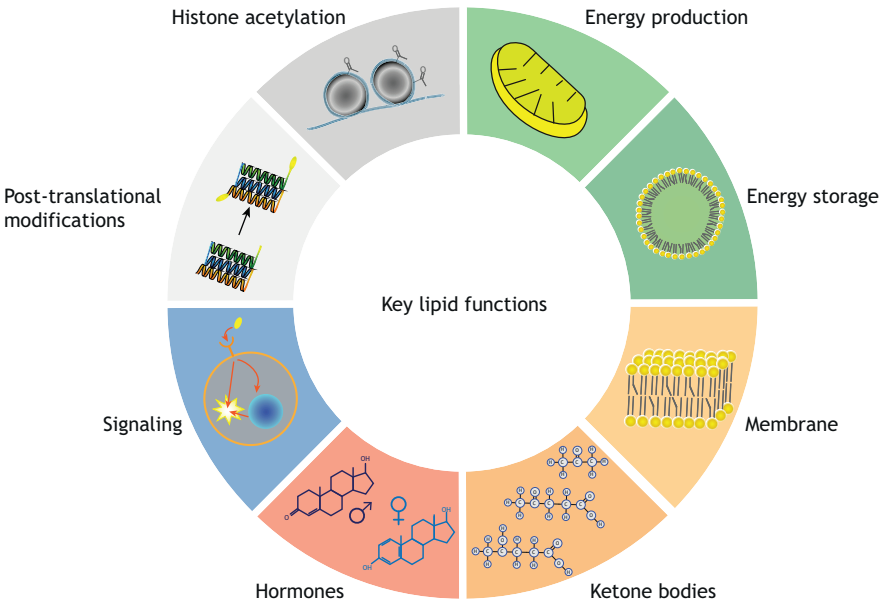

Fig. 2. Scheme representing some of the key functions of lipids. Lipids can be broken down for energy production through fatty acid beta-oxidation (FAO). They can also be newly produced by *de novo* lipogenesis (DNL) and can serve as energy storage. Lipids further provide important membrane building blocks. Breakdown products of lipids provide precursors for ketone bodies, and lipids are required for the synthesis of certain hormones, such as steroid hormones. Furthermore, lipids also have important signaling functions and can be added post-translationally to proteins, which influences, for instance, protein localization. When broken down, lipids yield acetyl-CoA, which can be used for many different purposes besides energy production. For example, lipid-derived acetyl-CoA has been found to be a key source of acetyl groups for histone acetylation.

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makes it almost impossible to pinpoint their most important functions related to stem cell behavior. Most likely, as is often the case in biological systems, several of their functions play a certain role at the same time. The contribution of FAO and DNL to energy production, energy storage and membranes is relatively straight forward to understand. The contribution to histone acetylation, however, opens up an additional level of complexity, namely that lipids might directly act on stem cells by changing their epigenetic landscape. Some of the studies discussed above have addressed this aspect and found histone changes in stem cells upon FAO manipulation (Cheng et al., 2019; Tiwari et al., 2020). Whether increased FAO always leads to increased histone acetylation or whether similar genes are affected by these epigenetic changes in different stem cells remains unknown. Furthermore, acetylation of proteins, one of the major post-translational protein modifications (Verdin and Ott, 2015), might also be influenced by FAO-derived acetyl-CoA. Whether or not this plays a role in stem cell maintenance has not been addressed in detail. Lipid modifications of proteins, such as palmitoylation (which requires palmitate, the major product of FASN), have been shown to be important for stem cells. Several key proteins for stem cell functions are known to be modified in this way (Chen et al., 2018). However, it remains to be addressed whether alterations in DNL affect palmitoylation in stem cells.

Are DNL and FAO instructive for stem cell behavior?

Given the important role of lipids for proper cellular functions, it is difficult to uncouple instructive roles for lipids over survival ones, especially when stem cells are negatively affected by disturbances in this machinery. However, to a certain extent, cells are theoretically able to compensate these two pathways in a flexible manner. They can, for example, take up extracellular lipids instead of producing them by DNL, or break down substrates other than fatty acids to cover their energy demand. Thus, altered stem cell behavior upon disturbance of DNL and FAO highlights the dependency of the stem cells for these specific lipid metabolic pathways, independent of their instructiveness. However, several of the studies discussed above do imply a certain instructiveness, such as the modulation of HSC and NSPC behavior with malonyl-CoA (Giger et al., 2020; Knobloch et al., 2017) or the epigenetic alterations upon FAO modulation (Cheng et al., 2019; Tiwari et al., 2020).

Are upstream regulators of lipid metabolism shared among the different stem cells?

So far, there have been no studies directly comparing the role of DNL and FAO in several stem cell types in parallel. However, it is not unlikely that the regulators of these two pathways are at least also partially shared, as indicated by the findings that PPARδ regulates FAO in both HSCs and ISCs (Beyaz et al., 2016; Ito et al., 2012; Mihaylova et al., 2018).

How are changes in lipid metabolism affecting other metabolic pathways?

Metabolic pathways are tightly linked together, sharing substrates, co-factors and reducing agents. Thus, alterations in DNL and FAO are likely to affect other pathways. To get an integrated view, further studies assessing the entire metabolic profile of stem cells upon alterations in DNL and FAO are required.

Conclusion

In this Review, we have covered a selection of recent publications about four stem cell systems that show the importance of the build-up and breakdown of lipids for stem cells. There is evidence for the importance of lipids in other stem cell systems, such as muscle stem cells or pluripotent stem cells, which we have not covered owing to space limitations. However, together, all of these publications support an emerging picture suggesting a common mechanism of regulation of stem cell activity through lipid build-up and breakdown, independent of the tissue origin of the stem cells. It is crucial to consider this when addressing stem cell-related diseases, such as the use of lipid metabolism-related therapies to target CSCs, as these treatments might have broad effects on other stem cells vital for normal tissue function.

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Competing interests

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