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Metabolic control of muscle stem cells

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Abstract

Muscle stem cells, or satellite cells, are a population of adult stem cells involved in muscle growth and indispensable for adult skeletal muscle regeneration. As the quiescent state is perturbed, satellite cells undergo profound metabolic changes, named metabolic reprogramming, driving cellular activation, commitment and differentiation. Thus, modulation of cellular metabolism, by altered nutrient availability or with aging, can impact satellite cell stemness and fate, as well as differentiation ability. Moreover, a direct link between cellular metabolism and chromatin dynamics is emerging. Indeed, metabolic intermediates act as cofactors for epigenetic modulators, thereby regulating their activity and influencing the epigenetic landscape. Consequently, environmental cues are critical regulators of satellite cell fate, linking nutrient availability with the epigenome to impact muscle homeostasis and regeneration. Further studies are necessary to dissect the intimate connection between environmental cues, metabolic reprogramming and epigenetics, to increase satellite cell regenerative capacity in aging or diseases.

Keywords: satellite cells, metabolic reprogramming, chromatin dynamic, epigenetic modulators

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Adult stem cells (ASCs), or somatic stem cells, are primarily responsible for maintaining homeostasis in many tissues throughout post-natal life. ASCs are usually maintained in a quiescent state in their specific niche (Bardelli and Moccetti 2017; Ferraro et al. 2010; Rezza et al. 2014). The ASC niche is defined as the in vivo microenvironment, characterized by several cellular and structural components: (i) the ASCs and their progeny which provide autocrine and paracrine regulation; (ii) neighboring mesenchymal or stromal cells providing paracrine signals; (iii) extracellular matrix (ECM) or cell–cell contacts involving membrane-bound molecules; and (iv) external signals from distant sources, such as blood vessels, neurons, or immune cells (Rezza et al. 2014). Overall, the ASCs reside and receive different signals in and from the niche that determine their fate in terms of quiescence or activation (Rezza et al. 2014). When activated, ASC proliferate and differentiate to replenish damaged tissues (Ferraro et al. 2010; Jones and Wagers 2008). ASC exhaustion is prevented by their dual capacity of self-renewal and differentiation. Indeed, ASC symmetric division produces either two identical replicating cells or two committed cells, depending on surrounding signals, while the asymmetric division results in one identical and one committed stem cell (Morrison and Kimble 2006; Shahriyari and Komarova 2013). The balance between self-renewal and cell differentiation preserves resident stem cell populations as well as tissue homeostasis (Renzini et al. 2018).

Several signaling events influence specification and maintenance of stem cell lineages in tissues. For instance, the cooperation between the Wnt, beta-catenin, and BMP/Notch signaling is essential to control stem cell self-renewal in the intestinal stem cell niche (Clarke 2006). Besides, Wnt3a has been implicated in self-renewal and proliferation in the hematopoietic (HSCs) and neuronal stem (NSCs) cells (Wexler et al. 2009). Another important pathway influencing the maintenance and differentiation of ASC is the TGF-beta signaling, including bone morphogenetic proteins (BMPs), Nodal, and activins (Watabe and Miyazono 2009). TGF-β1 modulates the proliferation of mesenchymal stem cells (MSC) by inducing Smad3-dependent nuclear accumulation of β-catenin in MSC, which is re-

quired for the stimulation of MSC proliferation (Jian et al. 2006; Watabe and Miyazono 2009). Further, TGF-β and activin promote chondroblast differentiation at early stages, while TGF-β inhibits osteoblast maturation at late stages during MSC differentiation (Maeda et al. 2004; Roelen and Dijke 2003). Finally, the Notch pathway is known to support the maintenance of tissue homeostasis during adult life. Indeed, cell-cell interactions activate notch signaling, thereby generating cell diversity from initially equivalent cell populations (Lowry and Richter 2007). For instance, specific Notch activity levels dictate progressive restrictions during adult hematopoiesis and in the adult brain (Bertrand et al. 2002; Demehri et al. 2008; Shimojo et al. 2011).

2. Cellular metabolism influences ASC

Energy metabolism is emerging as a key regulator in maintaining stemness and in determining cell identity (A. Harvey et al. 2019). Besides providing energy, metabolism and derived metabolites influence stem cell life-cycle, in addition to allowing cell adaptation to the systemic environment (Rossi et al. 2008; Shyh-Chang, Daley, et al. 2013).

Different metabolic pathways, including glycolysis, the pentose phosphate pathway, the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS), allow addressing cell energy requirement in specific cell state (Folmes et al. 2012). Nutrient resources actively modulate ASC survival, proliferation, commitment and differentiation (Oburoglu et al. 2014; Renzini et al. 2018; Scicchitano et al. 2016) and increasing evidence suggests that metabolic remodeling bring forward the cell fate establishment, from maintenance and acquisition of stemness to lineage commitment and specification.

The increased energy demand during ASC activation and differentiation requires higher ATP and ROS levels. Coherently, ASC metabolic profile shifts from glycolysis to mitochondrial OXPHOS, supported by a dynamic change in mitochondrial morphology and activity (Ochocki and Simon 2013; Yu et al. 2013) (Fig. 1). This rapid metabolic transition is finely regulated by the protein tyrosine phosphatase mitochondrial 1 (PTPMT1), as reported in HSCs. Ptpmt1-depleted HSCs failed to differentiate both in vitro and in vivo due to alterations of mitochondrial metabolism (Yu et al. 2013). Similarly, the glycolytic rate of NSCs declines significantly during differentiation. Indeed, NSCs display a general decrease in glycolysis genes and glucose transporters (Candelario et al. 2013; Zheng et al. 2016).

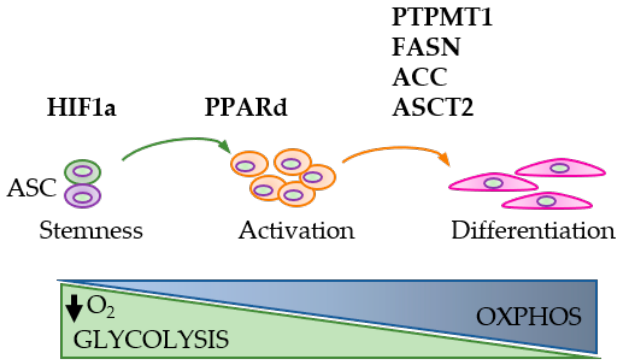

Figure 1. Metabolic and genetic control of adult stem cells. Adult stem cells (ASC) undergo a well-defined metabolic road map during their activation and differentiation, which is finely regulated by different genes.

Moreover, lipogenesis, mediated by fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC), is required for lipid membrane synthesis during mouse adult neurogenesis

Other findings uncover a role for amino acids in the regulation of ASC commitment and differentiation. For instance, the erythroid specification of HSCs is strictly dependent on glutamine metabolism. Indeed, by blocking the ASCT2 glutamine transporter or by inhibiting glutaminolysis, HSCs were diverted to a myelomonocytic fate (Oburoglu et al. 2014).

In addition to nutrients, numerous ASCs, including HSCs, MSCs, and NSCs, reside in a hypoxic niche (Chen et al. 2008; Parmar et al. 2007; Renault et al. 2009) (Fig. 1). Low levels of oxygen positively influence the maintenance of an undifferentiated state, affecting proliferation and cell-fate commitment (Mohyeldin et al. 2010). The hypoxic environment is associated with a glycolytic metabolism, which allows reducing ROS production from mitochondria. The pro-glycolytic metabolism is intrinsically established in quiescent ASCs through the upregulation of many glycolytic enzymes and the concomitant downregulation of oxidative phosphorylation proteins (Simsek et al. 2010; Takubo et al. 2013). The hypoxia-inducible transcription factors (HIF), which are stabilized and activated under low oxygen conditions, underpin the oxygen effect on stem cell fate, linking cell metabolism and stemness. For instance, HIF1α is a key transcriptional regulator of metabolism, in addition to directly regulating the wnt/β-catenin pathway to ensure the maintenance of ASCs. Indeed, HIF1α was shown to enhance the expres-

sion of pyruvate dehydrogenase kinase (PDK) 2 and PDK4, which prevent pyruvate from entering the TCA cycle, leading to mitochondrial respiration inhibition (Takubo et al. 2013). Further, Hif1α gene deletion in adult NSCs results in their gradual loss, due to impaired integrity of the vascular niche; similarly, in HIF1α-deficient mice, HSC quiescence state is lost, and HSC number decreased (Hu et al. 2016).

In addition to the glycolytic phenotype, the contribution of lipid catabolism to the maintenance of ASC quiescence has been partially elucidated. The PPAR-δ–Fatty Acid Oxidation (FAO) pathway has been reported in the control of HSC asymmetric division and maintenance. Indeed, pharmacological inhibition of mitochondrial FAO, or genetic deletion of Ppard, resulted in altered HCS asymmetric division and increased symmetric commitment, leading to decreased HSC function and exhaustion (Ito et al. 2012). Further, lipid oxidation via the eicosanoid pathway might generate molecules able to affect HSCs fate, such as prostaglandin E2, that enhance HSC proliferation by activating Wnt signaling (Goessling et al. 2009). Similarly, NSCs depend on FAO for their proliferation, while quiescent muscle satellite cells rely on FAO and pyruvate oxidation once they become activated (Ryall, Dell'Orso, et al. 2015).

Therefore, beyond the well-known role in the energetic support, increasing evidence implicates that metabolism drives stem cell fate. Further metabolome characterizations will provide an opportunity to map stem cell metabolism aiming to suggest potential targets for improving tissue homeostasis and regeneration, also during aging and disease.

3. Muscle stem cells

Muscle stem cells, named satellite cells (SCs), are responsible for muscle homeostasis, growth and repair throughout life. Upon stimuli, as ASCs, SCs are activated and can either divide symmetrically to generate two stem cells, favoring stem cell expansion, or divide asymmetrically, to generate a stem cell and a committed one (Kuang et al. 2007). SC self-renewal capacity is a prerequisite to maintain muscle stem cell number under physiological conditions, to ensure repetitive muscle repair and to ensure the life-long preservation of contractile tissue. Importantly, a perturbed balance between symmetric and asymmetric divisions contributes to muscle diseases, such as Duchenne Muscular Dystrophy (Dumont et al. 2015), or aging (Madaro and Latella 2015; Price et al. 2014).

SCs were initially identified for their unique position, between the basal lamina and the sarcolemma, by using electron microscopy (MAURO 1961). All SCs do express the paired box transcription factor Pax7, whereas only a sub-population of SCs co-expresses Pax3. Both these paired box transcription factors are genetically located upstream of the myogenic regulatory factors (MRFs), basic helix-loop-helix (bHLH) factors, which include Myod1, Myf5, MRF4 and myogenin (Buckingham and Relaix 2007; Yin et al. 2013). Upon activation, satellite cells need to sequentially express MRFs to permit their commitment and differentiation towards myogenic lineage (Weintraub et al. 1991). Myogenic commitment is ensured by the sequential expression of Myf5 and MyoD (Rudnicki et al. 1993), while myogenin triggers myocyte terminal differentiation (Venuti et al. 1995). Ensuing expression of MRFs is guaranteed by numerous transcriptional and post-transcriptional regulatory mechanisms, including reciprocal inhibition between Pax7 and Myod1 and myogenin expression (Olguin et al. 2007), or epigenetic control of Myf5 expression in mRNP granules (Crist et al. 2012).

Despite being initially considered a homogeneous population of committed muscle progenitor cells (Bischoff and Heintz 1994), accumulating evidence supports that SCs are a heterogeneous population regarding gene expression, engraftment efficiency and muscle regeneration potential. Single-cell analyses revealed the presence of a subset of satellite cells expressing high levels of Pax7 and low levels of Myf5, at both RNA and protein levels, within satellite cell pool (Cho and Doles 2017). Moreover, a subset of satellite cells never expressed Myf5 (Kuang et al. 2007), highlighting the considerable heterogeneity within the satellite cell population. The differential expression of MRFs leads to distinctive abilities in self-renewal and niche engraftment (Kuang et al. 2007).

3.1. Metabolic control of SCs

Several pathways, including those of cell metabolism, have been identified as potential contributors to SC heterogeneity (Cho and Doles 2017). Indeed, metabolism is no longer a functional endpoint of signaling pathways. Rather, it is an active player in modulating enzyme activity and SC biology. For instance, two satellite cell subpopulations have been identified in rats with distinct metabolic profiles: Low Proliferative Clones and High Proliferative Clones. These are more characterized by glycolytic and stemness-like characteristics

than the Low Proliferative Clones, which result already committed (Repele et al. 2013).

Under physiological conditions, quiescent SCs possess reduced metabolic activity (Pala et al. 2018), characterized by fatty-acid oxidation metabolism (Fig. 2). This has been reported in freshly isolated SCs, without or after an in vivo fixation that prevents isolation artifacts (A. J. Harvey et al. 2016; Machado et al. 2017; Ryall, Cliff, et al. 2015). By inhibiting fatty-acid oxidation, SCs undergo commitment, without modifying their proliferation rate (Gatta et al. 2017). Similarly, pharmacological inhibition of fatty acid oxidation leads to altered SC differentiation, proving that SC physiology relies on peroxisomal, rather than mitochondrial fatty-acid oxidation (Pala et al. 2018).

Quiescent SCs actively and reversibly transit between a G0 and a GAlert phase in response to injury, becoming primed for cell cycle entry and possessing enhanced tissue regenerative function. Such transition, from quiescent to activated state, is accompanied by a metabolic reprogramming, from fatty acid and pyruvate oxidation in quiescent SCs to glycolysis and glutaminolysis in activated SCs, with a concomitant decrease of NAD+/NADH levels and increase in mitochondriogenesis (Pala et al. 2018; Rodgers et al. 2014; Ryall, Cliff, et al. 2015) without a an increase in oxygen consumption (Ryall, Cliff, et al. 2015; Ryall, Dell'Orso, et al. 2015) (Fig. 2).

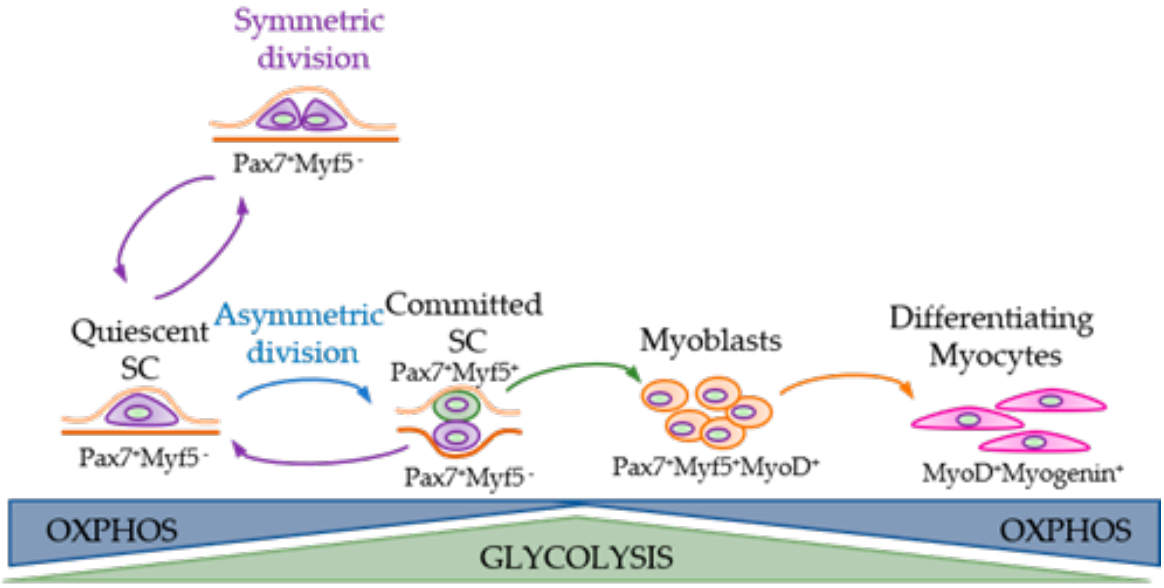

Figure 2. Metabolic control of satellite cell biology. Satellite cells (SC) division, commitment, and differentiation is defined by specific gene markers and controlled by different metabolic states.

Several studies identified the intracellular signaling autophagy and the molecular players Sirtuin 1 (SIRT1) and 5′ adenosine monophosphate-activated protein kinase (AMPK) as pivotal regulators of such metabolic reprogramming (Cantó et al. 2009, 2010; Cerletti et al. 2012; Ryall, Dell'Orso, et al. 2015; Tang and Rando 2014), providing experimental tools to push satellite cells towards stemness or differentiation processes. In particular, the nutrient sensor SIRT1, through AMPK, triggers the autophagic flux, thereby promoting SC activation (Tang and Rando 2014) (Fig. 3). Similarly to what observed when autophagy is inhibited, the deletion of SIRT1 in SCs compromises autophagic flux, deregulates the activation of the myogenic program and compromised muscle regeneration in response to cardiotoxin-induced muscle injury (Ryall, Dell'Orso, et al. 2015). After activation, SCs can either undergo self-renewal or commit to skeletal muscle lineage (Kuang et al. 2007). Self-renewal is tightly controlled by cellular metabolism: deletion of AMPK in SCs provokes a decrease in oxidative capacity and correlates with an increase in self-renewal, delaying SC differentiation and compromising muscle regeneration (Theret et al. 2017). Instead, SC differentiation correlates with an increase in the OXPHOS state (Pala et al. 2018). Besides, skeletal muscle differentiation is accompanied by decreased NAD+/NADH levels, which, in turn, reduce SIRT1 activity (Fulco et al.2003; Sartorelli and Caretti 2005).

Coherently, an increase in NAD+/NADH levels inhibits muscle cell differentiation (Fulco et al. 2003). Similarly, glucose restriction inhibited muscle cell differentiation by activating AMPK and the transcription of the NAD+ biosynthetic enzyme Nampt, which increases the NAD+ intracellular levels, thereby activating SIRT1 (Fulco et al. 2008) (Fig. 3). All these studies highlight the importance of metabolism and autophagy-mediated generation of ATP for SC activation and differentiation. It will be interesting to assess whether changes in SC autophagy are associated with pathological conditions characterized by compromised muscle regeneration, such as muscular dystrophies.

In agreement with the above, upon injury, SC metabolic reprogramming progresses from low oxygen consumption and mitochondrial activity of a quiescent state to higher glycolysis and fatty-acid metabolism and OXPHOS soon after injury, indicative of a proliferative state. As regeneration proceeds, glycolysis declines, and respiration increases (Pala et al. 2018).

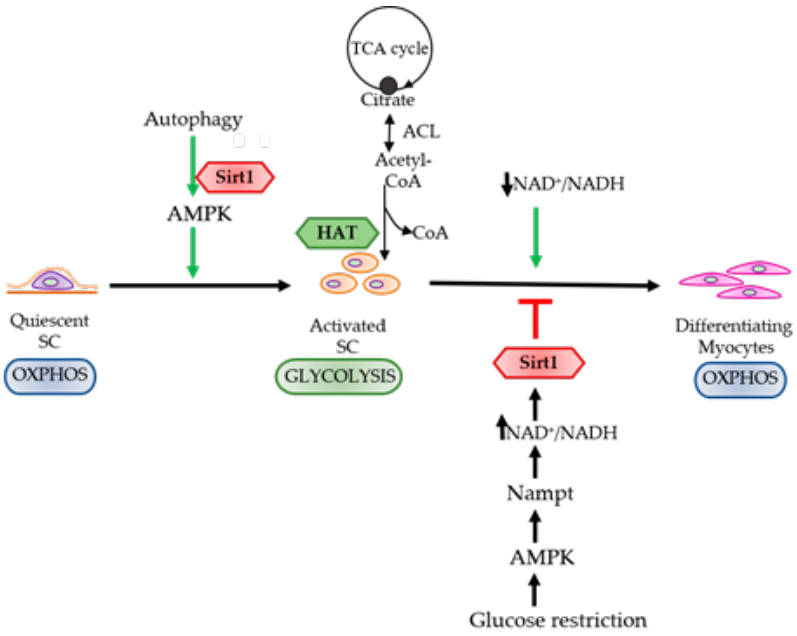

Figure 3. Interplay between metabolism and epigenetics in satellite cells. Epigenetic regulators tightly depend on nutrient availability and control satellite cell (SC) quiescence, activation and differentiation.

Aging is accompanied by a decline in adult SC function, termed SC senescence, which leads to the loss of tissue homeostasis and regenerative capacity (Kuilman et al. 2010; López-Otín et al. 2013). In aging, muscle stem cell dysfunction may be caused by both extrinsic (Chakkalakal et al. 2012; Conboy et al. 2005) and intrinsic cellular signaling (Sousa-Victor et al. 2014). Altered metabolism has been well documented in senescent SCs, which present a reduction in most of the metabolic pathways, except for glycolysis. Indeed, senescent SCs rely on glycolysis rather than OXPHOS for ATP production (Abreu 2018; Baraibar et al. 2016; Pala et al. 2018). Concerning the signaling, senescent SCs show compromised autophagy and reduced AMPK activation (García-Prat et al. 2016). Importantly, AMPK activation by an AMP analog triggers autophagy and modulates numerous cellular pathways by promoting SC proliferation and improving in vivo transplantation efficiency, overall reverting the aged phenotype in muscle stem cells (White et al. 2018). Moreover, nutritional intervention, e.g., providing NAD+ or subjecting SCs to caloric restriction, improve SC function (Cerletti et al. 2012; Zhang et al. 2016).

Thus, metabolic reprogramming may be considered as a potential tool to manipulate muscle stem cells in sarcopenia and potentially in disease states. Further studies on SC metabolic rate are needed and will likely lead to the identification of novel cellular targets able to regulate muscle stem cell biology.

3.2 Metabolic control of epigenetics in SCs

In addition to providing cellular energy and to directly influence stem cell behavior, metabolism regulates

epigenetic mechanisms by modulating nutrient and metabolite availability (Kaelin and McKnight 2013). Indeed, most of the epigenetics writers or erasers, i.e., the enzymes able to modify chromatin structure, use metabolites as co-factors (Berger and Sassone-Corsi 2016).

A clear example in SC biology is represented by NAD+, a co-substrate for Sirtuin deacetylases (Verdin 2015). During the metabolic reprogramming from the quiescent to the proliferative state, the increased glycolysis induces a decrease in cellular NAD+ levels. As a result of reduced SIRT1 deacetylases activity, global acetylation of histone 4 (H4K16) occurs, contributing to SC activation (Ryall, Cliff, et al. 2015; Ryall, Dell'Orso, et al. 2015) (Fig. 3). Interestingly, NAD+ cellular levels decline with age (Imai and Guarente 2014), but the consequent epigenome change has not been defined yet.

Acetyl-CoA is another metabolite that directly affects cellular epigenome, being used as the acetyl donor for histone acetylation (Everts et al. 2013; Wellen et al. 2009). Acetyl-CoA derives from carbohydrates through glycolysis, from fatty acids through β-oxidation and from threonine metabolism. Acetyl-CoA can also be produced by the conversion of citrate, derived from the TCA cycle, via the enzyme ATP-citrate lyase (ACL). Modulation of ACL expression in SCs directly affects the net amount of acetyl groups available, thus altering the acetylation status of H3(K9/14) and H3(K27) at several differentiation gene loci, including Myod1 and fast myosin heavy chains, thereby regulating their expression (Das et al. 2017; Moussaieff et al. 2015). Overexpression of ACL enhances Myod1 expression, promoting SC differentiation in vitro and muscle regeneration following injury in vivo (Moussaieff et al. 2015) (Fig. 3).

Another epigenetic mechanism, acting on both DNA and histones, is the methylation, which finely tunes gene expression in SCs (Dilworth and Blais 2011; Laker and Ryall 2016). The addition of the methyl group is mediated by different methyltransferases, specific for DNA or histone proteins. However, the methyl group resource is S-adenosyl-methionine (SAM) in either case, derived from the one-carbon cycle (Etchegaray and Mostoslavsky 2016; Mentch et al. 2015).

SC proliferation is characterized by the enrichment in permissive H3K4me3 marks in genes involved in cell-cycle progression (Laker and Ryall 2016; Segalés et al. 2015), while repressive H3K27me3 mark mediated by Ezh2 is required on the Pax7 gene when SC exit the cell cycle to terminally differentiate (Palacios et al. 2010). Although a role for one-carbon cycle has not yet been reported in SCs, several studies highlighted that amino acids are crucial for determining mouse and human embryonic stem cell self-renewal (Shiraki et al. 2014; Shyh-Chang, Locasale, et al. 2013; Wang et al. 2009) or differentiation (Comes et al. 2013) via modulation of the epigenetic landscape.

While SAM is the methyl group donor for both DNA and histone methylation, α-ketoglutarate (αKG) is a necessary cofactor for both histone and DNA demethylation, by interacting with Jumonji domain-containing histone demethylases, or ten-eleven translocation methylcytosine dioxygenases (Laker and Ryall 2016). Although no data are yet available regarding αKG levels in SCs, is has been reported that αKG can either promote self-renewal or induce differentiation of the embryonic stem cells (depending on the pluripotent state) by affecting both DNA and histone methylation levels in the regulatory regions of pivotal transcription factors (Carey et al. 2015; Hwang et al. 2016), thus confirming that αKG can be used to manipulate stem cell fate.

Stem cell biology is therefore tightly and dynamically modulated by the interplay between metabolism and epigenetics, implying that changes in metabolism may have global consequences on SC epigenome and, consequently, on their function. It is of interest to better define the intimate connection between metabolism and epigenome in SCs, both in physiological and pathological conditions, in order to consider nutrient availability as a potent tool to manipulate SC functions.

Our growing comprehension about the link between cell metabolism and the epigenome raises significant questions particularly relevant for the efficacy and safety of cell transplantation and disease models: 1) does *in vitro* manipulation of nutrients alter downstream cell function? 2) does/how the in vivo metabolic environment delay cell integration following transplantation? Plausibly, low nutrients may lead to poor stem cell transplantation retention and integration. Furthermore, metabolic and epigenetic factors may have developmental, stage- and tissue-specific functions. Whether modulating the culture environment is, therefore, capable of improving SC expansion and/or engraftment remains to be explored. This information will be useful for the development of more physiological media formulations and culture conditions to support long-term SC viability.

Further studies focusing on how metabolites or nutrients directly affect SC epigenome, linking these epigenetic changes to different SC destinies, are demanded.

4. Conclusions

SCs constitute a promising tool for regenerative medicine approaches. Maintaining their number and function is of particular relevance to skeletal muscle pathologies, including aging or genetic diseases. Furthering our understanding of the underlying molecular mechanisms and fundamental aspects of stem cell heterogeneity will be relevant to clinical applications exploiting somatic stem cell populations, either through cell replacement or pharmacological manipulation.

Accumulating evidence indicates a metabolic roadmap during SC transition from the quiescent to the activated, committed, or differentiating state, a process known as metabolic reprogramming. The influence of metabolic reprogramming on SC self-renewal, commitment, or differentiation, as well as the use of pharmacological inhibitors of the intracellular pathways involved in these processes, provide a proof-of-concept for developing effective therapeutic interventions for SC therapies, improving muscle regeneration or augmenting the SC pool in degenerative muscle disorders.

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