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Stem Cell Metabolism and Diet

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Abstract

Purpose of Review—Diet has profound impacts on health and longevity. Evidence is emerging to suggest that diet impinges upon the metabolic pathways in tissue-specific stem cells to influence health and disease. Here, we review the similarities and differences in the metabolism of stem cells from several tissues, and highlight the mitochondrial metabolic checkpoint in stem cell maintenance and aging. We discuss how diet engages the nutrient sensing metabolic pathways and impacts stem cell maintenance. Finally, we explore the therapeutic implications of dietary and metabolic regulation of stem cells.

Recent findings—Stem Cell transition from quiescence to proliferation is associated with a metabolic switch from glycolysis to mitochondrial OXPHOS and the mitochondrial metabolic checkpoint is critically controlled by the nutrient sensors SIRT2, SIRT3, and SIRT7 in hematopoietic stem cells. Intestine stem cell homeostasis during aging and in response to diet is critically dependent on fatty acid metabolism and ketone bodies and is influenced by the niche mediated by the nutrient sensor mTOR.

Summary—Nutrient sensing metabolic pathways critically regulate stem cell maintenance during aging and in response to diet. Elucidating the molecular mechanisms underlying dietary

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Conflict of Interest Marine Barthez, Zehan Song, Chih Ling Wang, and Danica Chen have no conflict of interest.

and metabolic regulation of stem cells provides novel insights for stem cell biology and may be targeted therapeutically to reverse stem cell aging and tissue degeneration.

Keywords

SIRT2; SIRT3; SIRT7; mTOR; calorie restriction; stem cell metabolism

Introduction

Diet exerts major effects on health and longevity. Calorie restriction (CR) is the most effective dietary intervention to extend lifespan and has been actively studied for almost a century. Pioneering research from McCay and colleagues showed that CR, a dietary regimen with a long term reduction of dietary intake for 20–40% without malnutrition, is a nutritional approach that makes rats live longer (1). Since then, other research groups have demonstrated that CR not only delays aging but ameliorates the development of age-associated diseases (2). Besides CR, intermittent fasting and methionine restriction have also been described to extend lifespan and prevent chronic diseases (3,4).

Conversely, overnutrition through a high fat diet (HFD) can accelerate aging, as it has detrimental metabolic consequences and promotes multiple aging-associated diseases such as diabetes, cancer, and cardiovascular disease. HFD, which is composed of 45% fat compared to about 10% fat in a normal diet, was first described in 1959 as a diet causing obesity due to an increase in energy intake in rats (5). Besides promoting obesity, HFD can also result in a phenotype in rodents similar to the human metabolic syndrome, characterized by insulin resistance, hyperglycemia, and hepatic steatosis (6). Importantly, the age at which dietary restriction or hypercaloric diet is started and the degree of restriction or excess define the extent of lifespan extension or reduction respectively (7).

It was thought that diet impacts health and longevity by passively changing the metabolic rate and therefore the production of the free radicals, a cause of aging and numerous diseases (8,9). However, recent advances support the view that the physiological changes triggered by diet is an actively regulated process. Prominently, the activity of nutrient sensitive metabolic regulators is modulated by diet and elicit profound physiological responses by regulating diverse metabolic pathways (10). The observations that nutrient sensitive metabolic regulators are critically required for the maintenance of tissue-specific stem cells raise an interesting possibility that nutrient sensors mediate the physiological effects of diet in part by modulating stem cell maintenance and tissue homeostasis (11–14).

In this review, we summarize the recent advances in the metabolic regulation of tissue-specific stem cells and highlight the mitochondrial metabolic checkpoint regulating stem cell maintenance. We discuss how diet affects the metabolism of stem cells through the nutrient sensing pathways, thereby influencing stem cell fate decision and tissue regeneration. Manipulation of these metabolic and nutrient sensing pathways via therapeutic interventions holds the promise for improving stem cell function and ameliorating aging-related tissue degeneration.

Metabolic Regulation in Stem Cells

The cell cycle state is a determining factor for the metabolic status of stem cells. Once animals enter the adulthood, stem cells in many tissues, such as the hematopoietic stem cells (HSCs) and neural stem cells (NSCs), mostly remain quiescent and only enter the cell cycle and proliferate periodically to self-renew and replenish the tissue (15–19). Quiescent stem cells have low mitochondrial activity and primarily rely on glycolysis for energy production (20–22). Compared to mitochondrial oxidative phosphorylation (OXPHOS), glycolysis leads to less ATP production, but is sufficient to sustain the low energy demand of quiescent stem cells. Reliance on glycolysis bypasses mitochondrial OXPHOS and protects stem cells from reactive oxygen species (ROS), and ensure long term stem cell maintenance, as elevated levels of ROS lead to loss of stem cell quiescence, differentiation, and apoptosis (11,19,23–29).

Stem cell transition from quiescence to proliferation is associated with increased mitochondrial biogenesis and a metabolic switch from glycolysis to OXPHOS to meet the increased energy demand of proliferating cells (22,30,31). This metabolic switch is critical to maintain stem cell self-renewal and function, as deletion of PTPMT1, a PTEN-like mitochondrial phosphatase, causes changes in the cell cycle and a block in differentiation, and an expansion of the HSC pool (30). The importance of the metabolic switch is also supported by the extensive studies of the PI3K/AKT/mTOR pathway, a central metabolic pathway that regulate cell growth and proliferation. Aberrant activation of the PI3K/AKT/mTOR pathway leads to loss of stem cell quiescence and the depletion of the stem cell pool, while enforced inhibition of the pathway results in persisted stem cell quiescence and impaired regenerative function (24,32–36) (Figure 1).

While stem cells from many tissues are mostly found in a quiescent state to prevent oxidative stress and maintain stem cell integrity, intestine stem cells (ISCs), which are crypt base columnar cells expressing the WNT target gene Lgr5, are highly proliferative (37). Consistent with the proliferative status, $Lgr5^+$ ISCs have abundant mitochondria and are dependent on OXPHOS for the production of ATP and ROS, which act as signaling molecules to drive cellular differentiation (38). $Lgr5^+$ ISCs quiescence can be induced *in vitro* and quiescent $Lgr5^+$ ISCs acquire gene expression pattern indicative of reduced energy metabolism (39). A second ISC population, called +4 ISCs, is located four cells above the base of the crypt and represents a quiescent population of reserve stem cells (40). Quiescent +4 ISCs and proliferative $Lgr5^+$ ISCs can be interconverted (41,42), suggesting that the metabolic paradigm observed in HSCs and NSCs could be conserved in ISCs. Studies on metabolic regulation in +4 ISCs and other quiescent ISC populations are much needed.

The metabolism of stem cells is influenced by the niche, the microenvironment stem cells reside in. HSCs and NSCs reside in the hypoxic niches, which keep the stem cells in a quiescent state and engage in glycolysis (43–47). Indeed, ablation of HIF1α, the master transcriptional regulator of cellular response to hypoxia, or its downstream mediator pyruvate dehydrogenase kinase (PDK), leads to loss of stem cell quiescence and exhaustion (43,48). Paneth cells, which are in direct contact with $Lgr5^+$ ISCs, constitute a major

component of the ISC niche (37). Paneth cells produce lactate through glycolysis, which is back converted to pyruvate and used to fuel the mitochondrial OXPHOS in ISCs (38).

Mitochondrial Metabolic Checkpoint Regulation of Stem Cell Maintenance

The metabolic switch from glycolysis in quiescent stem cells to mitochondrial OXPHOS in proliferative stem cells supports the concept of the mitochondrial metabolic checkpoint: because a major cellular event during the transition from quiescence to proliferation is increased mitochondrial biogenesis, a cellular condition that is monitored at the restriction point of the cell cycle is the mitochondrial health, to ensure that only cells with healthy mitochondria and the capacity to meet the energy demand of the proliferative cells can enter the cell cycle (49). Consistent with this model, impaired mitochondrial function due to LKB1 deletion results in loss of HSC quiescence, HSC death, compromised HSC repopulation capacity, and defective hematopoiesis (50–52), and perturbation of mitochondrial function by ablation of the mitochondrial transcription factor A (TFAM) leads to neurogenesis defects (53).

Recent studies reveal that the mitochondrial metabolic checkpoint is critically controlled by sirtuins, a family of NAD^+-dependent deacetylases (Figure 1). SIRT3, a mitochondrial deacetylase, monitors mitochondrial oxidative stress and improves oxidative stress resistance, while SIRT7, a histone deacetylase, monitors mitochondrial protein folding stress and regulates mitochondrial unfolded protein response (11,12,54–56). Consistent with a role in monitoring the mitochondrial metabolic checkpoint at the restriction point, deletion of SIRT3 or SIRT7 results in loss of HSC quiescence, increased cell death, and compromised HSC function (11,12). Mitochondrial stress triggers HSC death that is mediated by the NLRP3 inflammasome (13). SIRT2 suppresses the activation of the NLRP3 inflammasome and prevents mitochondrial stress-induced HSC death (13,57). Mitochondrial unfolded protein response is also a conserved regulatory mechanism of stem cell maintenance across tissues (12,58,59). Other mitochondrial protective mechanisms in stem cells include mitophagy (60) and mitochondrial fusion and fission (61,62).

Dietary Regulation of Stem Cells

Given its location, the intestinal epithelium constantly encounters diet-derived nutrients and is strongly responsive to changes in nutrient intake (63). CR leads to reduced small intestine mass, shorter villi, and fewer enterocytes (64). While the number and proliferation of $Lgr5^+$ ISCs are increased, proliferation of transit amplifying cells, more differentiated progenitors, is reduced in CR mice. Thus, CR supports self-renewal of $Lgr5^+$ ISCs at the expense of differentiation. Short term fasting does not change the number of $Lgr5^+$ ISCs but enhances their function (65). Surprisingly, HFD is also associated with shorter small intestine with reduced intestine weight, and similar morphologic modifications of the intestinal epithelium induced by CR, including a reduction in villi length, a decrease in the number of enterocytes, and an increase in crypt depth (66). HFD causes an increase in both the number and function of ISCs. Despite at the opposite spectrum of calorie intake, CR/fasting and HFD are both associated with increased fatty acid metabolism. The similar effects of these

dietary regimens on ISC maintenance and intestine structure may reflect a central role of fatty acid metabolism in ISC homeostasis.

Indeed, the effect of HFD on ISCs is mediated by certain fatty acids contained in HFD, which activate a PPAR-δ transcriptional program, leading to the activation of the Wnt/β-catenin pathway, a central regulator of ISC self-renewal (66). Similarly, short term fasting increases ISC and progenitor cell function through the induction of the fatty acid oxidation program downstream of PPAR signaling (65). 3-hydroxy-3-methylglutaryl-coenzyme A [CoA] synthetase 2 (Hmgcs2), which encodes the rate-limiting enzyme in the production of ketone bodies, is highly expressed in ISCs. The production of ketone bodies modulates the Notch signaling, which promotes ISC self-renewal and instructs lineage differentiation (67). The Hmgcs2 signaling in ISCs is enhanced by CR, contributing to improved ISC self-renewal and reduced differentiation (68).

In addition to directly impacting the metabolic pathways in ISCs, diet can also modulate ISC homeostasis through the niche. The effects observed on increased ISC number and proliferation during CR are associated with a modulation of the mTOR signaling in Paneth cells (64). CR reduces mTOR activity in Paneth cells, leading to the induction of the ectoenzyme Bst1 and secretion of the paracrine factor cyclic ADP ribose (cADPR), which promotes ISC self-renewal and expansion. Contrary to CR, under HFD, ISCs can grow in the absence of signals from Paneth cells through the activation of the Wnt signaling, allowing them to adjust to the decrease number of Paneth cells (66) (Figure 1).

Diet also impacts the HSC and NSC compartments, although the molecular mechanisms are largely unknown. Unlike ISCs, CR/fasting and HFD have opposite effects on HSCs and NSCs. CR increases HSC quiescence and improves HSC function (69,70). As to NSCs, CR enhances neurogenesis and memory performance (71–75). Prolonged fasting or intermittent fasting also give similar beneficial effects on HSCs (76,77) and NSCs (78–80). Conversely, HFD causes loss of HSC quiescence, loss of the HSC pool, promotes the expansion of myeloid progenitors, renders increased susceptibility to myeloablative stress and reduced HSC reconstitute capacity (81–84), as well as reduced neurogenesis (85,86). Much work is needed to understand how diet regulates metabolism in HSCs and NSCs, and whether the mitochondrial metabolic checkpoint is affected.

Therapeutic potential

The regenerative potential of stem cells declines during aging, accounting for much of aging-associated tissue degeneration and dysfunction (87–89). Recent studies attribute stem cell aging to dysregulated nutrient sensing metabolic pathway (11–13,90), which act as the mediators of diet-induced physiological changes (55,57,64,66,91,92), suggesting that the nutrient sensing metabolic pathways can be targeted therapeutically to mimic the physiological effects of diet on preventing stem cell aging and tissue degeneration (Figure 1).

Mitochondrial oxidative stress and protein folding stress are increased in aged HSCs (12,28), and increased mitochondrial stress results in loss of HSC quiescence, increased cell death,

reduced repopulation capacity, and myeloid-biased differentiation, resembling essential aspects of HSC aging (11,12,25,27). The expression of SIRT2, SIRT3, and SIRT7 is reduced in aged HSCs, resulting in increased mitochondrial stress and NLRP3-mediated cell death (11–13,93). Thus, HSC aging results from the dysregulation of the mitochondrial metabolic checkpoint. The activity of mTOR is increased in aged Paneth cells, which inhibits the activity of PPAR-α and the production of Notum, an extracellular inhibitor of the stemness-maintaining Wnt signaling (90). Importantly, genetic manipulations of these nutrient sensors or downstream mediators reverse stem cell aging, highlighting the reversibility and therapeutic potential of aging-associated stem cell decline and tissue degeneration (11–13,90).

Evidence for pharmacological manipulation of these pathways is emerging. The activity of sirtuins is critically dependent on NAD^+ and the supplementation of nicotinamide riboside, a precursor of NAD^+, reduces mitochondrial stress and improves stem cell maintenance across tissues (58,94,95). Rapamycin, an inhibitor of mTOR, also promotes the function of many tissue-specific stem cells (33,64). An inhibitor of Notum enhances the function of aged ISCs and promotes the recovery from injury (90). These observations support the notion that these nutrient sensing metabolic pathways can be targeted therapeutically as CR mimetics, which bring the benefits of CR without a dietary regimen that cannot be tolerated by most individuals.

Conclusions

The burgeoning research area of metabolic regulation in stem cell homeostasis is underscored by its physiological impacts and therapeutic potentials. Recent studies have revealed shared and unique metabolic regulatory mechanisms in stem cells from various tissues. A metabolic switch from glycolysis in quiescent stem cells to OXPHOS in proliferative stem cells appears to be a shared mechanism in stem cells of many tissues. The mitochondrial metabolic checkpoint at the restriction point is critical to ensure that only stem cells with healthy mitochondria and the capacity to meet the energy demand of the proliferative cells can enter the cell cycle. Highly proliferative ISCs are critically dependent on fatty acid metabolism and ketone bodies. In addition to cell-intrinsic metabolic regulatory mechanisms, stem cell metabolism is also influenced by the niche.

Stem cell metabolism regulated by diet is just emerging, opening the door for novel insights into stem cell biology. Nutrient sensing metabolic pathways critically regulate stem cell maintenance during aging and in response to diet. Elucidating the molecular mechanisms underlying dietary and metabolic regulation of stem cells provides novel insights for stem cell biology and may be targeted therapeutically to reverse stem cell aging and tissue degeneration.

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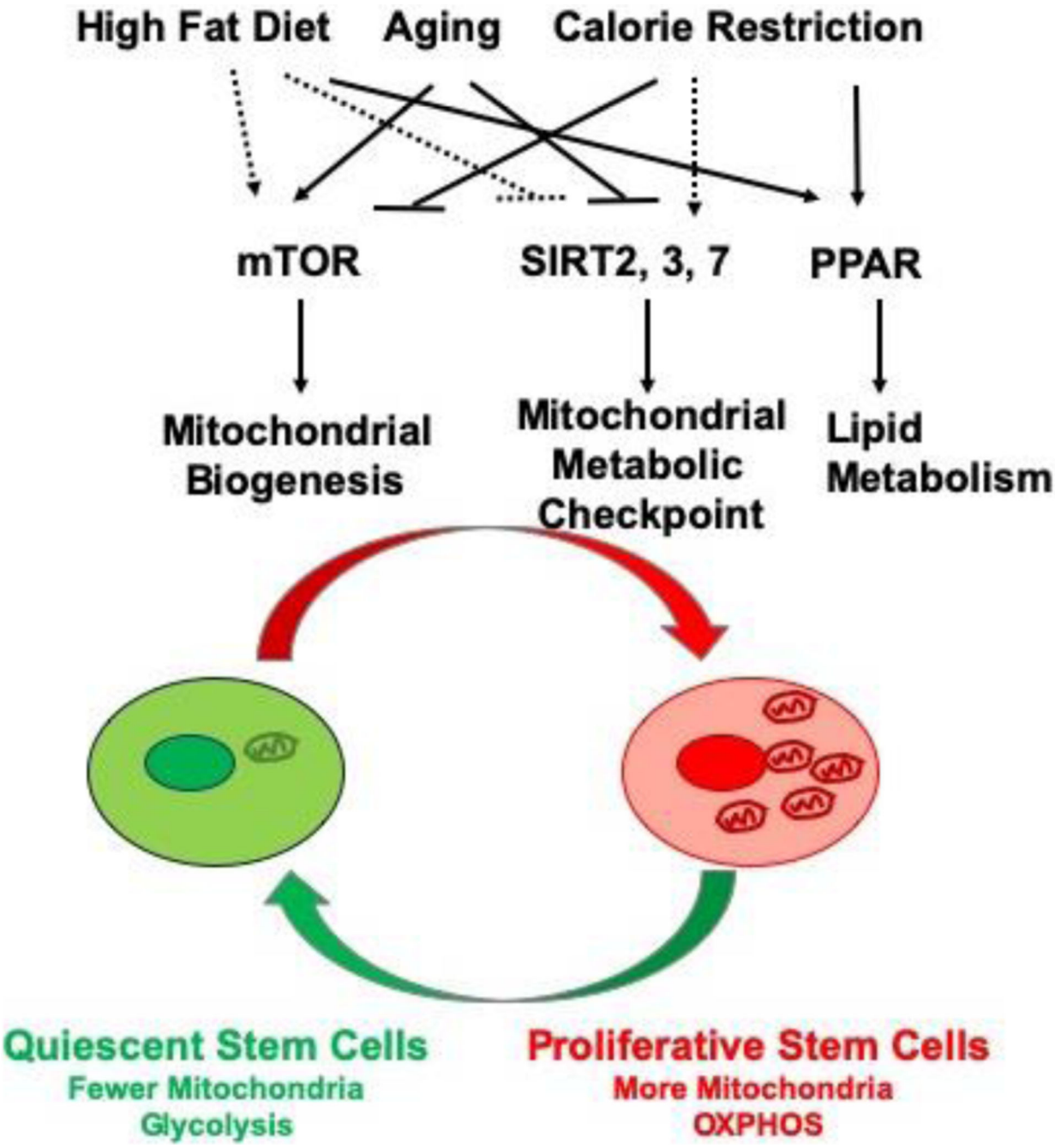

Figure 1. Stem Cell Metabolism and Diet.

Quiescent stem cells rely on glycolysis to prevent oxidative stress. Upon the mitogenic signals and the activation of mTOR, stem cells enter cell cycle and there is an increase in mitochondrial biogenesis and a metabolic switch from glycolysis to OXPHOS. The mitochondrial metabolic checkpoint at the restriction point monitoring the mitochondrial health is critically regulated by sirtuins (SIRT2, SIRT3, and SIRT7). The activity of sirtuins and mTOR is altered during aging, contributing to aging-associated loss of stem cell function and tissue degeneration. Diet can also change the activity of sirtuins and mTOR to regulate stem cell maintenance. $Lgr5^{+}$ ISCs are critically dependent on lipid metabolism and

respond to diet via PPAR. Solid lines and arrows indicate established links in stem cells. Dash lines and arrows indicate speculated links in stem cells based on studies in non-stem cells.