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Dietary Regulation of Adult Stem Cells

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Abstract

Purpose of review—Dietary intake is a critical regulator of organismal physiology and health. Tissue homeostasis and regeneration are dependent on adult tissue stem cells that self-renew and differentiate into the specialized cell types. As stem cells respond to cues from their environment, dietary signals and nutrients influence tissue biology by altering the function and activity of adult stem cells. In this review, we highlight recent studies that illustrate how diverse diets such as caloric restriction, fasting, high fat diets, and ketogenic diets impact stem cell function and their microenvironments.

Recent findings—Caloric restriction generally exerts positive effects on adult stem cells, notably increasing stem cell functionality in the intestine and skeletal muscle as well as increasing hematopoietic stem cell quiescence. Similarly, fasting confers protection of intestinal, hematopoietic, and neuronal stem cells against injury. High fat diets induce intestinal stem cell niche independence and stem-like properties in intestinal progenitors, while high fat diets impair hematopoiesis and neurogenesis.

Summary—Caloric restriction and fasting are generally beneficial to adult stem cell function, while high fat diets impair stem cell function or create opportunities for tumorigenesis. However, the effects of each diet on stem cell biology are complex and vary greatly between tissues. Given the recent interest in developing dietary interventions or mimetics as therapeutics, further studies, including on ketogenic diets, will be essential to understand how adult stem cells respond to diet-induced signals and physiology.

Keywords

Diet; mammalian adult stem cells

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Conflict of Interest

Miyeko D. Mana, Elaine Yih-Shuen Kuo, and Ömer H. Yilmaz declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Adult stem cells are long-lived cell populations with the ability to self-renew and differentiate into cell types of one (unipotent) or more (multipotent) lineages [1]. In many adult tissues, stem cells are critical for normal tissue renewal as well as repair after injury. For example, the intestinal epithelium typically turns over every four to five days. This high level of renewal is sustained by intestinal stem cells (ISCs) residing in the crypts of Lieberkühn that self-renew and generate transit-amplifying cells, which then divide into more differentiated cell types [2]. In the bone marrow, hematopoietic stem cells (HSCs) give rise to all blood lineages throughout the life of an individual [3]. During exercise or injury, normally quiescent satellite cells in the muscle expand and undergo myogenic differentiation, leading to the regeneration of skeletal muscle [4]. However, signaling pathways that regulate stem cell self-renewal are often dysregulated in cancer [5,6]. In addition, decreased stem cell functionality contributes to age-associated pathologies [7,8]. Therefore, tissues depend on careful regulation of adult stem cell renewal and differentiation for tissue homeostasis.

Organismal diet is emerging as an important regulator of adult stem cell function [9]. Studies over the past fifty years have consistently demonstrated that diet and nutritional status can significantly alter organismal physiology. Reduction in caloric intake is generally associated with health benefits, including extended lifespan, reduced cancer incidence, and reversal of age-related effects [10–12]. Similarly, intermittent fasting is associated with decreased blood pressure, cholesterol, and other cardiovascular risk markers [13]. In contrast, obesity is associated with diabetes, cardiovascular disease, and increased cancer incidence [14,15]. Ketogenic diets (high fat, adequate protein, and low carbohydrate diets) have been historically used to treat childhood epilepsy, and studies suggest that ketogenic diets can protect against neuron loss after brain damage [16,17]. Despite extensive research on diet-induced changes in physiology (and molecular signaling, in the case of caloric restriction), relatively few studies have focused on the impacts of diet on adult stem cell biology.

In this review, we highlight recent work in which dietary interventions alter the self-renewal and differentiation capabilities of adult stem cells in multiple mammalian tissues. In addition, adult stem cells typically reside in niches, where they receive metabolic, cellular, or physical cues from neighboring cells to differentiate or self-renew [18]. Therefore, we also review findings that demonstrate how the stem cell niche integrates organismal diet and physiology to alter stem cell function (Table 1). Because of the strong interest in dietary interventions and mimetics as therapeutics, it is critical to uncover the mechanisms by which diet influences adult stem cell function and affects regeneration of healthy tissue over the lifespan of an organism.

Caloric restriction

Caloric restriction (CR), typically defined as a 20–40% reduction in caloric intake without causing malnutrition, is associated with extended lifespan, delayed onset of age-related diseases, and reduced cancer incidence in various organisms and tissue types [10–12,19]. The effects of caloric restriction on longevity are thought to be mediated by downregulation

of key nutrient-sensing pathways, including insulin/insulin-like growth factor 1 (IGF-1) and mTOR (mechanistic Target of Rapamycin) signaling [10,20,21]. Although the benefits of CR have been investigated in the context of various mammalian tissue types, relatively few studies have focused on the positive or negative effects of CR on adult stem cells.

Studies of the mammalian intestine indicate that CR affects stem cell function through modulation of the stem cell environment (Fig. 1). CR elevates numbers of Lgr5+ ISCs and Paneth (niche) cells with decreased numbers of mature enterocytes in mice, indicating that CR shifts ISCs towards self-renewal [22••]. Furthermore, CR promotes stem cell function, as CR enhances the ability of intestinal crypts to form organoids (i.e. mini-intestines in culture) in vitro and regenerate crypts after damage in vivo. Interestingly, CR augments ISC functionality by creating a more favorable niche environment as culturing ISCs with Paneth cells from CR mice significantly enhances organoid formation, regardless of whether ISCs are isolated from CR or ad libitum-fed mice. The mTORC1 inhibitor rapamycin mimics the effects of CR by reducing mTORC1 signaling in Paneth cells. In addition, Bst1 (bone marrow stromal cell antigen-1) induction in the Paneth cell niche drives the enhanced activity of ISCs in CR. A recent study by Igarashi & Guarente (2016) confirms that CR boosts ISC self-renewal and proliferation [23]. In addition, this study shows that a reciprocal mTORC1-S6K1 signaling axis in ISCs is necessary for the enhancement of ISC functionality observed when ISCs are co-cultured with CR Paneth cells. Collectively, these findings indicate that CR influences intestinal homeostasis by promoting ISC function non-cell-autonomously through downregulation of mTORC1 signaling in the Paneth cell niche. This highlights a role for mTORC1 inhibitors such as rapamycin as agents that may improve intestinal regeneration and repair in old age by boosting the function of the stem cell niche.

Although the effects of CR on physiology have been found to promote health, a recent study by Tang et al. [24•] suggests that caloric restriction may exert both beneficial and adverse effects on hematopoiesis. It has been observed that during aging in C57BL/6 mice, HSCs expand in number but have reduced functionality, such as lowered self-renewal capability and skewing of differentiation towards the myeloid lineage, due to stress associated with active HSC cycling [25]. Four to nine months of caloric restriction in mice increases HSC quiescence and prevents age-related increases in HSC numbers, suggesting that CR conditions are beneficial in reducing proliferation-associated stress [24•]. CR conditions also rescue HSC skewing towards the myeloid lineage, as the number of lymphoid-biased HSCs and myeloid-biased HSCs are similar. However, CR reduces common lymphoid progenitor and pro-B cell numbers while enhancing the number of erythroid and myeloid progenitors, indicating that CR impairs differentiation of lymphoid-biased HSCs. The decrease in lymphoid progenitor numbers with CR in aged mice may hamper their ability to respond to infections [26]. Interestingly, treatment of aged CR mice with IGF-1 decreases the number of quiescent HSC numbers close to ad libitum levels and further increases myeloid numbers compared to CR mice [24•]. On the other hand, treatment with IL-7 and IL-6 (cytokines that promote lymphoid development) in aged mice restores lymphoid progenitor differentiation. These results suggest that suppression of IGF-1, IL-7, and IL-6 are important for the CR HSC phenotype. Although the precise mechanism by which CR affects hematopoiesis remains to be understood, CR is beneficial in maintaining HSC quiescence but may have deleterious effects on mounting immune responses by impairing lymphopoiesis.

In contrast to the hematopoietic system, a recent study on skeletal muscle stem cells demonstrates that CR preserves muscle stem cell function during aging. Satellite cells, or adult skeletal muscle stem cells, are quiescent under normal conditions but have the ability to rapidly proliferate upon injury and restore tissue integrity [4]. Short-term caloric restriction in both young and old mice leads to enhanced frequency and myogenic function of satellite cells, likely due to a metabolic shift to more mitochondrial oxidative phosphorylation [27]. Interestingly, satellite cells isolated from ad libitum-fed mice have higher engraftment frequencies into injured CR mice than into injured ad libitum-fed mice, highlighting that CR also modulates the stem cell environment to regulate stem cell biology. These results also indicate that CR controls muscle stem cells both intrinsically and extrinsically. However, further studies are required to understand how CR influences stem cell function and environment.

Fasting

Fasting is a dietary intervention defined as no or minimal consumption of calories for periods of 12 hours to multiple days [28]. It is distinct from CR in which food restriction is chronic and meal frequency is sustained. Both dietary interventions promote healthspan and lifespan, and their effects on physiology and molecular pathways overlap, such as lower glucose and IGF-1 levels. However, fasting states are known to induce ketogenesis, promote stress resistance against DNA damage, and mitigate the untoward side effects associated with chemotherapy [28–31]. These findings raise the possibility that fasting interventions may augment adult stem cell function in injury (e.g. post-chemoradiation) or aging. Furthermore, brief durations of fasting may be more amenable to use in a clinical setting, compared to chronic dietary restriction like CR.

In the small intestine, for example, a prolonged food withdrawal for 48 hours (PF) does not change the numbers of Lgr5+ stem cells per crypt compared to non-fasted mice [32]. In contrast to a CR regimen [22], actively cycling Lgr5+ stem cells in PF decrease in number and contribute less towards repopulation of the intestinal epithelium [32]. However, a subset of crypt progenitor cells, shown to require PTEN for maintenance, become molecularly primed to respond to restored nutritional cues after fasting. In this context, these non-Lgr5+ cells become active and contribute to repopulating the intestinal epithelium upon refeeding [32]. Interestingly, fasting in mice also protects ISCs from lethal doses of chemotherapy and associated DNA damage compared to control mice, highlighting that fasting may represent a potential intervention to dampen the side effects of chemotherapy [31].

CR and fasting regimens similarly induce changes in HSC numbers and differentiation patterns. For instance, PF for 48 hours leads to multiple changes in HSCs and progenitors. First, PF boosts HSC, multipotent progenitor and myeloid precursor proliferation while preserving the total number of the stem and progenitor cells compared to non-fasted animals [33•]. Second, stromal niche cells from fasted animals also stimulate the expansion of multipotent progenitors derived from ad libitum HSCs. As previously noted, the population of HSCs in aged animals under normal feeding conditions is biased towards the myeloid lineage compared to young controls. Cycles of prolonged fasting restore this balance between aged blood cell populations to a state observed in young controls.

Mechanistically, the IGF-1/PKA axis mediates many of these effects of PF in HSCs; interventions that reduce IGF-1 signaling augment HSCs and multipotent progenitors, similar to a PF regimen [33•]. Importantly, 48 hours of fasting prior to chemotherapy protects HSCs from the effects of DNA damage and apoptosis. Again, reduced IGF-1 signaling, independent of fasting, prevents chemotoxicity to normal tissues [33•].

Neural stem cells (NSCs) reside in the subventricular zone, dentate gyrus and hypothalamus and have access to nutrients due to their proximity to blood vessels. Intermittent fasting in animal models (i.e. alternate fasting days or fasting 2 days a week) reduces the age-related clinical symptoms of neuronal maladies such as Alzheimer's disease, and fasted animals fare better after acute injuries such as stroke [28]. Despite these advantageous outcomes, few studies have focused on the direct effect of fasting on adult NSCs. One such example is an increase in NSC proliferation within the dentate gyrus of rats and mice three weeks after completing a 3-month regimen of intermittent fasting [34–36]. These positive neurogenic effects are associated with increases in Brain-Derived Neurotrophic Factor (BDNF). However, the studies conclude that fasting seems to alter the ability of neurons to survive rather than induce proliferation within the NSC population.

A minimal nutrient diet was developed to recapitulate the physiological and molecular features of fasting without inducing starvation when adhered to for extended durations of time [37]. For example, within 72 hours, this fasting mimicking diet (FMD) alters the composition of the dentate gyrus in mice by increasing the numbers of neurons and glia, as previously observed, and reducing IGF-1/PKA signaling [34,37]. Moreover, the authors observed that repeated rounds of a FMD lead to increased numbers and proliferation of mesenchymal stem and progenitors cells in aged animals as well as rebalanced output from HSCs and progenitors in aged mice [33•,37].

High Fat Diet

Excess caloric intake leads to imbalances in metabolic, hormonal and cytokine signaling [38–40]. Chronic overnutrition promotes obesity and multiple diseases such as metabolic syndrome, type 2 diabetes, hypercholesterolemia, heart disease, NAFLD (non-alcoholic fatty liver disease), systemic inflammation and certain types of cancer [41–43]. Recent studies are beginning to uncover the impact of pro-obesity diets like high fat diets (HFDs) on tissue resident stem cells and their role in regeneration.

The intestine is at the interface of nutrient uptake and responds to diet-induced signals. For example, a long-term (more than six months) HFD expands ISC numbers and reduces the numbers of their niche Paneth cells (Fig. 1) [44–47]. In addition to these quantitative changes, ISCs, identified by the Lgr5-eGFP^{high} reporter, and non-stem cell progenitors (Lgr5-eGFP^{low}) undergo qualitative changes: 1) ISCs acquire niche independence—no longer requiring Paneth cells to initiate ex vivo organoids, and 2) non-stem cell progenitors obtain features of stemness—acquiring the potential to form ex vivo organoids [46••]. Normally, such organoid-forming capability is ascribed to ISCs but in a HFD these differentiated progenitor cells co-opt functional attributes of ISCs.

Fatty acid components of the HFD, rather than consequences of obesity, may directly drive many of these changes in ISCs and progenitors. For instance, organoids exposed to lipids commonly found in the HFD have more ISCs and greater self-renewal capacity. Mechanistically, a HFD activates a robust PPAR-delta (a nuclear receptor that senses intracellular lipids) program within the ISCs and progenitors. Treatment of mice with a PPAR-delta agonist recapitulates many of the HFD-induced ISC and progenitor phenotypes in vivo. Furthermore, treatment of naïve organoids with PPAR-delta agonist mimics many of the features observed with lipid exposure (i.e. expansion of ISC numbers and more organoid self-renewal).

These findings are also relevant in terms of understanding the link between obesity and cancer in the intestine, where epidemiological data implicates obesity as a risk factor for the development of colon cancer [48]. In a HFD, there are not only more ISCs but also progenitors that acquire features of stemness, including the capability of forming tumors. Because stem cells are the cells-of-origin for early intestinal cancers, a HFD effectively increases the number of target cells (i.e. ISCs and stem-like progenitors) that can undergo oncogenic transformation to initiate tumors [46••]. Therapeutically, it remains to be determined whether PPAR-delta inhibition in a HFD can be exploited to dampen intestinal tumorigenesis.

In addition to the intestine, a HFD evokes changes in the hematopoietic system. Whereas a few weeks of a HFD leads to a reduction in HSC numbers [49,50], a longer-term HFD boosts HSCs numbers and function such as increased myeloid cell colony forming units [51]. Notably, this HFD phenotype is partially reversible; after removal from a HFD, HSC numbers in HFD mice return to that of control mice [51]. Both short-term and long-term HFD also skews differentiation within the hematopoietic system towards myelopoiesis [49,51]. In addition to changes in HSC lineages with a HFD regimen, a functional consequence of excess nutrition is impairment of hematologic regeneration. After 6 weeks of a HFD and subsequent treatment with fluorouracil (5-FU) to reduce myeloid and lymphoid lineages, the recovery results in fewer progenitors and myeloid cells compared to standard chow-fed mice [49]. Although a HFD clearly impacts HSC and progenitor numbers and differentiation, the mechanisms governing these effects are unclear. Interestingly, altered HSC number and differentiation pattern in HFD-fed mice are recapitulated in standard chow-fed mice following gut microbial transfer from HFD-fed mice, as HSCs and myeloid progenitor cell numbers increase while lymphoid progenitor numbers decrease [49], implicating a role for the gut microbiome.

In contrast to the positive effects of dietary restriction on neurogenesis in the CNS, a HFD and diabetes impede neurogenesis [52–54]. In the hypothalamus, where feeding behavior neural circuits are found, NSCs are vulnerable to inflammatory signals induced by dietary fats [55•]. For example, a chronic HFD through activation of IKKβ/NFκB in hypothalamic NSCs diminishes stem cell numbers in part due to apoptosis and defects in Notch-mediated differentiation [55•,56]. Persistent activation of IKKβ/NFκB in these NSCs results in the loss of POMC neurons, which suppress appetite, ultimately leading to over-eating, obesity and diabetes even when mice are fed a standard chow. Conversely, a short-term HFD enhances the proliferation of hypothalamic NSCs, suggesting that the response to acute

versus chronic high fat feeding may differentially regulate neural progenitor biology [57]. Similarly, specific dietary constituents, such as n-3 polyunsaturated fatty acids (Omega-3 fatty acids), appear to increase hypothalamic neurogenesis, implying that dietary approaches have the potential to rescue neuronal loss in diseases and aging [58].

Skeletal muscle satellite cells are also significantly affected by diet-induced obesity. Diabetics and rodent models of diabetes show impaired muscle regeneration [59]. Recent findings reveal that HFD-induced obesity hinders satellite cell activation and hampers muscle regeneration [60]. Many of these effects in satellite cells in response to a HFD depend on AMPK (AMP-activated protein kinase, an energy ATP/ADP/AMP sensor). For instance, AMPK-agonist treatment improves satellite cell function and muscle regeneration in HFD-fed obese mice, raising the possibility that AMPK activation may represent a therapeutic opportunity for enhancing muscle function in obese patients.

Ketogenic Diet

Ketogenic diets (KDs) are defined as high fat, moderate protein and low carbohydrate content diets, which induce elevated ketone bodies in circulation [61,62]. A diet low in carbohydrates forces utilization of ketone bodies as an alternative energy source. KDs were originally designed as anticonvulsant therapy in epilepsy to reduce glucose levels and maintain dietary fats. Interest in KD is currently increasing due to potential neuroprotective benefits against late-stage disorders such as Alzheimer's and Parkinson's disease. The diet is associated with improved mitochondrial and cellular metabolism, which may confer neuroprotective properties [61,62]. However, KDs are not restricted to treatment of neurological ailments; recent clinical studies reveal that a low carbohydrate, ketogenic diet improves the prognosis of obese and T2 diabetic patients [63–65]. However, how KDs impact adult tissue stem cell function requires further investigation.

Future Considerations

Diet is a modifiable lifestyle factor that influences organismal health and in many cases contributes to disease such as cancer incidence and progression [9]. Dietary restriction in particular is associated with many favorable effects that accrue over a lifetime. Different diets offer potential therapeutic benefits in certain clinical settings [11,66]. For example, a low glycemic diet has been proposed for diabetic patients [67,68]. The benefits of dietary restriction are multifactorial, and the task to substitute dietary consumption or mimetics of dietary restriction such as the mTOR inhibitor rapamycin remains a challenge [69].

An important question is whether nutrients play an instructive or permissive role in adult stem cell biology. Recent advances in organoid technologies will enable assessment of diverse nutrients in controlled ex vivo assays. Organoids have become instrumental for studying development and disease in multiple tissues, as stem cells can be isolated and grown in vitro to form structures that closely resemble organs [70–72]. Exposure of organoids to individual nutrients allows for precise investigation of how different nutrients regulate adult stem cell self-renewal and differentiation capabilities. Similarly, organoids can be used to screen for synthetic dietary mimetics. Organoid technologies will be instrumental

for understanding the effects of dietary constituents on adult stem cell function, metabolism, and nutrient signaling in many tissues.

In addition to organoids, other technological improvements will facilitate investigations on dietary regulation of stem cell function. Advancements in gene editing technology, such as the CRISPR/Cas9 system, will permit investigators to genetically manipulate nutrient-sensing pathways both in organisms and in organoids [73]. Improvements in isolating stem cell populations, regeneration assays, and single-cell analyses will greatly enhance our understanding of stem cell function, heterogeneity, and microenvironment. However, further studies on stem cells under different dietary conditions will be dependent on our capability to identify stem cell populations (e.g. quiescent versus proliferating stem cells) as well as effectively measure stem cell activity ex vivo and in vivo.

Finally, interpretation of dietary effects is largely hindered by the variation in experimental conditions across different studies. For example, CR extends longevity in some mice strains while not affecting others, indicating that genetic factors modify how diet influences stem cell biology [74,75]. In addition, studies differ in their method, duration, and age of diet onset. As stem cells are tightly regulated and sensitive to their environment, it will be crucial to closely examine and compare experimental conditions across studies, especially if findings are to be translated for therapeutic purposes in human populations.

Conclusions

Diet is a major modulator of adult stem cell biology in a wide variety of tissues. Caloric restriction and fasting generally confer benefits to stem cell function, such as reversing age-related defects. Although a high fat diet enhances intestinal stem cell numbers and niche independence (creating opportunities for tumorigenesis), the consequences on other adult stem cells can vary with duration of diet. Of the four diets examined, investigations on ketogenic diets are the most lacking. Given the association between ketogenic diets and neuroprotection, it will be intriguing to determine whether ketogenic diets can be utilized to boost neural stem cell function. For all diets, substantially more studies will be required to determine the molecular mechanisms between nutritional intake and stem cell biology.

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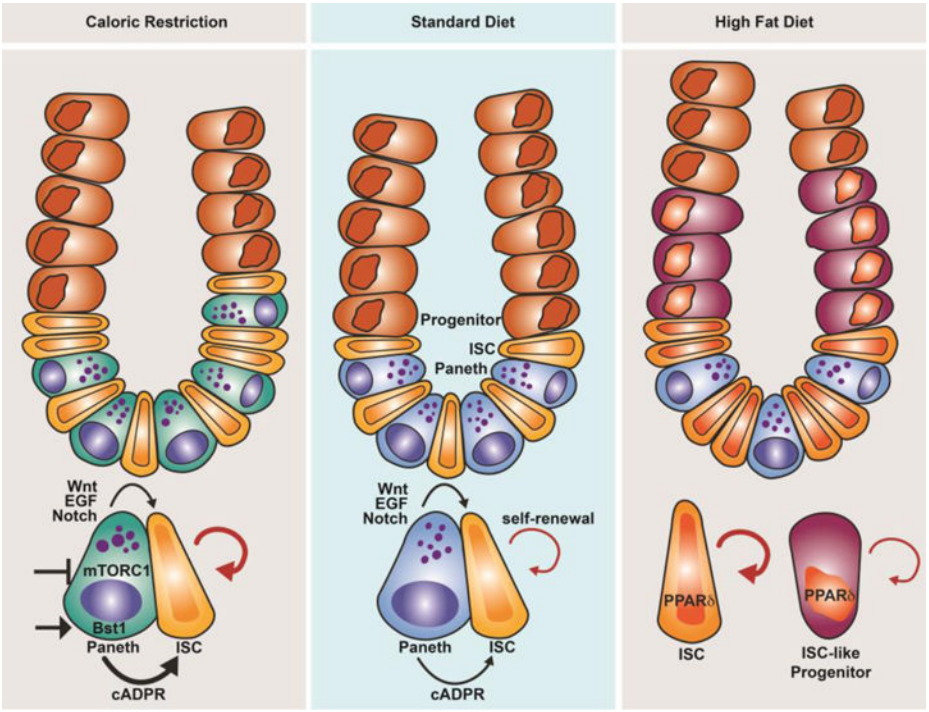

Fig. 1.

Model of intestinal adaption to caloric restriction and high fat diet. In a standard diet **(center)**, Paneth cells elaborate several growth factors (e.g. Wnt3, Notch ligands, and EGF) and play an important role in governing ISC function and intestinal homeostasis. Caloric restriction **(left)** decreases mTORC1 activity in the Paneth cell niche, inducing Bst1 expression in these Paneth cells whose product cADPR enhances ISC self-renewal in a paracrine manner. A high fat diet **(right)** induces PPAR-delta activation in intestinal stem cells and progenitors permitting ISCs numbers to expand and depend less on Paneth cells, while conferring stem-like properties such as organoid-initiating capacity to non-stem cell progenitors.

Table 1

Dietary effects on adult stem cells

	Caloric Restriction	**Fasting**	**High Fat Diet**
HSC	⇑ HSC quiescence; Impaired lymphopoiesis [24]	⇑ HSC numbers; Skew towards myeloid lineage [33]	⇓HSC numbers in short-term HFD [49,50]; ⇑ HSC numbers in long-term HFD [51]
ISC	⇑ ISC numbers; ISCs dependent on niche Paneth cells [22]	⇓ ISC numbers [32]	⇑ ISC numbers; ⇑ Progenitor numbers [46]
NSC	Unknown	Unknown	⇓ NSC numbers [55]
SMSC	⇑ SMSC frequency & function [27]	Unknown	⇓ SMSC function [60]

HSC = hematopoietic stem cell; ISC = intestinal stem cell; NSC = neuronal stem cell; SMSC = skeletal muscle stem cell; HFD = high fat diet.