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Control of adult stem cells *in vivo* by a dynamic physiological environment: diet-dependent systemic factors in *Drosophila* and beyond

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Abstract

Adult stem cells are inextricably linked to whole-body physiology and nutrient availability through complex systemic signaling networks. A full understanding of how stem cells sense and respond to dietary fluctuations will require identifying key systemic mediators, as well as elucidating how they are regulated and integrated with local and intrinsic factors across multiple tissues. Studies focused on the *Drosophila* germline have generated valuable insights into how stem cells are controlled by diet-dependent pathways, and increasing evidence suggests that diverse adult stem cell populations respond to nutrients through similar mechanisms. Systemic signals, including nutrients themselves and diet-regulated hormones such as Insulin/Insulin-like growth factor or steroid hormones, can directly or indirectly affect stem cell behavior by modifying local cell-cell communication or intrinsic factors. The physiological regulation of stem cells in response to nutritional status not only is a fascinating biological problem, but also has clinical implications, as research in this field holds the key to non-invasive approaches for manipulating stem cells *in vivo*. In addition, given the known associations between diet, stem cells, and cancer risk, this research may inspire novel anti-cancer therapies.

Keywords

diet; adult stem cells; Insulin; AMPK; TOR; steroid hormone; nuclear hormone receptor; ecdysone; FOXO; PTEN; *Drosophila*; *C. elegans*; mouse; human

Introduction

The ability of a species to adapt to nutrient availability is crucial for the success of future generations; therefore, the physiological response to diet involves ancient, conserved cellular functions. In multicellular organisms, changes in nutrient intake at the organismal level are translated into specific cellular responses via an intricate web of metabolic pathways, circulating factors, and signaling relays to ensure physiological homeostasis.

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Stem cells in particular must be tightly linked to nutrient sensing systems to adjust the production of new differentiated cells to varying physiological constraints and demands.

Evidence ranging from human epidemiological to model organism experimental data suggests that nutrients impact a variety of adult stem cells. Diet influences wound healing, hematopoietic transplants, and cancer risk in humans¹⁻³. In *Drosophila melanogaster*, germline stem cells (GSCs) have well-characterized dietary responses⁴⁻⁶. This review focuses on *in vivo* experimental systems (Figure 1) to illustrate our current state of knowledge on how adult stem cells sense and respond to multiple interconnected diet-dependent systemic signals that are integrated with local and intrinsic factors to determine stem cell behavior. While many questions remain regarding how diet controls adult stem cells, it is clear that this complex web of regulation is an essential part of their basic biology. Further, the remarkable evolutionary conservation across diverse organisms and the primal nature of dietary responses point to research using genetically tractable model organisms as the logical avenue towards future fundamental and broadly relevant discoveries concerning stem cell regulation by diet.

ADULT STEM CELLS RESPOND TO DIET VIA MULTIPLE MECHANISMS

The *in vivo* response of adult stem cells to dietary changes was first described in *Drosophila* female GSCs⁴, and growing evidence demonstrates that stem cells in many tissues and organisms respond to diet. *Drosophila* female and male GSCs reside in niches composed of cap and hub cells, respectively, that create a local signaling milieu⁷ (Figure 1a,b), but GSCs also respond to nutritional inputs^{4-6, 8}. Specifically, female GSCs proliferate robustly under a yeast-rich diet, but without yeast, GSCs divide slowly and are frequently lost from the niche^{4, 5, 8}. Male GSCs also show reduced numbers and proliferation rates under a yeast-free diet⁶, although halving the yeast concentration relative to a control diet increases GSC number⁹. *Drosophila* intestinal stem cells (ISCs) respond to diet by altering proliferation rates and modulating the balance between asymmetric and symmetric divisions^{6, 10, 11}. In the nematode *Caenorhabditis elegans*, a small population of mitotic germ cells is protected from death during starvation and can later reconstitute the germline⁹. In mammals (Figure 1c,d), diet impacts multiple tissues^{1, 9, 12}, but specific *in vivo* stem cell effects are largely unknown. In most cases, the effects of diet on stem cells are at least partially reversible, demonstrating that this is a dynamic process.

Stem cells could hypothetically sense and respond to diet in different ways (Figure 2). Nutrients might signal directly to stem cells (Figure 2a). Alternatively, nutrients might have indirect effects on stem cells through any of three general strategies. First, hormones produced downstream of nutrients by endocrine cells may directly stimulate stem cells (Figure 2b). Second, either diet-dependent hormones or nutrients may act on adjacent support cells (e.g. the stem cell niche), inducing a secondary signal to stem cells (Figure 2c). Third, more complex systemic hormonal relays may impose increasing degrees of separation between nutrients and their effects on stem cells, incorporating the impact of diet on multiple tissues into the final stem cell response (Figure 2d). Most likely, dietary factors shape stem cell behavior using all of these mechanisms, thereby generating a complex physiological network that coordinates a fine-tuned response of multiple types of stem cells with specific changes in the availability of nutrients.

Direct nutrient-sensing pathways—In general, nutrients signal through conserved intracellular pathways to regulate various cellular processes (Figure 3). Target of rapamycin (TOR) signaling is activated by amino acids, promoting protein synthesis and cell growth¹³. AMP-activated protein kinase (AMPK) is stimulated by upstream kinases such as Serine/threonine kinase 11 (LKB1/STK11) in response to low intracellular ATP levels¹². AMPK

phosphorylation of upstream regulators inhibits TOR and downstream energy-intensive processes, and AMPK also downregulates anabolism and upregulates catabolism to restore ATP levels within the cell^{12, 13}. The Sirtuin (SIRT) family of protein deacetylases/mono-ADP-ribosyltransferases, which require nicotinamide adenine dinucleotide (NAD⁺) for their enzymatic activity, also links metabolism to nutrient availability¹². The integration of TOR, AMPK, and SIRT signaling into the Insulin/Insulin-like growth factor (IGF) pathway (described below) via crosstalk and common downstream effectors couples multiple nutritional inputs to metabolism and other diet-dependent cellular processes (Figure 3). Recent studies indicate that direct nutrient sensing via these pathways plays an important role in modulating stem cell number and activity.

Target of rapamycin (TOR): TOR activity has profound effects on *Drosophila* GSCs (Figure 1a,b). *Tor* function within female GSCs is required for proper rates of GSC proliferation through an effect on the G2 cell cycle phase¹⁴ (Figure 4). *Tor* mutant GSCs in genetic mosaic females are also frequently lost from the niche¹⁴. Interestingly, hyperactivation of TOR through the removal of its upstream inhibitors Tuberous sclerosis (TSC)1 or TSC2 (Figure 3) results in even more severe GSC loss^{14, 15}, which is rescued by treatment with the TOR inhibitor rapamycin¹⁵. These studies suggest that tightly regulated TOR activity is crucial for GSC maintenance (Figure 4). Indeed, GSCs lacking *Tsc1* function have markedly reduced levels of phosphorylated Mothers against decapentaplegic (MAD)¹⁵, a downstream target activated in response to niche-derived bone morphogenetic protein (BMP) signals and required for stem cell self-renewal⁷. How intrinsic TOR activity regulates BMP signaling within GSCs, however, is unknown. It also remains unclear what effect TOR has on other GSC populations, including *Drosophila* male GSCs, *C. elegans* mitotically dividing germ cell precursors, and male spermatogonial stem cells in mammals.

Mammalian hematopoietic stem cells (HSCs), which neighbor mesenchymal stem cells (MSCs; see Sidebar 1) and their progeny in a vascularized niche in the bone marrow⁷ (Figure 1d), are also sensitive to TOR activity¹⁶⁻¹⁹. Conditional *Tsc1* or *phosphatase and tensin homolog (Pten)* deletion or expression of a constitutively active, myristoylated AKT1 (Figure 3) increases mouse HSC proliferation and depletes the HSC pool¹⁶⁻¹⁹. These effects are reversible by rapamycin, indicating that they occur via TOR hyperactivation¹⁷⁻¹⁹. Reactive oxygen species may contribute to these phenotypes¹⁶, but additional mechanisms are likely involved because mutation of a cell cycle inhibitor reverses *Pten*-deficient HSC depletion²⁰. Intriguingly, myristoylated AKT1 expression in endothelial cells triggers the release of factors that support HSC expansion²¹, suggesting that TOR may control HSCs via additional indirect mechanisms.

TOR signaling may regulate downstream targets in a stem cell-dependent context, potentially reflecting the varied nutritional demands of different stem cell populations, even within the same tissue. For example, despite the requirement for optimal TOR activity levels for GSC maintenance in *Drosophila* ovaries, neither *Tor* nor *Tsc1* are required for the maintenance of nearby follicle stem cells (FSCs)¹⁴ (Figure 1a). In contrast, *Tor* is required for proliferation of both GSCs and FSCs, although the cell cycle of FSC descendants is surprisingly insensitive to TOR signaling¹⁴. In the *Drosophila* midgut, *Tsc1/2* knockdown causes TOR- and MYC-dependent ISC overgrowth and S phase defects, with no apparent ISC number reduction. These ISC phenotypes appear to require intrinsic TOR activity based on genetic mosaic analysis²². These results suggest that widely conserved nutrient-sensing pathways regulate stem cell activity in specific ways.

AMP-activated protein kinase (AMPK): Adult stem cell roles for AMPK (Figure 3) remain unclear. Recent studies suggest that *Lkb1* is required for mouse HSC activity²³⁻²⁵ (Figure 1d). Conditional *Lkb1* inactivation leads to abnormal proliferation of HSCs, but not

of their more differentiated progeny, and to HSC depletion²³⁻²⁵. Despite similarities to the *Tsc1* phenotype, *Lkb1* mutant defects are independent of TOR²³⁻²⁵. Further, genetic or chemical inhibition of AMPK does not rescue the *Lkb1* phenotypes, suggesting that LKB1 controls HSC proliferation and survival largely independently of AMPK²³⁻²⁵. AMPK, however, might be required in other stem cell populations. For example, AMPK has roles in neural precursor proliferation during development²⁶. Multiple genes encode each of the three AMPK subunits in mammals¹², while in *Drosophila*, a single gene encodes each subunit and the nutrient-sensing function of AMPK is conserved²⁷; therefore, future studies on potential AMPK roles in *Drosophila* adult stem cells should be informative.

Sirtuins (SIRT1): Although SIRT1 (Figure 3) control organismal metabolism¹², it is unclear how they function in adult stem cells. Neural SIRT1 expression increases under caloric restriction²⁸, and AMPK enhances SIRT1 activity by raising NAD⁺ levels^{29, 30} (see Figure 3), suggesting potential roles in NSCs. Mouse *Sirt1* global mutants have decreased hematopoietic progenitor cell numbers based on *in vitro* culture of bone marrow cells³¹. It is unknown, however, if SIRT function is specifically required in adult HSCs or other stem cells.

Diet-dependent hormonal pathways—Dietary factors also induce global physiological responses through changes in hormone levels. The peptide hormone Insulin is secreted by vertebrate pancreatic β cells in response to glucose or specific amino acids and signals through the Insulin receptor (InR)³² (Figure 3). Insulin-like growth factors (IGFs) produced mainly by the liver and also locally within tissues stimulate closely related IGF receptors, acting through a very similar pathway³². In *Drosophila* and *C. elegans*, multiple Insulin-like peptides produced mainly by neuroendocrine cells act through single Insulin/IGF receptor homologs³². Insulin/IGF signaling has highly conserved roles in metabolism, growth, proliferation and survival, and shares downstream effectors with the TOR and AMPK pathways¹³ (Figure 3).

Steroid hormones are diverse molecules derived from sterol precursors³³. Mammals acquire cholesterol from their diet and synthesize it *de novo*, while *Drosophila* and *C. elegans* are solely dependent on dietary cholesterol-related molecules³³. Other dietary factors can also serve as steroid hormone precursors (e.g., vitamin A for retinoic acid), and hormone biosynthetic enzyme expression can be nutritionally regulated³⁴. Steroid hormones achieve cellular responses by binding to nuclear hormone receptors (NHRs), a family of proteins with highly conserved DNA-binding and variable ligand-binding domains^{35, 36}. Some nutrients act as NHR ligands, including cholesterol, fatty acids, and vitamin D^{33, 34, 36}. Finally, extensive crosstalk adds to the complexity of NHR-diet connections^{33, 35, 36}. As discussed below, Insulin/IGF hormones and NHR signaling are important regulators of adult stem cells.

Insulin, Insulin-like growth factor (IGF), and other Insulin-like signals: Insulin-like signals have extensive roles in GSC regulation (Figure 1a,b). Insulin/IGF signaling controls proliferation and maintenance of *Drosophila* female GSCs through clearly distinct mechanisms^{4, 5, 37} (Figure 4). Insulin-like peptides act directly on GSCs to control their proliferation rates, based on genetic mosaic lineage tracing^{8, 37}, and this occurs through Phosphoinositide 3-kinase (PI3K)-mediated inhibition of the downstream transcription factor Forkhead box, subgroup O (FOXO) (see Figure 3) to modulate G2⁸. Independent evidence that Insulin promotes GSC progression through G2 comes from cultured *Drosophila* ovary studies³⁸. In contrast, Insulin-like signals indirectly control GSC numbers through niche effects^{5, 39}, suggesting that diet-dependent hormones can affect a single stem cell system in diverse ways. Genetic inhibition of Insulin/IGF signaling leads to reduced numbers and slowed G2 progression of *Drosophila* male GSCs⁹. *InR* mutant GSCs are lost

at high rates in genetic mosaics, suggesting an intrinsic requirement for GSC maintenance in males⁶ (in contrast to females^{5, 39}). In *C. elegans*, *InR/daf-2* mutants have a smaller population of mitotically-dividing germ cells than wildtype, yet have normal proliferation rates in adult gonads; instead, *daf-2* acts through *Pten/daf-18* and *Foxo/daf-16* to control larval germ cell division rates⁴⁰. Cultured mouse spermatogonial stem cell studies suggest that Leydig cell-secreted IGF-1 may promote their maintenance⁴¹; future *in vivo* studies should carefully examine how Insulin/IGFs affect mammalian GSCs.

Insulin-like signals also control diverse populations of somatic stem cells. Both systemic and locally produced Insulin-like peptides modulate *Drosophila* ISC proliferation^{6, 9-11} via direct effects on the ISC itself and indirect effects through its immediate daughter¹⁰. In mammals, conditional *Foxo1*, *Foxo3* and *Foxo4* deletion causes increased proliferation and apoptosis of HSCs⁴². Peripherally administered IGF-1 enhances neurogenesis in the adult rat hippocampus, and intraventricular infusion of an inhibitory IGF-1 antibody inhibits ischemia-induced proliferation of neural progenitors in the subgranular zone of the hippocampal dentate gyrus^{43, 44}. Consistent with these results, *Pten* deletion in neural progenitors stimulates self-renewal and proliferation, although simultaneous deletion of *Foxo1*, *Foxo3*, and *Foxo4*, or *Foxo3* alone increases proliferation and, paradoxically, inhibits self-renewal^{12, 45-47}. Specific effects on NSCs versus their immediate progeny, however, remain unclear.

Ecdysone: The *Drosophila* steroid hormone ecdysone is structurally similar to human sex steroids and regulates many developmental processes^{33, 35}. In adult females, ecdysone is produced by vitellogenic ovarian follicles in a diet- and Insulin-dependent manner^{48, 49}. Ecdysone signals through the Ecdysone receptor (EcR), which functions as a heterodimer with the Retinoid X receptor (RXR) homolog Ultraspiracle (USP)³⁵. USP can also heterodimerize with Hormone receptor-like in 38 (Hr38)³⁵. USP/Hr38 can be activated by several ecdysteroids, and *Hr38* expression is diet-dependent during larval development^{35, 50}.

Ecdysone controls ovarian GSCs^{51, 52} (Figure 4). Reduction in ecdysone signaling using temperature-sensitive mutants causes decreased GSC numbers and proliferation⁵¹. GSCs deficient for *usp* or *Ecdysone-induced protein 74EF* (*Eip74EF*), a direct transcriptional target of EcR, are rapidly lost in genetic mosaics, reflecting an intrinsic requirement⁵¹. Interestingly, GSCs lacking *usp* or *Eip74EF* show reduced BMP signaling, suggesting that ecdysone modulates the GSC response to niche signals⁵¹. Adult-specific dominant-negative *EcR* expression in surrounding somatic cells disrupts early germ cell differentiation⁵², indicating an additional indirect role for ecdysone in promoting differentiation of GSC daughters outside of the stem cell niche.

EcR/USP signaling in GSCs involves distinct mechanisms relative to those in other cells. Mutation of the known EcR co-activator *taiman* has no effect on GSC maintenance^{51, 52}; however, *taiman* downregulation in surrounding cells phenocopies dominant-negative EcR expression⁵². As another example, *Eip74EF*, but not *Ecdysone-induced protein 75B* (*Eip75B*; another direct transcriptional target of EcR), promotes GSC proliferation and maintenance⁵¹, while both *Eip74EF* and *Eip75B* are required at later stages of oogenesis³⁵. Identifying additional direct and indirect targets of ecdysone in GSCs and in other potential ecdysone-sensitive stem cell populations, and studying how they control stem cell behavior will shed light on how steroid hormones may induce specific responses in different types of stem cells.

Retinoic Acid: Mammalian Retinoic acid receptors (RARs) heterodimerize with RXRs to regulate retinoic acid transcriptional responses^{34, 53}. Although multiple RAR and RXR isoforms exist⁵³, *Rara* and *Rarg* phenotypes reveal isoform-specific roles in the mouse HSC

lineage⁵⁴ (Figure 1d). *Rara* controls granulocyte terminal differentiation but has no apparent role in HSCs, while *Rarg*-deficient mice have decreased HSC numbers⁵⁴. Mechanisms underlying this specificity, however, are unknown.

Conflicting data suggest that retinoic acid might regulate adult neural progenitors. Rats fed retinol palmitate display increased numbers of proliferating subventricular neural progenitors⁵⁵ and enhanced ischemia-induced neurogenesis⁵⁶. In apparent contrast, retinoic acid intraperitoneal injection suppresses hippocampal and subventricular zone proliferation in mice⁵⁷. Specific effects of retinoic acid on NSCs versus their diverse progeny, however, are unclear. For example, retinoid acid-treated neurospheres show increased BrdU incorporation in neuronal cells, but not in astrocytes⁵⁸, and retinoic acid is required *in vivo* for an early step in neuronal differentiation⁵⁹. Future studies analyzing the effects of retinoic acid specifically on NSCs will require cell type-specific markers and lineage tracing analysis.

Peroxisome proliferator-activated receptors (PPARs): Mammalian Peroxisome proliferator-activated receptors (PPARs) may control multiple adult stem cell populations. In general, PPAR/RXR heterodimers function as lipid sensors that regulate transcription in response to various fatty acids to regulate triglyceride metabolism and fatty acid oxidation³⁶. Systemic administration of a PPARG agonist in adult rats increases proliferating neural progenitor numbers⁶⁰, suggesting a potential role for PPARG in adult NSCs. PPARB/D is expressed throughout intestinal crypts, and *pparb/d*-deficient mice have decreased numbers of Paneth cells⁶¹, which are thought to serve as the ISC niche and are themselves ISC-derived⁶² (Figure 1c). It is therefore conceivable that PPARB/D might regulate ISCs, either by intrinsic activation of transcriptional programs, or indirectly via the regulation of Paneth cell numbers or function.

Sex steroids: Sex steroids play key roles in regulating adult stem cells and are, in some cases, influenced by diet. Estrogen levels are increased in postmenopausal females on a high fat diet, resulting in a higher risk for breast cancer⁶³. Estrogen and progesterone control mouse mammary stem cell (MaSC) proliferation^{64, 65}. Mice deficient for estrogen and testosterone production have fewer MaSCs, which also perform poorly in transplantation assays⁶⁴. MaSCs do not express detectable levels of estrogen or progesterone receptors, suggesting that MaSCs respond indirectly to these hormones, perhaps by alterations in local signaling^{64, 65}. Nevertheless, these studies do not rule out potential direct effects of estrogen or progesterone on MaSCs.

The role of sex steroids in other stem cell populations is less clear. Estrogen and androgen receptors are expressed in sites of neurogenesis within the adult rat brain, and estrogen injection rescues the decreased hippocampal proliferation displayed by ovariectomized rats⁶⁶⁻⁶⁹. Androgen administration, however, results in decreased neural proliferation in both sexes⁶⁶. Estrogen requirements apparently differ between brain regions: estrogen is not required for postnatal neurogenesis in the subventricular zone, but is necessary for the survival of new neurons in the main and accessory olfactory bulbs⁷⁰. It will be important to examine the role of estrogen and testosterone specifically in NSCs and also in other stem cell populations including MSCs, which appear to be regulated by sex steroids in culture⁷¹ (see Sidebar 1), and in the muscle, where these hormones promote satellite cell proliferation⁷².

THE COMPLEX DIETARY RESPONSE OF STEM CELLS REQUIRES INTEGRATION OF SIGNALS

Diet-dependent systemic factors control stem cells via many different mechanisms. As discussed (Table 1), nutrients themselves and multiple hormones each have the potential to impact various stem cell lineages in similar or distinct ways, underscoring the complexity of systemic influences. Local signals and intrinsic factors also control stem cell self-renewal and proliferation⁷. The ultimate behavior of any given stem cell population under specific dietary and physiological conditions thus results from the integration of these various interconnected systemic factors with local and intrinsic regulators (see Figure 2d). As illustrated below, stem cells have elaborate ways of integrating these diverse signals into a distinct cellular response.

Systemic signals and local signaling pathways—Examples of diet-dependent systemic factors influencing stem cells by altering local signaling are evident for *Drosophila* female GSCs (Figure 4). Insulin-like peptides stimulate niche cap cells to indirectly control GSC maintenance via two separate mechanisms^{5, 39}. Insulin signaling via PI3K/FOXO promotes locally-induced Notch activation to maintain cap cell number (and thereby niche size)^{5, 39} and, in parallel, it enhances GSC-cap cell attachment and E-cadherin levels at their junction^{5, 39}. Both TOR and ecdysone signaling control how GSCs respond to niche-secreted BMP signals, as indicated by reduced BMP signaling in the absence of *Tsc1*¹⁵, *usp*, or *Eip74EF*⁵¹, and by strong genetic interactions between *EcR* and BMP receptor genes⁵¹. It will be important to understand how systemic factors are integrated with local signals in other adult *Drosophila* stem cell systems.

In mammals, ovarian sex hormones activate local signals in the mammary luminal epithelium^{64, 65}. Estrogen plus progesterone induces Tumor necrosis factor receptor superfamily member 11a (RANK/TNFRSF11a) and the WNT receptor Low density lipoprotein receptor-related protein 5 (LRP5) in MaSCs, and the ligands RANKL/TNFSF11 and WNT4 in adjacent luminal cells^{64, 65}. *RANK*-deficient mammary glands have impaired proliferation during mouse pregnancy⁷⁶, while ductal cells from *Lrp5*-deficient mice are defective in transplantation assays⁷⁷. Progesterone may therefore stimulate MaSC proliferation at least in part through RANKL and WNT ligands secreted from luminal cells^{64, 65}; however, this model has not been directly tested. Finally, WNT signaling is activated in *Pten*-deficient MaSCs⁷⁸, suggesting that both steroid hormones and Insulin/IGF signaling might regulate MaSCs.

Systemic signals appear to cooperate with WNTs in several mammalian stem cell systems. WNT and PI3K signaling synergize to promote mouse HSC division, self-renewal, and survival⁷⁹, and the NHR NR2E1/TLX activates WNT signaling to stimulate adult mouse NSC proliferation and maintenance⁸⁰. Intriguingly, the putative ISC marker LGR5⁸¹ associates with WNT receptors and binds systemic R-spondins, which could perhaps potentiate the ISC response to local WNTs secreted by Paneth cells^{62, 82} (Figure 1c). Thus, systemic signals may employ diverse mechanisms to alter stem cell behavior.

Systemic factors and the intrinsic chromatin modifying machinery—Increasing evidence indicates that stem cell function is epigenetically regulated, and broad control over gene expression in response to dietary cues might be achieved via the integration of systemic factors with the intrinsic chromatin modifying machinery. Progressive epigenetic changes accompany the differentiation of mammalian HSC progeny⁸³ and early germ cells in the adult *Drosophila* testes and ovary^{84, 85}. Mouse Lysine(K)-specific demethylase 1 (LSD1/KDM1A) functions with NR2E1/TLX in adult NSCs to control their proliferation⁸⁰. Histone methyltransferases are required for HSC and NSC self-renewal⁸⁶, for maintenance

of the adult *C. elegans* proliferative germ cell population^{87, 88}, and for *Drosophila* female GSC progeny differentiation⁸⁵. The *Drosophila* histone ubiquitin protease *scrawny* is required for GSC, FSC, and ISC maintenance⁸⁹, and the SWI/SNF complex Nucleosome Remodeling Factor (NURF) promotes reception of niche factors necessary for GSC self-renewal in males and females^{90, 91}. In *Drosophila* females, ecdysone appears to control the levels of the NURF complex as a potential mechanism to modulate BMP signaling in GSCs⁵¹, suggesting that systemic factors might regulate local signaling by modifying the intrinsic epigenetic state of stem cells (Figure 4).

The chromatin landscape of surrounding cells also contributes to stem cell regulation⁹². Down-regulation of the *Drosophila* histone demethylase Su(var)3-3 (LSD1) in escort cells abutting niche cap cells results in ectopic BMP signals and excessive GSC numbers, suggesting that LSD1 plays a key role in restricting BMP signal expression to the niche to allow differentiation of GSC daughters⁹². Although the similarity with the dominant-negative EcR phenotype⁵² is intriguing, it is not known if systemic hormones or dietary factors modulate LSD1 function (Figure 4).

Future studies should address how NHRs and other diet-regulated signals interact with the epigenetic machinery of stem cells (or neighboring cells) to broadly control transcriptional programs required for their proliferation, survival, or self-renewal. It is possible that stimulation by certain systemic factors actively modifies the overall epigenetic state of the cell. For example, NHRs are known to physically interact with epigenetic regulators including histone modifiers and chromatin remodellers⁸⁰. In response to NHR ligand stimulation, these types of interactions may prime cells for a specific transcriptional response by other signaling molecules (Figure 5). Other systemic factors may not directly modify the stem cell chromatin, but the specificity of their responses in each cell type may instead be dictated by the particular epigenetic signature set by NHRs or other intrinsic factors.

Crosstalk between systemic signals—Stem cells simultaneously receive signals from multiple sources in response to diet, and these signals likely crosstalk to induce an adequate stem cell response for the physiological state of the organism (see Figure 2d). As described earlier, *Drosophila* female GSCs intrinsically require InR, TOR, and EcR activity for timely cell cycle progression, and signals activating these pathways originate from various sources^{14, 37, 51} (Figure 4). TOR and EcR appear to act largely in parallel to InR signaling to control GSC proliferation, despite the common targeting of G2^{14, 51}. Based on genetic interactions, TOR activation in GSCs appears to involve input(s) other than Insulin signaling¹⁴, such as perhaps circulating amino acids or other systemic factors. Although it is unclear whether or how TOR and EcR signaling interact, they are both intrinsically required for GSC maintenance^{14, 51} (as opposed to InR, which is required in the niche^{5, 39}) and both pathways appear to regulate BMP signaling levels^{15, 51}, suggesting that different systemic inputs can be integrated by impinging on a common local signaling pathway.

Molecular crosstalk between NHR signaling and other diet-dependent pathways also occurs in mammals. Estrogen and IGF-1 crosstalk is important for neurogenesis and in breast cancer progression^{63, 97}; however, it is largely unclear whether relevant mechanisms involve stem cells themselves. Interestingly, there is considerable crosstalk between nutrient-sensing pathways and NHRs in the control of circadian rhythms³⁰. Many metabolic hormones exhibit circadian oscillation, and circadian rhythms can be modified by nutrients (e.g., glucose, amino acids, and retinoic acid) and changes in cellular energy levels (likely via AMPK and SIRT6)³⁰. Conversely, the molecular oscillator driving circadian rhythms is regulated by the activity of two NHRs (NR1D1/REV-ERB and RORα) and targets enzymes required for cholesterol metabolism, amino acid regulation, and glycolysis³⁰. HSC

proliferation and mobilization are reportedly influenced by circadian rhythms⁹⁸; however, these data must be carefully interpreted, as stem cell marker expression itself might exhibit circadian cycling.

Finally, there is considerable regulation of *Drosophila* and mammalian NHRs at the transcriptional level by autoregulatory and feedback mechanisms^{33, 35, 36}. For example, NR2E1/TLX regulates RARB expression in mouse retinal cells⁹⁹, and neuronal NR2E1/TLX-expressing cells are responsive to retinoic acid⁵⁹. In fact, since some evidence suggests neural roles for NR2E1/TLX⁸⁰, it might be interesting to examine potential crosstalk between RAR signaling and the NR2E1/TLX in NSC lineage control. Estrogen stimulates Progesterone receptor expression⁶⁵, and EcR/USP likely regulates other NHRs³⁵. It is therefore conceivable, for instance, that EcR/USP may be part of an as yet unidentified diet-responsive NHR network contributing to the dietary regulation of *Drosophila* GSCs. Developing a complete picture of how various systemic signals are integrated to control stem cells in response to nutrients will require the continued investigating of adult stem cell populations within their native physiological context.

NUTRIENT SENSING IN STEM CELLS: PARALLELS TO REGULATION OF TUMOR CELLS?

Notwithstanding the controversies regarding the model that cancer stem cells sustain tumor growth¹⁰⁰, it is noteworthy that adult stem cells and cancers in general share an indefinite proliferative potential and the ability to produce differentiated cells, and appear to rely extensively on nutrient-sensing pathways. For example, *PTEN* mutations are common in human cancers, and the InR and TOR pathways are often constitutively active in cancer cells^{101, 102}. There is also a high correlation between cancers and obesity, metabolic syndrome, and energy-rich diets³. Determining how stem cells receive and interpret systemic signals may therefore inspire innovative ideas and approaches for cancer prevention and treatment.

Conclusion

Coordinating adult stem cell behavior with the systemic environment is crucial to adjust the production of new cells for reproduction and tissue maintenance, remodelling, and repair to the organism's physiological demand and the constraints imposed by diet. Initial lessons derived from studies in a variety of model systems suggest that despite the conserved and ubiquitous nature of many nutrient-sensing pathways, remarkably specific responses are achieved to finely regulate stem cell behavior (see Table 1). As exemplified by TOR function in *Drosophila* ovarian stem cell populations¹⁴, although stem cells and their progeny often reside in physical proximity in the same tissue and are thus exposed to similar environmental cues, stem cells may respond to those cues differently from their progeny or from other nearby stem cell types.

The response of stem cells to diet requires multiple layers of regulation integrating systemic, local, and intrinsic factors. Some important questions remain: How do changes in levels of individual types of macronutrients, such as proteins, carbohydrates, and lipids, affect the actions of specific systemic factors and nutrient-sensing pathways on stem cells? How do stem cells respond *in vivo* to micronutrients such as metals, vitamins, or other dietary components, such as flavonoids, sulforaphane, curcuminoids, catechins, or resveratrol? How are different systemic signals integrated with each other? How do interactions with local and intrinsic factors control the specificity of stem cell responses? Do stem cells have a feedback effect on circulating factors and organismal physiology through the differentiated progeny they produce? Do different types of stem cells communicate with each other via systemic factors? Due to the very nature of the relationship between stem cells and whole-body physiology, further progress towards a more complete, detailed understanding of the

complex regulatory mechanisms involved will require *in vivo* models in which gene function can be easily manipulated in specific cells and the behavior of stem cells monitored, and methods for detecting changes in stem cell metabolism *in situ*. This will facilitate identification of the sites of requirement for the production and reception of systemic signals in response to specific dietary factors, and elucidating how they are integrated at the cellular and molecular level with other systemic signals, local stimuli, and intrinsic regulators. These studies will illuminate some of the great mysteries of stem cell biology, and likely provide valuable insights into non-invasive strategies to manipulate stem cells *in vivo*.

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Sidebar 1: A connection between adult MSCs and metabolic syndrome?

In addition to responding to systemic factors, stem cells may have profound effects on our physiology. It was recently proposed that MSC malfunction may contribute to the development of metabolic syndrome (a combination of hyperlipidemia, hypertension, hyperglycemia, Insulin resistance and other symptoms), which is often associated with obesity and hormonal alterations⁷³. In adults, adipocytes are thought to arise from MSCs that can produce muscle, bone, and adipose lineages in culture⁷⁴, and appear to be influenced by systemic sex steroids^{71, 75}. Estrogen induces higher expression of osteogenic markers, including BMPs, in cultured MSCs, while ovariectomized rats display increased bone resorption and enlarged fat depots, which are reversed by estrogen or testosterone administration, respectively⁷¹. Overexpression of androgen receptor in MSCs results in significant reductions in fat mass *in vivo*⁷⁵. Changes in the hormonal milieu might therefore alter MSC activity, potentially causing an imbalance in the production of different types of differentiated daughters and subsequent impaired function of various tissues that leads to metabolic syndrome⁷³. Establishing causal relationships in *in vivo* models, however, will be essential to experimentally elucidate how systemic and local regulation of MSC lineages and metabolic syndrome impact each other.

Sidebar 2: Epigenetic effects of diet on the germ line

The heritability of epigenetic modifications underscores the potential ramifications of diet-dependent GSC changes on subsequent generations. In fact, maternal nutrition has been linked to the development of adult-onset metabolic disease, and paternal nutrition is critical for normal β cell function in female offspring⁹³. In addition, various nutrients impact the activity of histone modifying enzymes; for example, garlic and cinnamon polyphenols inhibit histone deacetylases, whereas green tea polyphenols inhibit histone acetyltransferases⁹⁴. Dietary components also may affect the availability of methyl donors or DNA methylation enzyme (DNMT) activity⁹⁴. For example, silencing *Dnmt3* in honeybee larvae mimics feeding “royal jelly” to larval honeybees selected to become queens, biasing development towards the fertile queen rather than the sterile worker fate⁹⁵. Further, adding the soy isoflavone genistein to the diet of pregnant obese *agouti viable yellow* (A^{vy}) mice - in which a CpG methylation-sensitive retrotransposon promotes ectopic *agouti* expression leading to adult-onset diabetes and yellow fur in the absence of methylation - results in increased DNA methylation and decreased incidence of obesity and hyperinsulinemia in their adult offspring⁹⁶ (see Figure). These studies suggest the interesting possibility that diet-dependent epigenetic changes might occur within parental GSCs that are stably inherited by their progeny, with long-term consequences for the physiology of the resulting offspring.

SIDEBAR 2 FIGURE: Epigenetic effects of diet on the germ line. Maternal genistein supplementation at levels comparable to a human high-soy diet leads to methylation of the IAP murine retrotransposon inserted in *agouti viable yellow* (A^{vy}) mice. A gradient of CpG methylation in genetically identical A^{vy} /a littermates inversely correlates with coat color and obesity, from yellow (left, unmethylated) to leaner pseudoagouti (right, hypermethylated). For details, see original reference⁹⁶ from which figure was adapted.

FIGURE 1.

Examples of adult stem cells influenced by whole-body physiology. (a) *Drosophila* female GSCs reside in a specialized niche (yellow), and their differentiating progeny (blue) are intimately associated with somatic escort cells (purple). FSCs give rise to follicle cells (green) that surround germ cells to form follicles. (b) GSCs (enveloped by cyst progenitor cells) in the *Drosophila* testis reside in the hub niche; the differentiating GSC progeny (blue) are enveloped by cyst cells. (c) Mammalian ISCs in the intestinal crypts generate transit amplifying cells (blue) that give rise to differentiated cells including Paneth cells, thought to serve as the ISC niche. Crypts are in close proximity to blood vessels (red) and other differentiated cells. (d) Mammalian HSCs reside in a niche composed of MSCs, vasculature (red), and other differentiated cells in the bone marrow, and HSCs can also be mobilized into the bloodstream. See references⁷ for detailed descriptions.

FIGURE 2.

Possible mechanisms for dietary regulation of adult stem cells. (a) Nutrients may directly stimulate stem cells. (b-d) Alternatively, nutrients may affect stem cells through the direct action of systemic hormones (b), or through indirect effects of nutrients and/or systemic hormones acting on adjacent cells to modulate local signaling (c). Most likely, stem cell activity is regulated by a complex web of signaling (d), including all of the above mechanisms and additional hormonal crosstalk and signaling relays. The stem cell itself may also signal back to the niche or influence hormonal production indirectly (hatched lines) as a result of the function of its differentiated progeny.

FIGURE 3.

Integration of conserved nutrient-sensing pathways. Cells respond to Insulin/IGF and amino acids via the Insulin receptor (InR) and TOR pathways, which share common downstream effectors to control cell growth, proliferation, and survival. Insulin receptor substrate (IRS) is a major direct target of InR. AMPK, which is activated by LKB1 under low intracellular ATP levels, and SIRT1, which require NAD^+ , also interact with the InR and TOR pathways. See references^{12, 13, 103} for in-depth description of pathways.

FIGURE 4.

Working model for *Drosophila* female GSC regulation by diet-dependent signaling. Insulin-like peptides (ILPs) act directly on GSCs to control their proliferation, but indirectly promote GSC maintenance through the niche. TOR signaling controls GSC proliferation, and optimal TOR activity is also required for GSC maintenance by modulating BMP signaling. Ecdysone directly stimulates GSC division and maintenance; ecdysone signaling functions with the NURF chromatin remodeler to stimulate the GSC response to niche BMP signals. In addition, ecdysone also acts on escort cells to promote differentiation of GSC daughters; this function is similar to that described for LSD1. For details, see text and references^{5, 7, 8, 14, 15, 37, 39, 51, 52, 92}.

FIGURE 5.

Model for interaction between NHRs and the epigenetic machinery. (a) In the absence of ligand, heterodimeric NHRs are bound by co-repressors, inhibiting transcription at target promoters (pink line). (b) Upon ligand-induced activation, chromatin remodelers replace co-repressors, promoting relaxation of the histone (light green)-DNA (blue) interaction or an open chromatin configuration via nucleosome sliding. (c,d) Transcription is facilitated by (c) open DNA at target promoters to allow the binding of additional target-specific transcription factors (e.g., FOXO, MAD, STAT, or Notch), thus promoting indirect transactivation of target genes, or by (d) direct transactivation of target genes by the NHR complex. Chromatin remodelers could also be exchanged for other NHR co-activators (c) that potentiate the transcriptional response.

Table 1

Summary of the main roles of diet-dependent regulators of adult stem cells

MODEL SYSTEM		FACTOR	REPORTED ROLES
<i>Drosophila</i>	GSC (ovary)	TOR	Intrinsically promotes proliferation, maintenance ^{14, 15}
		Insulin	Directly promotes proliferation, indirectly promotes maintenance (via the niche) ^{5, 8, 37, 39}
		Ecdysone	Directly promotes proliferation, maintenance; additional indirect roles in differentiation of progeny (via adjacent escort cells) ^{51, 52}
	FSC	TOR	Intrinsically promotes proliferation ¹⁴
	GSC (testes)	Insulin	Directly promotes proliferation, maintenance ^{6, 9}
	ISC	TOR	Intrinsically promotes growth, proliferation ²²
		Insulin	Directly and indirectly (through effects on enterocyte growth) promotes proliferation ^{6, 9-11}
<i>C. elegans</i>	Germline	Insulin	Promotes proliferation of germline progenitors during development, but not required in adult germ cells ^{40 *}
Mouse/Rat	Spermatogonial stem cell (testes)	IGF-1	Promotes maintenance ⁴¹
	ISC	PPAR	Unknown (expression in crypts and reduction of Paneth cell numbers upon global <i>pparb/d</i> deficiency ⁶¹)
	HSC	TOR	Intrinsically suppresses proliferation and promotes survival; indirectly promotes proliferation (via regulation of adjacent endothelial cells) ¹⁶⁻²¹
		AMPK	Unknown (LKB1 intrinsically suppresses proliferation and promotes survival, but effects apparently independent of AMPK ^{24, 25, 104})
		SIRT6	Unknown (decreased hematopoietic progenitors from global Sirt1 mutants in bone marrow culture ³¹)
		IGF-1	Unknown (FOXO intrinsically inhibits proliferation and promotes survival of HSCs ^{12, 42, 79} , but upstream signals not determined)
		Retinoic Acid	Promotes proliferation [*] ; additional roles in differentiation of progeny ⁵⁴
	NSC	AMPK	Unknown (promotes proliferation and survival of neural progenitor cells during development ²⁶)
		SIRT6	Unknown (neural SIRT expression increases during caloric restriction ²⁸)
		Insulin/IGF-1	Promotes proliferation ^{12, 43-47 *}
		Retinoic Acid	Promotes neurogenesis [*] ; additional roles in differentiation of progeny ⁵⁵⁻⁵⁹
		PPAR	Promotes proliferation of progenitors during development and adults ^{60 *}

MODEL SYSTEM	FACTOR	REPORTED ROLES
MaSC	Estrogen	Promotes hippocampal proliferation ^{66-70 *}
	Androgen	Suppresses neuronal proliferation ^{66 *}
	Estrogen plus Progesterone	Promotes proliferation and maintenance (an indirect mechanism has been proposed) ^{64, 65, 76, 78}
	Testosterone	Inhibits differentiation to adipogenic lineage ^{71, 75 *}
MSC	Estrogen	Promotes proliferation, differentiation to osteoblastic lineage ^{71 *}

* In these experiments, it is unclear whether the effect is on the stem cells or their immediate daughters.