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REVIEW

Nutrient regulation of development and cell fate decisions

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ABSTRACT

Diet contributes to health at all stages of life, from embryonic development to old age. Nutrients, including vitamins, amino acids, lipids and sugars, have instructive roles in directing cell fate and function, maintaining stem cell populations, tissue homeostasis and alleviating the consequences of aging. This Review highlights recent findings that illuminate how common diets and specific nutrients impact cell fate decisions in healthy and disease contexts. We also draw attention to new models, technologies and resources that help to address outstanding questions in this emerging field and may lead to dietary approaches that promote healthy development and improve disease treatments.

KEY WORDS: Cell fate decision, Dietary nutrient, Metabolism, Stem cell

Introduction

Diet is an important contributor to health throughout life. Overabundance or deficiencies of specific nutrients at certain periods of life can lead to or exacerbate diseases, such as developmental defects, obesity, cancer, cardiovascular diseases and neurological conditions (Bose et al., 2020; Longo and Anderson, 2022). Nutrients and their downstream metabolites rewire intracellular metabolic processes, affect nutrient-sensing signaling pathways, alter epigenetic states and direct transcription factor activity and gene expression (Dai et al., 2020; Kim and Guan, 2019). Through these various mechanisms, nutrients can facilitate the maintenance of stem cell (SC) identity or the transition of SCs to other cell types, which are integral to fetal development, adult homeostasis and disease mitigation (Ito and Suda, 2014; Shyh-Chang and Ng, 2017). Therefore, understanding how particular nutrients impact these key biological and pathological processes will enable the development of defined dietary strategies to optimize fetal development, prevent pregnancy complications, improve disease outcomes and reduce the progression and symptoms of aging.

In this Review, we highlight recent findings in mammals that illustrate how common diets and specific classes of nutrients impact developmental processes and cell fate decisions in healthy and disease contexts, with a particular focus on *in vivo* findings (Fig. 1). We also underscore common principles and key mechanisms by which nutrients act on signaling pathways and chromatin and transcriptional states to influence cell state maintenance and fate changes. Finally, we pose outstanding questions that warrant further investigation and highlight new models, technologies and resources that can help with answering these questions.

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Influence of nutrients on cell fate decisions during development and in adults

The maternal diet supplies nutrients that influence fetal development. In adults, specific nutrients affect tissue SCs to facilitate homeostatic maintenance and injury response and may contribute to pathological conditions. We describe recent findings on how specific nutrients and downstream metabolites integrate with and impact on signaling, epigenetic and transcriptional pathways to modulate cell fate decisions during development and in adult tissues.

Vitamins

Vitamin A

Vitamin A is a fat-soluble vitamin that is converted to retinoic acid (RA), which is a ligand for the retinoic acid receptor (RAR) family of transcription factors (Ghyselinck and Duester, 2019) (Fig. 2A). Vitamin A is essential for mammalian development as dietary deficiency and genetic disruption of RA signaling have been shown to impair organ and limb formation (Ghyselinck and Duester, 2019). During fetal development, for example, RA metabolism and RAR activity are crucial for the differentiation of hematopoietic SC (HSC) precursors to functional HSCs through the activation of specific genes, including those of the developmentally regulated *HOXA* cluster of homeobox transcription factors (Fig. 2A). These play a fundamental role in proper embryologic development and are necessary for HSC formation and maintenance (Calvanese et al., 2022; Chanda et al., 2013; Dou et al., 2016). Adult HSCs in mice are also impacted by deficiencies in dietary vitamin A; the HSC population is depleted as HSCs have decreased self-renewal activity and lose their quiescent state, leading to increased energy metabolism and differentiation signatures (Cabezas-Wallscheid et al., 2017; Schönberger et al., 2022). Loss of HSC self-renewal activity occurs through decreased RA metabolite (4-oxo-RA) activation of RARβ (Schönberger et al., 2022).

RA also promotes the differentiation of naïve B and T cells to functional immune cells (Bang et al., 2021; Mucida et al., 2007). Dietary vitamin A and the microbiome induce the transport protein serum amyloid A to facilitate retinol transport and metabolism to RA in the intestine, where RA stimulates B and T cell differentiation as part of adaptive immunity, which protects against infection (Bang et al., 2021). Intestinal epithelial cells are themselves affected, as vitamin A and RAR activity promote enterocyte differentiation and intestinal regeneration while limiting goblet cell differentiation to support the intestinal immune system (Jijon et al., 2018; Lukonin et al., 2020).

Vitamin B3 and NAD^+

Vitamin B3, also known as niacin, is converted in the body to nicotinamide adenine dinucleotide (NAD^+) via the NAD^+ salvage pathway. NAD^+ is a co-factor in core energy metabolism pathways and for enzymes such as sirtuin (SIRT) deacetylases (Covarrubias

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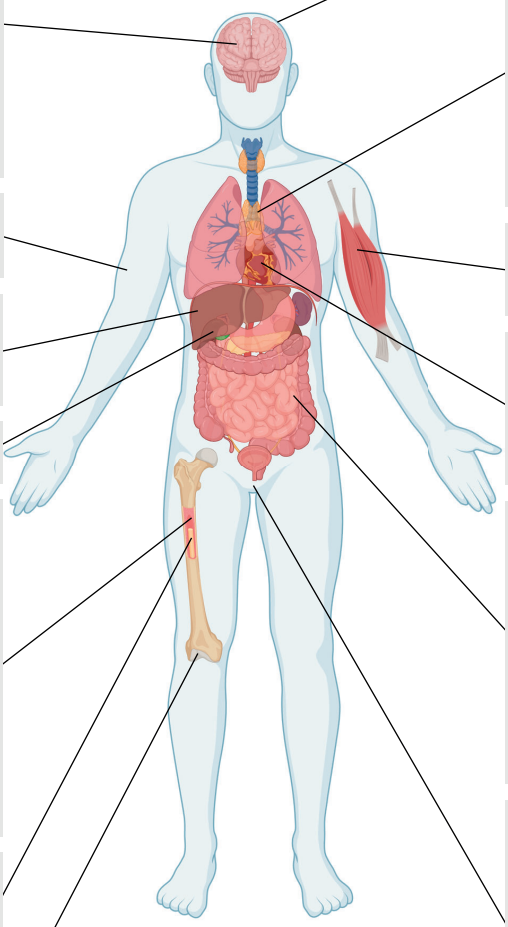

Nervous system
- Vitamin B3 (via NAD^+): ↑ aging NSC proliferation and differentiation
- Vitamin B9: ↑ neural tube development and fetal NSC proliferation and differentiation
- Tryptophan (via serotonin): ↑ neural development and differentiation
- High fat: ↓ neurological and behavior changes
- PUFAs: ↑ neural lineage differentiation
- Sterols: ↓ oligodendrocyte differentiation

Epidermis
- Serine: ↑ epidermal SC growth and self-renewal

Liver
- Vitamin B3 (via NAD^+): ↑ tissue repair
- Vitamin D: ↑ fetal liver metabolic function
- Fructose: ↑ lipogenesis

Kidney
- Vitamin B3 (via NAD^+): ↑ tissue repair

Hematopoietic stem cells
- Vitamin A: ↑ fetal HSC development and adult HSC maintenance
- Vitamin C: ↑ adult HSC maintenance and erythroid lineage differentiation
- Vitamin D: ↑ fetal and adult HSC maintenance and macrophage lineage differentiation
- Aspartate: ↑ adult HSC proliferation
- Tryptophan (via FICZ): HSC precursor differentiation
- PUFAs: ↑ fetal HSC development and adult HSC maintenance

B cells
- Vitamin A: ↑ naïve B cell differentiation
- Short chain fatty acids: ↑ regulatory B cell differentiation

Bone
- Low fatty acids: ↑ chondrocyte differentiation and bone repair

Hair follicle
- Sterols: ↓ hair follicle cycle activation

T cells
- Vitamin A: ↑ $CD4^+$ T cell differentiation
- Aspartate: ↑ T helper cell differentiation
- Asparagine: ↑ $CD8^+$ T cell activation
- Tryptophan (via kynurenine or FICZ): ↑ regulatory T and T helper 17 cell differentiation
- Tryptophan (via FICZ): ↓ regulatory T differentiation

Skeletal muscle
- Vitamin B3 (via NAD^+): ↑ muscle SC activity and injury repair

Heart
- Saturated fatty acids: ↑ cardiomyocyte maturation
- PUFAs: ↑ cardiac lineage differentiation
- High glucose: ↓ cardiomyocyte maturation

Intestine
- Vitamin A: ↑ enterocyte differentiation
- Vitamin A: ↓ goblet cell differentiation
- High fat: ↑ ISC self-renewal and tumor susceptibility
- Ketogenic: ↑ ISC self-renewal
- High glucose: ↓ ISC self-renewal
- High fat, high sugar: ↑ ISC proliferation and differentiation
- Fructose: ↑ intestinal cell survival and nutrient absorption

Germ cells
- Vitamin C: ↑ germ cell development and offspring fecundity
- Serine: ↑ oocyte maturation and zygote formation
- PUFAs: ↓ meiotic maturation
- High glucose: ↓ oocyte influence on offspring metabolic health

Germ cells
- Low total protein: ↓ germ cell influence on offspring metabolic health

Fig. 1. Nutrient influence on tissue-specific processes and cell fate decisions. The effects of different nutrients and metabolites on various fetal and adult tissues and on tissue-specific stem cells (SCs) and cell fate decisions. FICZ, 6-formylindolo[3,2-*b*]carbazole; HSC, hematopoietic SC; ISC, intestinal SC; NAD^+, nicotinamide adenine dinucleotide; NSC, neural SC; PUFA, polyunsaturated fatty acid.

et al., 2021) (Fig. 3A). NAD^+ can also be generated *de novo* from the amino acid tryptophan. Inborn errors in *de novo* NAD^+ synthesis enzymes lead to developmental defects in humans and mice, which in mice can be ameliorated with niacin supplementation (Shi et al., 2017).

NAD^+ levels in tissues broadly decline with age, suggesting that NAD^+ metabolism influences aging processes (Covarrubias et al., 2021). Supplementation with nicotinamide riboside (NR), a NAD^+ precursor (Fig. 3A), can increase the lifespan of mice by impacting neural and muscle SCs (Zhang et al., 2016). In the case of neural SCs, proliferation and differentiation are improved with NAD^+ precursor treatments (Stein and Imai, 2014; Zhang et al., 2016). In the muscle, NR rejuvenates aged SCs by inducing the mitochondrial unfolded protein response and preventing senescence (Zhang et al., 2016). The response to immune challenge also declines with age, and enhancing *de novo* NAD^+ synthesis in macrophages increases their phagocytic activity and inflammation resolution abilities (Minhas et al., 2019). Thus, how vitamin B3 supplementation affects aging in humans warrants further investigation.

NAD^+ metabolism is also important for response to tissue injury. Increased *de novo* NAD^+ synthesis promotes liver and kidney repair from acute injury and long-term disease models through SIRT1 activity (Katsyuba et al., 2018). During muscle repair, resident macrophages within the muscle SC niche secrete the NAD^+ salvage pathway enzyme nicotinamide phosphoribosyltransferase to stimulate muscle SC proliferation (Ratnayake et al., 2021).

Vitamin B9

Vitamin B9 (folate) deficiency prior to conception and during the early weeks of pregnancy increases the risk of neural tube defects, which can lead to fetal death or physical disabilities; these can be prevented with folate supplementation (Copp et al., 2013). Folate

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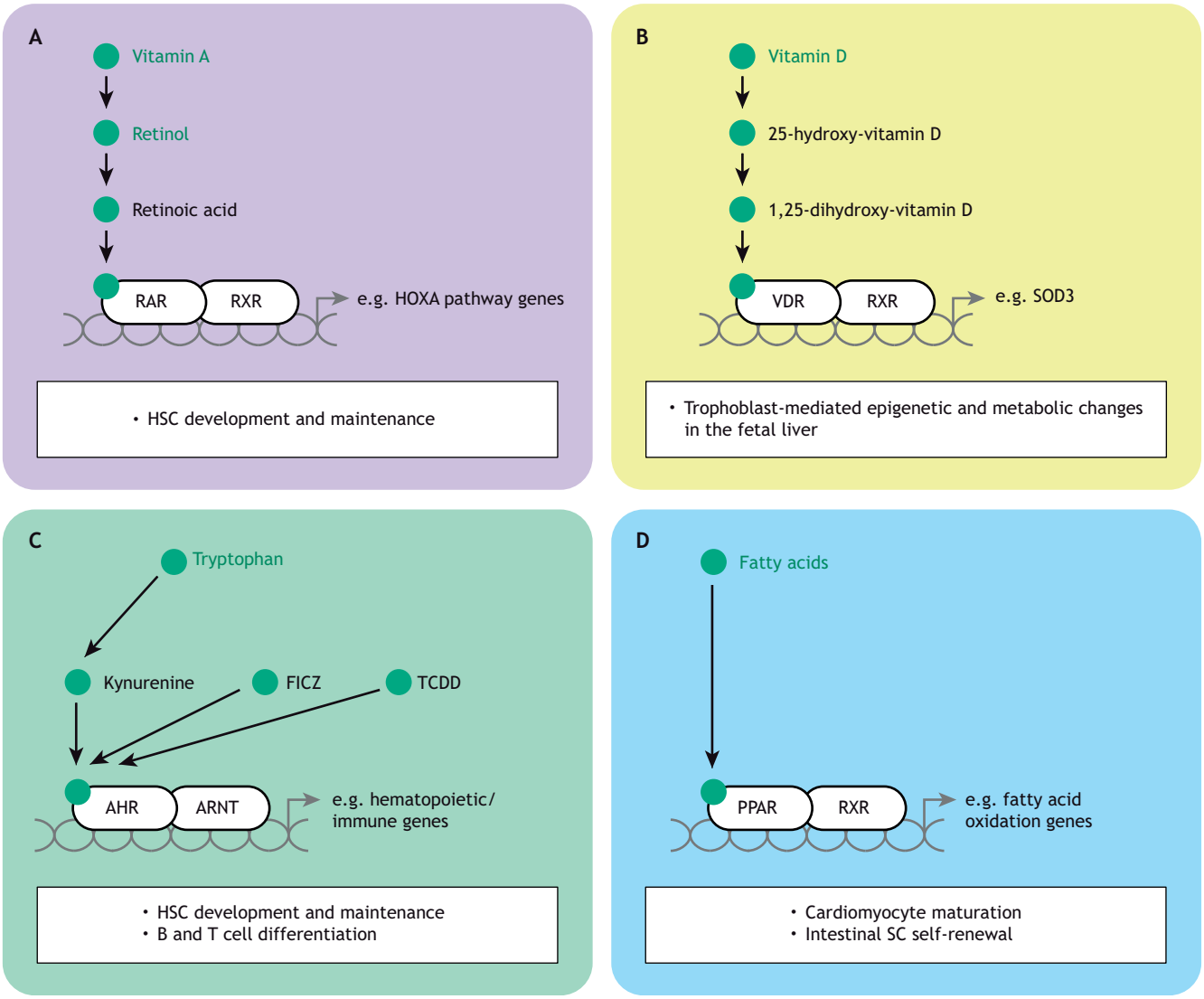

Fig. 2. Nutrient activation of transcription factors in stem cells and cell fate transitions. Dietary nutrients (highlighted in green) and their metabolites act as ligand activators of transcription factors. Transcription factor activity is dependent on multiple factors, including ligand specificity and co-factor interaction, to mediate gene expression programs important for the control of cell identity, cell fate transitions, metabolic processes and developmental signals. (A) The vitamin A metabolite retinoic acid binds retinoic acid receptor (RAR) to promote hematopoietic development and hematopoietic stem cell (HSC) maintenance. (B) In trophoblasts, dihydroxylated vitamin D binds vitamin D receptor (VDR) to induce superoxide dismutase 3 (SOD3) expression, which signals to the fetal liver to initiate long-term epigenetic and metabolic changes. (C) Tryptophan metabolites (e.g. kynurenine, FICZ) or exogenous toxins (e.g. TCDD) have different effects on the transcription factor aryl hydrocarbon receptor (AHR) during hematopoiesis and B and T cell differentiation. (D) Fatty acids are agonists for the peroxisome proliferator activated receptor (PPAR) transcription factor family, which controls fatty acid metabolism and genes that promote cardiomyocyte maturation and intestinal stem cell self-renewal. ARNT, aryl hydrocarbon receptor nuclear translocator; FICZ, 6-formylindolo[3,2-*b*]carbazole; HOXA, homeobox protein A; RXR, retinoid X receptor; TCDD, 2,3,7,8-tetrachlorodibenzodioxin.

participates in the folate and methionine cycles to generate S-adenosylmethionine (SAM), a methyl group donor to DNA, RNA and proteins (Fig. 3B). In the first 3-4 weeks post-conception in humans, folate uptake is required for neural tube cell proliferation and proper neural tube development, partly through DNA methylation and silencing at the *SOX2* locus (Alata Jimenez et al., 2018; Kur et al., 2014). Later in development, folate is required for neural SC proliferation and differentiation, as folate deficiency leads to fewer replicating and more apoptotic neural SCs (Craciunescu et al., 2004).

Vitamin C

Vitamin C (ascorbic acid) maintains the naïve pluripotent state of mouse embryonic SCs (mESCs), which resemble pre-implantation epiblast cells (Blaschke et al., 2013), and promotes transcription factor-induced reprogramming of somatic cells to induced pluripotent SCs (iPSCs) (Esteban et al., 2010). These effects are in part mediated through the co-factor activity of vitamin C for α-ketoglutarate (α-KG)-dependent dioxygenases, including ten-eleven translocation (TET) DNA demethylases and histone lysine demethylases 2A/B (KDM2A/B) (Blaschke et al., 2013; Chen et al., 2013; Wang et al., 2011) (Fig. 3C). During germline development in mice, maternal vitamin C ensures that female germ cells undergo proper DNA demethylation, particularly at genomic sites encoding for meiosis regulators (DiTroia et al., 2019). Although vitamin C deficiency during gestation does not affect overall development, it reduces the number of germ cells and delays meiosis in the

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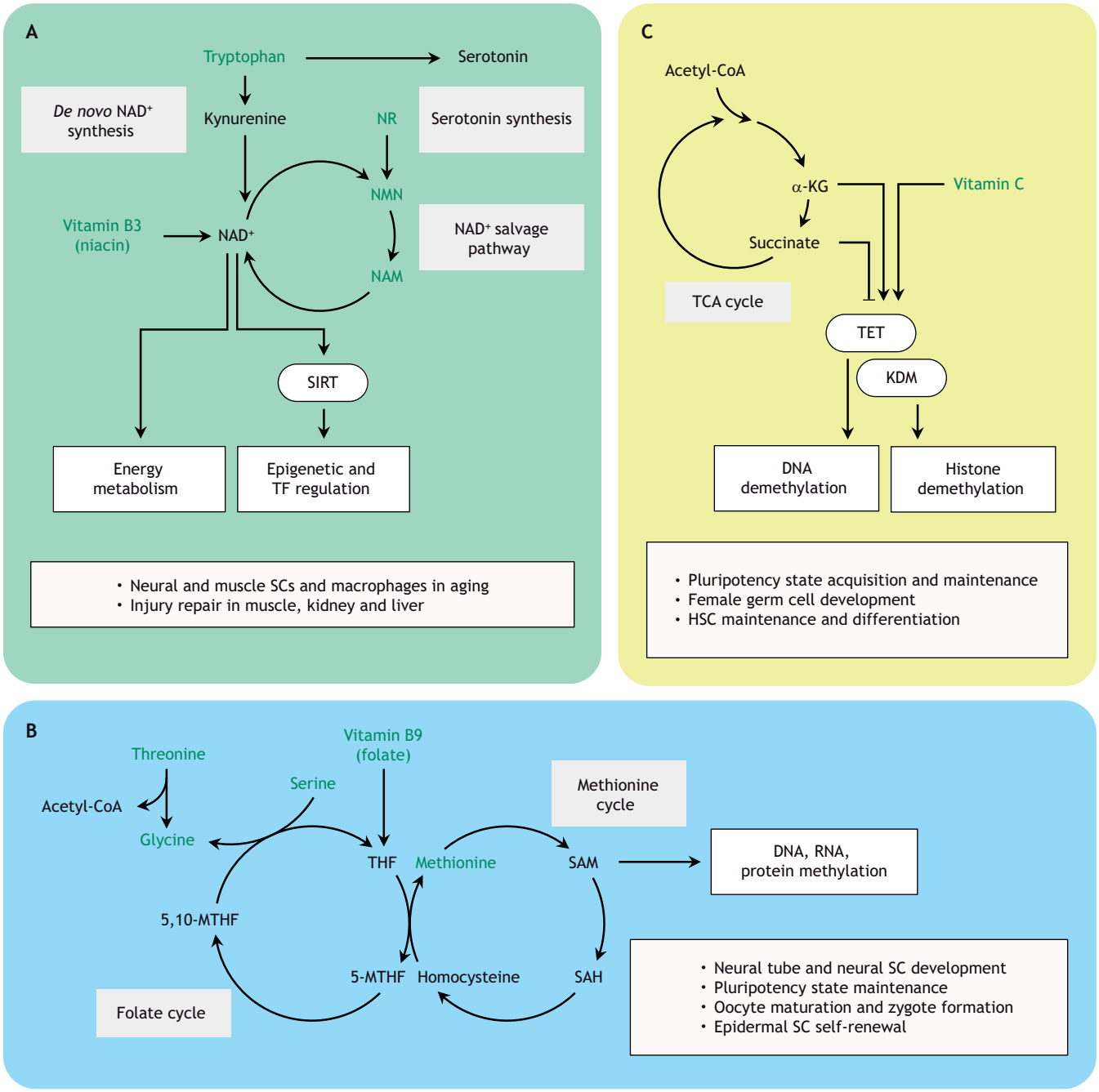

Fig. 3. Nutrient regulation of epigenetic processes. Dietary nutrients (highlighted in green) and their metabolites can serve as co-factors for epigenetic enzymes or supply substrates for epigenetic modifications. (A) Nicotinamide adenine dinucleotide (NAD^+) is generated through *de novo* synthesis from tryptophan, through the salvage pathway from nicotinamide riboside (NR), nicotinamide mononucleotide (NMN) or nicotinamide (NAM), or through the Preiss–Handler pathway from niacin (also known as vitamin B3). Among the many functions of NAD^+, it is a co-factor for the sirtuin family of deacylases (SIRT), which can regulate histone modifications and transcription factors during aging and tissue repair. (B) Amino acids (glycine, methionine, serine and threonine) and vitamin B9 (folate) feed into the one-carbon metabolism pathway (folate and methionine cycles) to generate S-adenosylmethionine (SAM), the methyl donor that modifies DNA, RNA, histones and other proteins to regulate many types. (C) Vitamin C and the tricarboxylic acid (TCA) cycle metabolite α-ketoglutarate (α-KG) are co-factors for α-KG-dependent dioxygenase enzymes that include ten-eleven translocation (TET) DNA demethylases and histone lysine demethylases (KDMs) in the regulation of various stem cell processes. 5-MTHF, 5-methyltetrahydrofolate; 5,10-MTHF, 5,10-methylenetetrahydrofolate; SAH, S-adenosylhomocysteine; THF, tetrahydrofolate.

offspring, leading to reduced fecundity (DiTroia et al., 2019). Vitamin C deficiency prevents DNA demethylation events that occur during female germline development; an epigenetic effect that is similar to loss of TET1 during development (DiTroia et al., 2019).

Vitamin C is also crucial for hematopoiesis. Vitamin C deficiency leads to increased HSC frequency and *in vivo* transplantation capacity, mimicking the effects of TET2 depletion (Agathocleous et al., 2017; Cimmino et al., 2017). This predisposes mice to leukemia development in cooperation with oncogenic events, but aberrant leukemic activity can be reversed by treatment with vitamin C (Agathocleous et al., 2017; Cimmino et al., 2017). In addition, the differentiation of HSCs into the erythroid lineage is

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controlled by the interplay between vitamin C and α-KG. Whereas initial erythroblast differentiation requires α-KG-dependent oxidative phosphorylation, maturation into red blood cells depends on the non-oxidized form of vitamin C, ascorbic acid, which provides an anti-oxidative balance to ensure proper erythropoiesis (Gonzalez-Menendez et al., 2021).

Another recent study also shows that α-KG supplementation extends mouse lifespan in part by reducing chronic inflammation (Asadi Shahmirzadi et al., 2020). Given the intertwined effects that α-KG and vitamin C have on demethylases in regulating pluripotent SCs and HSCs, it will be interesting to determine the role of dietary vitamin C on aging and other developmental processes.

Vitamin D

Vitamin D is obtained through diet or synthesized in the skin upon sunlight exposure. In a large clinical trial of over 1000 infants, vitamin D supplementation at prenatal or postnatal stages did not affect infant weight or height, birth outcomes or morbidity when assessed at 1 year of age (Roth et al., 2018). However, a recent study in humans showed that in highly active pregnant individuals, vitamin D activation of the vitamin D receptor (VDR) transcription factor in maternal placental trophoblasts increases the expression and secretion of superoxide dismutase 3 (SOD3), which produces lasting epigenetic changes in the offspring (Kusuyama et al., 2021) (Fig. 2B). Secreted SOD3 leads to TET-mediated DNA demethylation at glucose metabolism gene loci in the fetal liver, which manifests as increased glucose tolerance and metabolic health in the offspring (Kusuyama et al., 2021). These findings suggest that maternal vitamin D supplementation may yield health benefits on offspring that manifest in later life through epigenetic means.

Vitamin D activation of VDR is also necessary for hematopoiesis, as vitamin D supplementation supports the expansion of both fetal and adult HSC populations (Cortes et al., 2016). In a pathological setting, however, vitamin D-VDR signaling promotes HSC differentiation to the macrophage lineage, which contributes to myeloproliferative neoplasms (Wakahashi et al., 2019). Therefore, a low vitamin D diet may be a therapeutic approach to limit aberrant HSC differentiation (Wakahashi et al., 2019).

Amino acids

Total protein

Within weeks of conception in humans, amino acid metabolism changes to support rapid fetal development and maintain maternal homeostasis (King, 2000). Amino acids not only fuel fetal protein synthesis, but additionally produce metabolites that regulate signaling pathways and gene expression. Total protein requirement during pregnancy is not much higher than that needed by a non-pregnant woman (King, 2000). A high-protein diet may actually be harmful during pregnancy and is correlated with high blood pressure and high cortisol levels in the offspring (Herrick et al., 2003; Shiell et al., 2001). Conversely, a low-protein maternal diet can affect the offspring's birth weight, fat distribution and risk of obesity (Bellinger et al., 2006; Sutton et al., 2010). A paternal low-protein diet can lead to enduring epigenetic effects in the offspring by affecting testicular germ cells, including inhibition of ATF7-dependent epigenetic repression (Yoshida et al., 2020). This derepresses the expression of tRNAs for protein synthesis and cholesterol biosynthesis genes, an effect that persists in the liver of the offspring (Yoshida et al., 2020). It will be important to decipher whether total protein levels and specific amino acids in parental diets lead to long-term metabolic and health effects in the offspring through epigenetic means.

Amino acids that affect methylation (methionine, serine and threonine)

Naïve state mESCs are sensitive to the restriction of the essential amino acid threonine, which supplies acetyl-CoA for the tricarboxylic acid (TCA) cycle and generates glycine for one-carbon metabolism and SAM production (Shyh-Chang et al., 2013; Wang et al., 2009). The one-carbon metabolism pathway encompasses the folate and methionine cycles to generate one-carbon units (methyl groups) for DNA, RNA and protein methylation (Fig. 3B). In mESCs, threonine deprivation reduces global di- and tri-methylation of histone 3 at lysine 4 (H3K4me2/3), which are histone marks at active promoters and enhancers, and inhibits mESC growth and self-renewal (Shyh-Chang et al., 2013). In contrast, primed state human ESCs (hESCs), which reflect the post-implantation pluripotent state and lack functional threonine dehydrogenase, depend on methionine as the amino acid supply for SAM to maintain pluripotency (Shiraki et al., 2014) (Fig. 3B). Methionine deprivation promotes hESC differentiation into the three germ layers (Shiraki et al., 2014). hESCs are also sensitive to deprivation of leucine, lysine and tryptophan, but the mechanisms behind these dependencies are unknown (Shiraki et al., 2014).

In addition to affecting ESCs, specific amino acids can affect methylation to influence other cell fate decisions. In oocytes, increased serine-glycine-one-carbon metabolism generates SAM to establish DNA and H3K4me3 histone methylation (but not other histone methylation marks) during oocyte maturation and upon fertilization (Li et al., 2020b). Epidermal SCs, which regenerate the basal layer of the epidermis, depend on extracellular serine to maintain growth and self-renewal (Baksh et al., 2020). Limiting serine availability promotes differentiation by inducing *de novo* serine synthesis. This leads to increased α-KG levels and α-KG-dependent dioxygenase activity, which mediates demethylation of H3K27me3 repressive marks (Baksh et al., 2020). Further defining how different amino acids contribute to SAM production and the regulation of epigenetic enzymes, and how the specificity of DNA and histone methylation is achieved, will be instructive in understanding the different processes that change cell fate.

Aspartate and asparagine

Aspartate synthesis in the mitochondria is essential for cell proliferation (Birsoy et al., 2015; Sullivan et al., 2015). During quiescence, HSCs have low demand for aspartate, but upon regeneration proliferating HSCs increase *de novo* aspartate synthesis to supply nucleotides and other amino acids (Qi et al., 2021). Similarly, T-helper-cell differentiation requires aspartate synthesis to promote histone acetylation and expression of genes that activate T cells (Bailis et al., 2019).

Aspartate also generates asparagine, which signals active mitochondrial respiration to mTORC1, a nutrient-sensing kinase complex that controls cell growth (Krall et al., 2021). Asparagine promotes cytotoxic $CD8^+$ T cell activation, and dietary restriction of asparagine impairs the $CD8^+$ T cell-mediated anti-tumor response (Wu et al., 2021). It will be informative to distinguish the dependency of aspartate and asparagine in SC activation and quiescence to devise improved dietary strategies to influence disease.

Tryptophan

Over 95% of dietary tryptophan is catabolized to downstream metabolites, including kynurenine, serotonin and NAD^+ (Fig. 3A). In the first trimester, the placenta preferentially uses tryptophan to produce serotonin until the fetus can synthesize its own later in development (Karahoda et al., 2020). Interestingly, recent evidence shows that serotonin has a direct role in regulating gene expression in

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the developing brain and differentiation of serotonergic neurons (Farrelly et al., 2019). Serotonylation of H3K4me3-marked histones potentiates a permissive chromatin environment through recruitment of transcriptional regulators, such as TFIID (TBP), for neuronal differentiation (Farrelly et al., 2019). It will be interesting to investigate how brain development is influenced by serotonin and other tryptophan metabolites when levels of dietary tryptophan are altered.

Tryptophan is also necessary to maintain the primed pluripotent state; this is likely through its metabolite kynurenine, which is a ligand for the aryl hydrocarbon receptor (AHR) transcription factor (Shiraki et al., 2014; Someya et al., 2021; Yamamoto et al., 2019) (Fig. 2C). Upon differentiation of primed hESCs to the germ layers, kynurenine production decreases (Yamamoto et al., 2019). In accordance, inhibiting AHR promotes the differentiation of hESCs along the mesoderm lineage to HSC precursors (Angelos et al., 2017). AHR inhibition also promotes HSC expansion *in vitro* and HSC engraftment *in vivo* (Boitano et al., 2010). However, it is unclear whether these AHR inhibition effects on HSC differentiation and maintenance occur via the tryptophan pathway, as AHR has both endogenous [e.g. kynurenine or 6-formylindolo(3,2-*b*)carbazole (FICZ), a UV-generated by-product of tryptophan] and exogenous [e.g. the toxin 2,3,7,8-tetrachlorodibenzodioxin (TCDD)] ligands that can have different effects on cell fate processes (Fig. 2C). For example, AHR activation by FICZ enhances hESC differentiation to HSC precursors, whereas TCDD inhibits differentiation to HSC precursors but promotes HSC differentiation to the lymphoid lineage (Angelos et al., 2017; Smith et al., 2013). Although the mechanism is unknown, AHR knockout in mice can lead to developmental defects in the vasculature, possibly through aberrant hematopoietic lineage cells (Walisser et al., 2005). Thus, it will be crucial to dissect systematically the different effects of endogenous tryptophan metabolites and exogenous toxins in activation of AHR during hematopoietic development.

The different effects of AHR ligands are further shown in T cell differentiation. From the second trimester to conception, the placenta uses tryptophan for the kynurenine pathway (Karahoda et al., 2020; Murthy et al., 2021). This may be in support of maternal–fetal immune tolerance, as kynurenine has immunosuppressive effects through AHR activation during regulatory T cell differentiation (Mezrich et al., 2010). Conversely, AHR activation by FICZ inhibits regulatory T cell differentiation but induces T helper 17 cell differentiation, leading to exacerbated autoimmune phenotypes (Quintana et al., 2008). As these exogenous, artificial AHR agonists may not be physiologically relevant, it will be important to delineate the specific effects of dietary tryptophan-derived AHR ligands on immune cells in their contribution to pregnancy and pathological conditions.

Lipids

Fatty acids

Fatty acid usage and metabolism changes at different stages of mammalian development. Analysis of the transcriptional state of pre-implantation embryos suggests that *de novo* lipogenesis is a feature of mammalian pre-implantation embryos, potentially owing to lower availability and reliance on exogenous lipid sources (Cornacchia et al., 2019; Johnson et al., 2003). Intracellular lipid reserves are important for oocyte maturation and progression to the pre-implantation blastocyst (Sturmey et al., 2009). The late-stage, pre-implantation blastocyst also uses increased fatty acid oxidation as an additional energy source (Sharpley et al., 2021). Conversely, post-implantation embryos gain access to the extrinsic supply of lipids from the mother. Accordingly, culturing post-implantation, state-primed hESCs in lipid-free media shifts them towards the pre-implantation naïve state (Cornacchia et al., 2019). Differentiation from the pluripotent state can also be modulated by fatty acid metabolism. For example, during human pluripotent stem cell (hPSC)-to-cardiomyocyte differentiation, several means of promoting fatty acid oxidation are utilized. This includes the addition of a saturated fatty acid (palmitate) and activation of the fatty acid-responsive, peroxisome proliferator activated receptor α (PPARα) transcription factor, which enhances the maturation of cardiomyocytes that display metabolic and functional similarities to *in vivo* cells (Funakoshi et al., 2021) (Fig. 2D). This is consistent with the finding that the transition of fetal cardiomyocytes to neonatal and adult cardiomyocytes is accompanied by a switch from relying on glycolysis for their main energy source to fatty acid oxidation at birth (Piquereau et al., 2010).

Fatty acid availability can also direct the path of differentiation in adult tissues. In bone fracture healing, skeletal progenitor cells in poorly vascularized regions lack exposure to exogenous energy supplies, including fatty acids (van Gastel et al., 2020). Low fatty acid availability activates FOXO transcription factor activity to induce SOX9 expression in skeletal progenitors, directing them to chondrocyte differentiation and fracture repair. Simultaneously, fatty acid oxidation is inhibited to adapt the cells to a lipid-poor environment (van Gastel et al., 2020). In contrast, areas close to blood vessels are exposed to high levels of exogenous fatty acids that fuel fatty acid oxidation. This nutrient environment leads to skeletal progenitor differentiation to osteoblasts (Kim et al., 2017; van Gastel et al., 2020). Thus, controlling fatty acid availability may have therapeutic value in treating osteoarthritis. The short chain fatty acid butyrate can also ameliorate arthritic characteristics in mice by activating regulatory B cells and inhibiting germinal center B cell differentiation through tryptophan-metabolizing microbiome activation of AHR (Rosser et al., 2020). Collectively, these studies suggest that the quantity and specific species of fatty acids are important factors that influence cell fate and have implications for the treatment of diseases.

High-fat diet

Maternal high-fat diet during pregnancy is associated with whole-body metabolic consequences in the offspring, including weight gain (Desai et al., 2014) and neurological changes, particularly in the hypothalamus and hippocampus, leading to metabolic and behavioral changes, such as reduced cognitive function, depression and anxiety (Giriko et al., 2013; Janthakhin et al., 2017; Vogt et al., 2014). This may in part be due to the high oxidative stress of lipid accumulation in these brain regions (Hatanaka et al., 2016). Proinflammatory cytokines may adversely affect regional brain development by disrupting the vascular and immune architecture of the developing brain, which can result in behavioral alterations (Bilbo and Tsang, 2010; Bordeleau et al., 2022).

High-fat diet also impacts adult tissue SCs. This has been most prominently studied in intestinal SCs. Long-term high-fat diet enhances the self-renewal capacity of $LGR5^{+}$ intestinal SCs and their regenerative properties following intestinal injury *in vivo* (Beyaz et al., 2016). This is through PPARα/δ-dependent activation of downstream pathways, including β-catenin and fatty acid oxidation (Beyaz et al., 2016; Mana et al., 2021) (Fig. 2D). High-fat diet or activation of these pathways can contribute to the formation of intestinal tumors when in combination with loss of tumor suppressors, such as APC (Beyaz et al., 2016). More recent findings suggest that the interaction between the immune system

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and the microbiome adds further complexity to how high-fat diet regulates the intestinal environment (Beyaz et al., 2021). For example, high-fat diet suppresses the expression of major histocompatibility complex (MHC) class II molecules in intestinal SCs through reduced intestinal microbiome diversity. Decreased MHC class II helps tumor-prone intestinal SCs to evade immune surveillance, thus promoting tumorigenesis (Beyaz et al., 2021).

A ketogenic diet, consisting of high fat, moderate protein and low carbohydrates, also enhances intestinal SC self-renewal; this relies on ketone body inhibition of HDAC deacetylases, which promotes the NOTCH transcription factor activity that is necessary to maintain intestinal SC self-renewal (Cheng et al., 2019). In mice fed a high-fat, high-sugar diet, intestinal SC and progenitor populations show hyperproliferation and increased differentiation, in part through upregulated PPARγ signaling (Aliluev et al., 2021). Conversely, high-glucose diet alone inhibits the self-renewal properties of intestinal SCs and ketogenesis (Cheng et al., 2019). These data indicate that a high-fat diet, in conjunction with varying levels of other macronutrients, can have differing effects on intestinal SC populations and functions.

Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) are essential fatty acids needed for cell growth and physiological functions, as they form the phospholipids of cell membranes and their products have signaling roles (Wiktorowska-Owczarek et al., 2015). ESCs, compared with differentiated cells, are enriched with PUFAs (Yanes et al., 2010). Inhibiting oxidative metabolism of PUFAs to eicosanoids, a class of molecules with inflammatory and endocrine functions, maintains the pluripotent state (Yanes et al., 2010). Conversely, oxidative products of PUFAs, including eicosanoids, promote ESC differentiation to neuronal, cardiac and vascular lineages (Taha et al., 2020; Yanes et al., 2010). The meiotic maturation of oocytes is also sensitive to PUFA levels; PUFA downregulation is necessary to promote proper chromosome segregation and maternal RNA degradation through nuclear factor-κB (NF-κB) signaling (Li et al., 2020b).

Eicosanoid biosynthesis also has a role in fetal and adult hematopoiesis. During mouse development from embryonic day (E) 8.5 to E11.5, the expression of arachidonate 5-lipoxygenase (ALOX5), which produces leukotriene (an eicosanoid signaling product), is necessary for HSC and progenitor cell development *in vivo* (Ibarra-Soria et al., 2018; Jiang et al., 2017). Other eicosanoids, including prostaglandin E2 and epoxyeicosatrienoic acids, promote fetal hematopoiesis and improve the maintenance and engraftment abilities of adult HSCs (Li et al., 2015; North et al., 2007). With aging, chronic inflammation can lead to HSC depletion (Matatall et al., 2016; Pietras et al., 2016). In mice, a PUFA-augmented diet may protect HSCs from age-associated inflammation through increased levels of the circulating peptide hormone adiponectin (Meacham et al., 2022). Adiponectin binding to its cell surface receptors (ADIPOR1/2), which are expressed ubiquitously in hematopoietic cells, maintains adult HSC quiescence and reduces the detrimental effects of inflammatory cytokine signaling on HSCs (Meacham et al., 2022). It would be interesting to determine whether dietary PUFAs affect other developmental lineages and adult tissue SCs during homeostasis and aging.

Sterols

Oligodendrocytes are necessary for myelination in the central nervous system, and loss of these cells can lead to neurological diseases, such as multiple sclerosis (Fancy et al., 2010). Inhibiting a portion of the cholesterol biosynthesis pathway leads to the accumulation of 8,9-unsaturated sterols, which facilitates the differentiation of oligodendrocyte progenitors to mature oligodendrocytes and enhances remyelination following injury *in vivo* (Hubler et al., 2018; Najm et al., 2015). Another steroid-derived factor, corticosterone (the rodent version of cortisol in humans), can regulate hair follicle SCs (Choi et al., 2021). Chronic stress can lead to the production of corticosterone from the adrenal gland (Walczak and Hammer, 2015). Stress or exogenous corticosterone delays the regenerative cycle of hair follicle SCs and extends their quiescence period, whereas ablating corticosterone release by adrenal gland removal activates hair follicle SC cycle (Choi et al., 2021). Corticosterone mediates hair follicle SC quiescence by suppressing the secreted growth factor growth arrest-specific protein 6 (GAS6) in the SC niche (Choi et al., 2021; Enshell-Seijffers et al., 2010). Thus, modulating different sterol products may have therapeutic implications in different diseases.

Sugars

Glucose and hyperglycemia

Glucose is the main fuel for intrauterine growth (Clapp, 2002). In mouse pre-implantation embryos, glucose is a crucial nutrient source for trophectoderm specification through generation of nucleotides via glycolysis-independent mechanisms. These nucleotides signal to mTOR and through hexosamines to activate the cell polarity transcription factor yes-associated protein (YAP) (Chi et al., 2020). In contrast, glucose has no effect on the inner cell mass (Chi et al., 2020), which gives rise to pluripotent epiblast and primitive endoderm cells. During mouse development from E9.5 to E12.5, the fetal heart and brain use glucose to generate TCA cycle metabolites and purines to accommodate rapid growth at this stage (Solmonson et al., 2022). At later stages of cardiomyocyte differentiation, reducing glucose enables cardiomyocyte maturation, while limiting proliferation, through glucose shunting to pentose phosphate and nucleotide metabolism (Nakano et al., 2017). This decreased glucose usage is reflected during mouse development, as glucose uptake in the heart steadily decreases from E10.5 to postnatal day 7 (Nakano et al., 2017). In a mouse model of maternal hyperglycemia, high glucose promotes the proliferation, but inhibits maturation, of fetal cardiomyocytes (Nakano et al., 2017), providing insight into how hyperglycemic conditions contribute to congenital heart defects.

Pre-gestational maternal hyperglycemia also has long-term consequences for the offspring, including glucose intolerance (Chen et al., 2022). This is linked to reduced expression of the DNA demethylase TET3 in oocytes of hyperglycemic mice and humans with diabetes (Chen et al., 2022). TET3 insufficiency results in hypermethylation at the paternal alleles of several insulin secretion genes. This is maintained through to adulthood in pancreatic islet cells, manifesting as glucose intolerance in the offspring (Chen et al., 2022).

In adults, hyperglycemic conditions can affect progenitor populations. For example, high glucose impairs endothelial progenitor proliferation and induces apoptosis by suppressing the pro-growth AKT pathway, leading to reduced vascular repair activity (Chen et al., 2007; Nakamura et al., 2011). A broader examination of the effects of hyperglycemia on tissue stem cells may yield insights and therapeutic opportunities for diabetes.

Fructose

Fructose, prevalent in diets that include fast food and soda, is a major contributor to many diseases, including type 2 diabetes, liver diseases, cardiovascular diseases and cancer (Goncalves et al., 2019; Herman and Birnbaum, 2021). High fructose intake during

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pregnancy can lead to adult offspring exhibiting various metabolic pathologies, including hyperglycemia, hypertension (Koo et al., 2021) and an altered microbiome (Astbury et al., 2018). Whether metabolic alterations in offspring arising from a maternal high-fructose diet are inherited via epigenetic alterations or other mechanisms is unknown.

In adults, dietary fructose is first metabolized in the small intestine before it reaches the liver and the microbiome, where fructose is catabolized into acetyl-CoA and acetate, which contributes to induced hepatic lipogenesis (Jang et al., 2020; Zhao et al., 2020). High fructose levels directly affect the highly proliferative and regenerative small intestine, leading to fat accumulation and excess weight gain in mice fed a high-fat diet (Taylor et al., 2021). This is achieved by the fructose metabolite fructose-1-phosphate, which mediates suppression of pyruvate kinase muscle isozyme M2, an enzyme involved in glycolysis that promotes intestinal cell survival and enhanced nutrient absorption under a hypoxic gut environment (Taylor et al., 2021).

Nutrient regulation of development – common themes and mechanisms

The recent discoveries and concepts described above demonstrate the instructive roles of dietary nutrients and metabolic processes in maintaining cell states during homeostatic conditions and directing cell fate transitions during development, tissue repair and aging processes.

Dietary nutrients not only fuel the energetic needs of development and homeostasis (Ferenc and Ikmi, 2023), but also impact intracellular metabolism, signaling pathways, epigenetics and transcription to direct cell function and transition. Nutrients and their downstream metabolites signal to growth and developmental pathways, such as mTOR and WNT (Chi et al., 2020; Krall et al., 2021; Oginuma et al., 2020). Metabolites such as SAM, acetyl-CoA and serotonin are substrates for epigenetic modification of DNA and histones to regulate gene expression, whereas others, including α-KG and NAD^+, serve as co-factors for epigenetic enzymes (Baksh et al., 2020; Covarrubias et al., 2021; Farrelly et al., 2019; Shyh-Chang et al., 2013; Zhao et al., 2020). How the specificity of epigenetic enzymes, histone modification types and DNA loci are regulated by different metabolites in different cell states remains a pivotal question to be addressed. Metabolites can also directly affect transcription factors, such as activation of RAR (by vitamin A) and AHR (by tryptophan metabolites), to mediate cell type- and process-dependent gene expression programs (Ghyselinck and Duester, 2019; Quintana et al., 2008).

Diet also alters the microbiome and microbiota-produced metabolites, which in turn regulate a multitude of physiological functions. These include intestinal function and regeneration (Wu et al., 2020), immune cell differentiation and inflammatory responses (Paik et al., 2022) and neural activity and behavioral changes (Hsiao et al., 2013; Needham et al., 2022). Calorie restriction decreases microbiota abundance and changes microbiome composition; transplantation of calorie restriction-altered microbiota leads to decreased body weight and adiposity (von Schwartzenberg et al., 2021). Dietary fructose promotes hepatic lipogenesis through microbiota-produced acetate (Zhao et al., 2020). A high sulfur amino acid diet directly modifies microbial tryptophanase activity, leading to reduced toxin production and ameliorating chronic kidney damage (Lobel et al., 2020). Moreover, the maternal microbiome strongly influences fetal development and offspring outcome. Maternal microbiota-produced metabolites, such as short-chain fatty acids, are sensed in the embryo to ensure healthy metabolic and neural development while protecting the offspring from obesity later in life (Kimura et al., 2020; Vuong et al., 2020). Therefore, identifying and characterizing microbiota-produced metabolites through untargeted metabolomic approaches will yield new ways to affect *in vitro* cell fate systems and *in vivo* development and disease processes.

Further functional and mechanistic investigations will help bridge the understanding of nutrition and metabolism with physiological and pathological cell and tissue states. Below, we raise a fundamental question for this relatively new, yet vital, field, and suggest new approaches and model systems that can be used to address these knowledge gaps.

How can we identify nutrients that modulate cell states and transitions?

Nutrients and their metabolites have active roles in maintaining cell identity and affecting cell fate decisions *in vitro* and *in vivo*. Culturing of many cell states *in vitro*, such as naïve hPSCs and HSCs, is currently suboptimal owing to short-term survival, genomic instability and compromised functionality (Chen et al., 2021). Likewise, *in vitro* cell fate transitions are often inefficient and slow (in the order of weeks and even months) and often do not produce the desired cell type and cell maturity observed *in vivo* (Wang et al., 2021). Aberrant or absent SC activity and differentiation underlies the pathogenesis of many diseases, such as cancer, cardiovascular diseases and neurological diseases. Thus, identifying specific metabolites that modulate cell state and transition *in vitro* and *in vivo* may improve these processes, as well as ameliorate disease phenotypes, as metabolites can be readily modulated in the culture medium or in systemic circulation compared with gene and protein level manipulations.

One way to identify crucial molecules is to leverage metabolomics data to identify and test altered metabolites and metabolic pathways between two conditions or cell states (Guijas et al., 2018). This approach has been applied to identify metabolites that promote human naïve to primed pluripotency transitions, including the identification of SAM as a crucial regulator of this process (Sperber et al., 2015). This method also helped identify protectin D1 (a PUFA) as a regulator of ESC differentiation to motor neurons (Yanes et al., 2010). More cell fate modulatory metabolites can be identified from metabolomics data of human blood samples that have been used to establish metabolic markers of pregnancy (Liang et al., 2020; Stelzer et al., 2021; Wang et al., 2016) and aging (Menni et al., 2013; Robinson et al., 2020; Yu et al., 2012). These have predictive value in determining time of labor and progression of aging phenotypes, as well as generating hypotheses and insights into metabolic regulation of development and aging.

Conclusions and perspectives

Dietary nutrients affect health and diseases at all stages of life, from early embryonic development and pregnancy, through to adult homeostasis and aging. Shifts in metabolic dynamics not only mark different stages of development, but also have active roles in driving developmental progression. The maintenance and transition of different cell lineages and tissue types have preferential dependency on and sensitivity to specific nutrients and metabolites. The local metabolic environment of cells and cell–cell interactions are also important influences on cell fate decisions, for example through metabolite-mediated paracrine signaling events from resident or infiltrating immune cells and the microbiome (Bang et al., 2021; Beyaz et al., 2021; Paik et al., 2022). The development of more complex *in vitro* model systems and improved technical feasibility of *in vivo* studies (see Box 1) will shed light on this important aspect of cell fate decision.

In this context, it is notable that most *in vitro* cell cultures use media with drastically higher metabolite concentrations compared with

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Box 1. Measuring metabolic changes *in vivo*

Single-cell transcriptomic and epigenomic techniques to describe cell states and cell fate transitions are becoming more routine and accessible. Metabolomics at the single-cell spatial level is still in its infancy as a technique, but can provide insights into metabolic heterogeneity in tissues and metabolic interactions between different cell populations *in vivo*. SpaceM, a technique that combines imaging with matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS), approaches single-cell resolution, linking the metabolomic profiles of hundreds of metabolites to the spatial location of thousands of cells at a time (Rappez et al., 2021). This technique has been applied to determine changes in fatty acid composition in non-alcoholic steatohepatitis (Rappez et al., 2021). *In vivo* infusion of stable isotope followed by MALDI-MS (iso-imaging) has been used to determine nutrient usage through common pathways, including glycolysis, the TCA cycle, gluconeogenesis and glutaminolysis in mouse kidneys and brains, as well as organ responses to different dietary conditions (Wang et al., 2022).

How circulating metabolites from tissues, the microbiome and local microenvironment gradients contribute to cell states and transitions remains a challenge to investigate. *In vivo* metabolomic approaches in embryos and adult organisms are crucial for addressing these gaps. Metabolomic profiling of arterial and venous blood from different organs identifies metabolites that are consumed and released by specific organs (Jang et al., 2019). *In vivo* stable isotope infusion can further characterize how nutrients, such as glucose, are metabolized in cells and circulated systemically, and how diet can rapidly affect different organs and circulating metabolomes (Hui et al., 2020; TeSlaa et al., 2021). *In vivo* quantification of metabolite levels and isotope tracing are also possible in pregnant mice, in which maternal tissue (placenta) and embryos have distinct metabolic profiles and different utilization of glucose and glutamine across development (Solmonson et al., 2022). These approaches may provide insight into the metabolic and developmental consequences of inborn errors of metabolism (Adhikari et al., 2020; Solmonson et al., 2022).

physiological conditions. Using human plasma-like media on cultured cells can reveal physiologically relevant metabolic dependencies and drug interactions (Cantor et al., 2017; Rossiter et al., 2021). Thus, devising media composition to mimic that within the oviduct prior to implantation, in cord blood and amniotic fluid post-implantation, or in tissue-specific microenvironments may improve model resemblance to *in vivo* conditions (Bar et al., 2020; Liang et al., 2020; Stelzer et al., 2021). Furthermore, diet can have an impact on SC populations *in vivo*, which may lead to lasting differences after SC isolation, derivation and culturing that contribute to variation, as is the case for $LGR5^+$ intestinal SCs in response to high-fat versus normal diet (Beyaz et al., 2016; Li et al., 2020a). It remains to be determined how sensitive embryonic and other SCs are to the diet of their originating organism.

Integrating transcriptomic and other genomic approaches with advancements in metabolomics, especially at the single-cell and spatial levels, will be highly informative in dissecting the relationship of nutrients and metabolic changes to gene expression and cell state and functional outcomes. This important area of study will not only provide fundamental insights into development and aging, but could also lead to dietary and molecular strategies to combat pathological conditions across different stages of life, from developmental disorders and pregnancy complications to cancer and cardiovascular diseases.

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Competing interests

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