Published in final edited form as:

Annu Rev Cell Dev Biol. 2016 October 6; 32: 399–409. doi:10.1146/annurev-cellbio-111315-125134.

Metabolism and the Control of Cell Fate Decisions and Stem Cell Renewal

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Abstract

Although the stem cells of various tissues remain in the quiescent state to maintain their undifferentiated state, they also undergo cell divisions as required, and if necessary, even a single stem cell is able to provide for lifelong tissue homeostasis. Stem cell populations are precisely controlled by the balance between their symmetric and asymmetric divisions, with their division patterns determined by whether the daughter cells involved retain their self-renewal capacities. Recent studies have reported that metabolic pathways and the distribution of mitochondria are regulators of the division balance of stem cells and that metabolic defects can shift division balance toward symmetric commitment, which leads to stem cell exhaustion. It has also been observed that in asymmetric division, old mitochondria, which are central metabolic organelles, are segregated to the daughter cell fated to cell differentiation, whereas in symmetric division, young and old mitochondria are equally distributed between both daughter cells. Thus, metabolism and mitochondrial biology play important roles in stem cell fate decisions. As these decisions directly affect tissue homeostasis, understanding their regulatory mechanisms in the context of cellular metabolism is critical.

Keywords

stem cells; metabolism; cell fate; self-renewal; mitochondria

INTRODUCTION

Stem cells are both multipotent and self-renewing, and the critical roles they play in development and tissue homeostasis have been highlighted in several recent studies (Ito &

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

Suda 2014, McCulloch & Till 1960, Morrison et al. 1997, Ramalho-Santos & Willenbring 2007, Shyh-Chang et al. 2013a, Weissman et al. 2001). These unique capacities also offer opportunities for the development of novel stem cell–based therapies (Daley et al. 2003). For instance, hematopoietic stem cell (HSC) transplantation has been one of the most important therapeutic strategies for hematological disorders such as leukemia and aplastic anemia, as well as a number of immune disorders (Appelbaum 2007, Copelan 2006). Accumulating studies have shown that a single murine HSC has the high repopulating capacity required to achieve recovery from myeloablative irradiation injury and reconstitute and maintain long-term hematopoiesis in recipient mice (Benveniste et al. 2003, Dykstra et al. 2007, Ema et al. 2000, Kiel et al. 2005, Osawa et al. 1996, Wagers et al. 2002, Yamamoto et al. 2013).

Once tissue or hematopoietic recovery is complete after irradiation, it is believed that stem cells return to dormancy, or a quiescent state, as stem cell populations are precisely controlled within certain limits in vivo. This suspension of the cell cycle is thought to make a critical contribution to the maintenance of stem cells' self-renewal capacity and multipotency, as deletion of the genes involved in quiescence often leads to stem cell exhaustion due to uncontrolled proliferation (Cheng et al. 2000, Ito et al. 2012, Pietras et al. 2011, Trumpp et al. 2010, Wilson et al. 2008). Stress factors (e.g., infection or polyinosinic-polycytidylic acid, thrombopoietin, granulocyte-colony-stimulating factor, or chronic blood loss) also induce HSC cycling (Essers et al. 2009, Trumpp et al. 2010, Walter et al. 2015). This entry into the cell cycle is associated with DNA replication, upregulated energy production via oxidative phosphorylation (OXPHOS), and elevated levels of intracellular reactive oxygen species (ROS). As quiescent stem cells are generally sensitive to increased intracellular ROS, the DNA damage that accumulates with repeated cell divisions leads to reduced self-renewal capacity and, ultimately, stem cell exhaustion (Ito & Suda 2014; Ito et al. 2004, 2006; Maryanovich & Gross 2013; Miyamoto et al. 2007; Rossi et al. 2008; Shyh-Chang et al. 2013a). The hypoxic condition and the HIF (hypoxia-inducible factor) system are important for maintenance of the self-renewal capacity of stem cells (Panchision 2009, Suda et al. 2011), and cell-intrinsic networks integrate and cooperate with cumulative signals from the microenvironment to fine-tune their self-renewal capacity and maintain whole-tissue balance (Frenette et al. 2013, Morrison & Scadden 2014, Scadden 2006, Watt & Hogan 2000, Zon 2008).

Differing theories of the contributions of stem cells to unperturbed homeostasis and tissue recovery have been considered. The experimental approach of native nontransplant hematopoiesis, for instance, proposed that steady-state blood production could be provided mainly by long-lived progenitors, rather than by classically defined HSCs, during most of adulthood, although long-term HSCs could still be essential to hematopoiesis under stress conditions (Busch et al. 2015, Sun et al. 2014). In this review, we discuss stem cell maintenance and tissue homeostasis in the context of new research into stem cell metabolism and division balance. The specific capabilities of stem cells are the last resort for tissue recovery and maintenance and are used only in emergent situations; thus, in the steady state, stem cells can be seen as a reservoir for whole tissue. Therefore, cell divisions are the essential process whereby stem cells exhibit their restorative capacity, and in particular, the initial division of stem cells is an important determinant of either self-renewal or differentiation.

METABOLISM IN STEM CELLS

The importance of the hypoxic condition to stem cell maintenance has been shown for mesenchymal stem cells (MSCs) and neural stem cells, as well as for stem cells of various other tissues. In mammalian HSCs, the hypoxic niche is essential for maintaining HSCs through sustaining a quiescent state (Mohyeldin et al. 2010, Shyh-Chang et al. 2013a, Simon & Keith 2008, Suda et al. 2011) (Table 1). In the hypoxic state, the cellular metabolism of stem cells is reliant mainly on anaerobic glycolysis for energy production (Suda et al. 2011) (Figure 1). HIF-1α is a transcriptional factor that is highly expressed in stem cells under hypoxic conditions. Conditional deletion of *Hif1a* in HSCs leads to cell cycle entry, which results in a decreased number of HSCs available for high-stress conditions and in a consequent reduction in long-term reconstitution capacity after transplantation (Suda et al. 2011, Takubo et al. 2010). Stem cells and tissue progenitor cells have distinct metabolic profiles, yet high levels of pyruvate have been found in both types. These evidences suggest that the high levels of HIF-1α induced by the hypoxic state inhibit pyruvate dehydrogenase through activation of pyruvate dehydrogenase kinase (Takubo et al. 2013).

Embryonic stem cells (ES cells) exhibit high proliferative activity, whereas many tissue stem cells such as HSCs are normally quiescent. However, the metabolic pathways of ES cells are similar to those of HSCs and exhibit increased glycolysis, although glycolysis is inhibited in the totipotent stem cells of the preblastocyst stage (Barbehenn et al. 1978, Shyh-Chang et al. 2013a). In ES cells, OXPHOS is low, and ATP synthesis is more dependent on glycolysis (Shyh-Chang et al. 2013b) (Table 1). Additionally, carnitine palmitoyltransferase plays a key role in ATP synthesis, in resistance to nutrient deprivation, and in survival under conditions of metabolic stress in ES cells (Zaugg et al. 2011).

Signaling by phosphoinositide 3-kinase (PI3K)/AKT (also known as protein kinase B) induces the cell cycle in HSCs through activation of mammalian target of rapamycin (mTOR) and ROS production by repressing the FOXO-mediated stress response. Intriguingly, mTOR also promotes glycolysis through HIF-1α activation (Miyamoto et al. 2007, Tothova et al. 2007, Yamazaki et al. 2006). LKB1 (also known as STK11), acting upstream of AMP-activated protein kinase (AMPK) and mTOR pathways, also plays crucial roles in regulating stem cell function (Gan et al. 2010, Gurumurthy et al. 2010, Nakada et al. 2010) (Figure 1 and Table 1).

Lipid metabolism includes fatty acid synthesis and fatty acid oxidation (FAO). β-Oxidation is the catabolic process that generates acetyl-CoA through the breakdown of fatty acid molecules in the mitochondrial matrix (Figure 1). The highest levels ever observed of peroxisome proliferator–activated receptor-δ (PPAR-δ) and its signaling output, as well as of FAO, have been found in HSCs, although these levels are reduced during cell differentiation. Conditional deletion of *Ppard* in HSCs impairs repopulation capacity after in vivo transplantation. These results demonstrate that promyelocytic leukemia (PML)-PPAR signaling for FAO is essential for maintaining a viable population of self-renewing HSCs (Ito et al. 2012).

Both glycolysis and lipid metabolism are required for stemness. However, the questions remain as to whether a relationship exists between glycolysis and lipid metabolism and, if so, how these two metabolic pathways are successfully balanced in stem cells.

DIVISION PATTERN IS CONTROLLED BY METABOLIC REGULATORS

As the fate decisions of stem cells directly impact tissue homeostasis, identifying the regulatory mechanisms of division balance is critical to understanding stem cell maintenance. A number of cell-extrinsic signals (e.g., tissue microenvironment, intracellular ROS, and cytokines) as well as cell-intrinsic factors (e.g., epigenetic machineries, Polycomb group proteins, Hox genes, transcription factors, and DNA damage response) regulate the self-renewal capacity of stem cells. Recent studies have also revealed potential associations between cellular metabolism and division patterns in light of these factors.

The three possible division options of stem cells are as follows: asymmetric division (AD), which yields one stem cell and one differentiated daughter cell (stem cell maintenance); symmetric commitment (SC), which yields two differentiated daughter cells (stem cell exhaustion); and symmetric division (SD), which yields two daughter cells maintaining stem cell properties (stem cell expansion) (Figure 2a). The assessment of paired daughter cells through assay has proved to be a powerful tool for evaluating the cell fate of daughter cells, and the eventual division pattern of HSCs can be determined by the in vitro differentiation potential or by the in vivo repopulation capacity of their daughter cells (Ito et al. 2012, Kato et al. 2005, Suda et al. 1984, Yamamoto et al. 2013). The modulation of stem cell metabolism alters the proportions of division balance to increased SC (differentiation) and decreased AD, leading to stem cell exhaustion. Recent studies have provided evidence that PPAR-δ is essential to HSCs and that deletion of *Ppard* or *Pml*, and the subsequent inhibition of FAO, results in the SC of HSC daughter cells, whereas PPAR-δ activation restores asymmetric cell division (Ito et al. 2012) (Table 1). These findings revealed the key pathway inducing stem cell exhaustion (at least in the hematopoietic system). As shifting the division balance of cancer stem cells (or cancer-initiating cells) toward commitment (Ito et al. 2010, Kharas et al. 2010, Morrison & Kimble 2006) is a promising therapeutic strategy against cancer or leukemia, these findings are of high clinical importance and could lead to the development of new approaches to eradicating cancer stem cells by pharmacological targeting of cellular metabolism.

Although intestinal stem cells undergo symmetric stem cell divisions (Carulli et al. 2014, Lopez-Garcia et al. 2010, Snippert et al. 2010), these divisions are precisely controlled within certain limits and contribute to tissue homeostasis, which is further discussed in the next section. In contrast, previous analyses have reported that division patterns in hematopoietic stem and progenitor cells are closely controlled by the balance between SC and AD and that SD is rarely found in the initial division of currently available HSC-enriched fractions (Ito et al. 2012, Yamamoto et al. 2013). The link between cellular metabolism and stem cell expansion during development or after injury will therefore be an important focus of future stem cell research.

AD has also been observed in nontissue stem cells. For instance, during T cell differentiation and in plasma cells, fate determinants and cellular components such as proteins and organelles are unequally divided between daughter cells, thus enabling them to adopt distinct fates, with contributing pathways including metabolic regulators such as AMPK, SRC (spare respiratory capacity), OXPHOS, and/or nutrient-sensitive PI3K/AKT/mTOR (Arsenio et al. 2015, Chang et al. 2014, Lin et al. 2015). These pathways play a role in the function of many tissue stem cells; however, their contribution to stem cell division balance remains unclear.

MITOCHONDRIAL CONTROL OF DIVISION BALANCE IN STEM CELLS

Mitochondria are well-defined cytoplasmic organelles that take part in a variety of cellular metabolic functions, including energy production and biosynthesis of macromolecules (e.g., lipids, heme, and iron-sulfur clusters, amino acids, and nucleotides). Thus, mitochondria are central to diverse biological outcomes such as proliferation, differentiation, and adaptation to stress (Ahn & Metallo 2015, Chandel 2015, Pagliarini & Rutter 2013). Increasing evidence has shown that many types of stem cells rely heavily on anaerobic glycolysis rather than on mitochondrial OXPHOS and that the shift of metabolic process is a sign of cellular differentiation. For instance, HSCs and hematopoietic progenitors have distinct metabolic profiles. The HSC differentiation to progenitor cells corresponds to a critical metabolic change from glycolysis to OXPHOS (Mohrin et al. 2015, Piccoli et al. 2013, Takubo et al. 2013, Yu et al. 2013). Thus, mitochondria act as key regulators in stem cells, and stem cells adapt their mitochondrial bioenergetic metabolism and redox signaling to survive in the hypoxic niche and to control the balance between quiescence and differentiation.

SD is observed in intestinal stem cells (Carulli et al. 2014, Lopez-Garcia et al. 2010, Snippert et al. 2010), although many lines of evidence have also demonstrated AD of stem cells in various tissues, including blood, skin, muscle, the gut, and the mammary gland (Beckmann et al. 2007, Cicalese et al. 2009, Ito et al. 2012, Lechler & Fuchs 2005, Quyn et al. 2010, Shinin et al. 2006, Suda et al. 1984, Wu et al. 2007). Other recent studies have proposed an additional differentiation model in which HSCs can directly differentiate into lineage-restricted progenitors while bypassing the multipotent progenitor stage when mature cells must be rapidly replenished (e.g., respond to ablation stress) (Yamamoto et al. 2013). These findings suggest another possibility in which, as is usually the case with other cell types, first stem cells divide symmetrically, and then one of the daughter cells stochastically loses its stemness (for instance, through the availability of niche positions or interaction with cytokines), which yields two daughter cells with distinct fates: one stem cell and one differentiated cell (Figure 3a).

In contrast, a recent study of asymmetric stem cell division used the novel technique of separate labeling with two different-colored fluorophores, newly produced mitochondria (green fluorophores) and old mitochondria (red fluorophores), in mammary stem-like cells to demonstrate that the differential portioning of old mitochondria between daughter cells determines their cell fate after division. This study showed that the daughter cell receiving fewer old mitochondria maintained stem cell traits, whereas the daughter cell containing more old mitochondria lost its self-renewal capacity and was fated to cell differentiation

(Katajisto et al. 2015). In the case of SD, old and young mitochondria are equally segregated into two daughter cells, although their metabolic processes may differ from those of the mother cell. It will be an interesting task to understand how these cells and their mitochondria maintain the same function as mother cells (Figure 3b). Collectively, as mitochondria are essential subcellular components in the metabolic process, understanding their roles in division patterns and the subsequent cell fates of stem cells is critical.

CONCLUSIONS AND PERSPECTIVES

Recent assessments of the roles of the PI3K and PPAR signaling pathways have shown the critical roles played by metabolic processes in the division patterns of stem cells and the relative proportions of AD and SC. There is now clear evidence that the modulation of lipid metabolism shifts division balance toward stem cell differentiation, which leads to stem cell exhaustion (Ito & Ito 2013, Ito et al. 2012). It will be interesting to explore whether division balance is affected by alteration of other metabolic pathways (e.g., glycolysis, glutamine metabolism, and OXPHOS) in stem cells.

Due to heterogeneity within the available stem cell fraction, assessing the behavior and division patterns of individual stem cells is difficult. The establishment of assay systems in which stem cell markers are associated with particular functions (e.g., multipotency of neural stem cells, repopulation capacity of HSCs) will enable researchers to prospectively track the division patterns of stem cells. This development will be a breakthrough in identifying the key regulatory machineries of stem cell fate decision and will significantly improve our understanding of the fundamental properties of stem cells.

Furthermore, the assessment of stem cell maintenance by AD and the detailed analysis of stem cell expansion via symmetric self-renewing division (a form of SD) hold great promise for clinical applications. Although intestinal stem cells have been shown to undergo SD to yield two stem cells after tissue damage, symmetric self-renewing division, which produces two functional long-term HSCs, is believed to be extremely rare (Ema et al. 2000, Ito et al. 2012, Yamamoto et al. 2013). This observation leads to many open questions. Why are SDs rare in HSCs? How do metabolic pathways contribute to division balance? The metabolic comparison between SD and AD will be of especially high interest because it is directly linked to therapeutic applications for transplantation cases in which stem cell expansion ex vivo is required with a limited number of donor cells. Better understanding of the molecular mechanisms and cross-links behind all three division options, i.e., stem cell exhaustion by SC, stem cell maintenance by AD, and stem cell expansion by SD, will enable the manipulation of the cell fate of stem cells. This stem cell fate control will be a central theme of ongoing research, as it illuminates the key metabolic requirements of cancer stem cells, and these metabolic requirements hold great promise for therapeutic applications in the clinic.

Acknowledgments

We are thankful to the members of the Ito Lab and Einstein Stem Cell Institute and to Rajat Singh for comments and discussion on metabolic pathways in stem cells. Keisuke Ito is supported by grants from the NIH

(R01DK98263 and R01DK100689) and NYSTEM (C029154). We apologize that many original articles were omitted due to space limitations.

LITERATURE CITED

Ahn CS, Metallo CM. Mitochondria as biosynthetic factories for cancer proliferation. Cancer Metab. 2015; 3:1. [PubMed: 25621173]

Appelbaum FR. Hematopoietic-cell transplantation at 50. N Engl J Med. 2007; 357:1472–75. [PubMed: 17928594]

Arsenio J, Metz PJ, Chang JT. Asymmetric cell division in T lymphocyte fate diversification. Trends Immunol. 2015; 36:670–83. [PubMed: 26474675]

Barbehenn EK, Wales RG, Lowry OH. Measurement of metabolites in single preimplantation embryos; a new means to study metabolic control in early embryos. J Embryol Exp Morphol. 1978; 43:29–46. [PubMed: 580293]

Beckmann J, Scheitza S, Wernet P, Fischer JC, Giebel B. Asymmetric cell division within the human hematopoietic stem and progenitor cell compartment: identification of asymmetrically segregating proteins. Blood. 2007; 109:5494–501. [PubMed: 17332245]

Benveniste P, Cantin C, Hyam D, Iscove NN. Hematopoietic stem cells engraft in mice with absolute efficiency. Nat Immunol. 2003; 4:708–13. [PubMed: 12766767]

Busch K, Klapproth K, Barile M, Flossdorf M, Holland-Letz T, et al. Fundamental properties of unperturbed haematopoiesis from stem cells in vivo. Nature. 2015; 518:542–46. [PubMed: 25686605]

Carulli AJ, Samuelson LC, Schnell S. Unraveling intestinal stem cell behavior with models of crypt dynamics. Integr Biol Quant Biosci Nano Macro. 2014; 6:243–57.

Chandel NS. Evolution of mitochondria as signaling organelles. Cell Metab. 2015; 22:204–6. [PubMed: 26073494]

Chang JT, Wherry EJ, Goldrath AW. Molecular regulation of effector and memory T cell differentiation. Nat Immunol. 2014; 15:1104–15. [PubMed: 25396352]

Cheng T, Rodrigues N, Shen H, Yang Y, Dombkowski D, et al. Hematopoietic stem cell quiescence maintained by $p21^{cip1/waf1}$. Science. 2000; 287:1804–8. [PubMed: 10710306]

Cicalese A, Bonizzi G, Pasi CE, Faretta M, Ronzoni S, et al. The tumor suppressor p53 regulates polarity of self-renewing divisions in mammary stem cells. Cell. 2009; 138:1083–95. [PubMed: 19766563]

Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med. 2006; 354:1813–26. [PubMed: 16641398]

Daley GQ, Goodell MA, Snyder EY. Realistic prospects for stem cell therapeutics. Hematology. 2003; 2003:398–418.

Dykstra B, Kent D, Bowie M, McCaffrey L, Hamilton M, et al. Long-term propagation of distinct hematopoietic differentiation programs in vivo. Cell Stem Cell. 2007; 1:218–29. [PubMed: 18371352]

Ema H, Takano H, Sudo K, Nakauchi H. In vitro self-renewal division of hematopoietic stem cells. J Exp Med. 2000; 192:1281–88. [PubMed: 11067877]

Essers MA, Offner S, Blanco-Bose WE, Waibler Z, Kalinke U, et al. IFNα activates dormant haematopoietic stem cells in vivo. Nature. 2009; 458:904–8. [PubMed: 19212321]

Frenette PS, Pinho S, Lucas D, Scheiermann C. Mesenchymal stem cell: keystone of the hematopoietic stem cell niche and a stepping-stone for regenerative medicine. Annu Rev Immunol. 2013; 31:285–316. [PubMed: 23298209]

Gan B, Hu J, Jiang S, Liu Y, Sahin E, et al. Lkb1 regulates quiescence and metabolic homeostasis of haematopoietic stem cells. Nature. 2010; 468:701–4. [PubMed: 21124456]

Gurumurthy S, Xie SZ, Alagesan B, Kim J, Yusuf RZ, et al. The Lkb1 metabolic sensor maintains haematopoietic stem cell survival. Nature. 2010; 468:659–63. [PubMed: 21124451]

Ito K, Carracedo A, Weiss D, Arai F, Ala U, et al. A PML-PPAR-δ pathway for fatty acid oxidation regulates hematopoietic stem cell maintenance. Nat Med. 2012; 18:1350–58. [PubMed: 22902876]

Ito K, Hirao A, Arai F, Matsuoka S, Takubo K, et al. Regulation of oxidative stress by ATM is required for self-renewal of haematopoietic stem cells. Nature. 2004; 431:997–1002. [PubMed: 15496926]

Ito K, Hirao A, Arai F, Takubo K, Matsuoka S, et al. Reactive oxygen species act through p38 MAPK to limit the lifespan of hematopoietic stem cells. Nat Med. 2006; 12:446–51. [PubMed: 16565722]

Ito K, Ito K. Newly identified roles of PML in stem cell biology. Front Oncol. 2013; 3:50. [PubMed: 23504288]

Ito K, Suda T. Metabolic requirements for the maintenance of self-renewing stem cells. Nat Rev Mol Cell Biol. 2014; 15:243–56. [PubMed: 24651542]

Ito T, Kwon HY, Zimdahl B, Congdon KL, Blum J, et al. Regulation of myeloid leukaemia by the cell-fate determinant Musashi. Nature. 2010; 466:765–68. [PubMed: 20639863]

Katajisto P, Dohla J, Chaffer CL, Pentinmikko N, Marjanovic N, et al. Asymmetric apportioning of aged mitochondria between daughter cells is required for stemness. Science. 2015; 348:340–43. [PubMed: 25837514]

Kato Y, Iwama A, Tadokoro Y, Shimoda K, Minoguchi M, et al. Selective activation of STAT5 unveils its role in stem cell self-renewal in normal and leukemic hematopoiesis. J Exp Med. 2005; 202:169–79. [PubMed: 15998795]

Kharas MG, Lengner CJ, Al-Shahrour F, Bullinger L, Ball B, et al. Musashi-2 regulates normal hematopoiesis and promotes aggressive myeloid leukemia. Nat Med. 2010; 16:903–8. [PubMed: 20616797]

Kiel MJ, Yilmaz OH, Iwashita T, Yilmaz OH, Terhorst C, Morrison SJ. SLAM family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells. Cell. 2005; 121:1109–21. [PubMed: 15989959]

Lechler T, Fuchs E. Asymmetric cell divisions promote stratification and differentiation of mammalian skin. Nature. 2005; 437:275–80. [PubMed: 16094321]

Lin WH, Adams WC, Nish SA, Chen YH, Yen B, et al. Asymmetric PI3K signaling driving developmental and regenerative cell fate bifurcation. Cell Rep. 2015; 13:2203–18. [PubMed: 26628372]

Lopez-Garcia C, Klein AM, Simons BD, Winton DJ. Intestinal stem cell replacement follows a pattern of neutral drift. Science. 2010; 330:822–25. [PubMed: 20929733]

Maryanovich M, Gross A. A ROS rheostat for cell fate regulation. Trends Cell Biol. 2013; 23:129–34. [PubMed: 23117019]

McCulloch EA, Till JE. The radiation sensitivity of normal mouse bone marrow cells, determined by quantitative marrow transplantation into irradiated mice. Radiat Res. 1960; 13:115–25. [PubMed: 13858509]

Miyamoto K, Araki KY, Naka K, Arai F, Takubo K, et al. Foxo3a is essential for maintenance of the hematopoietic stem cell pool. Cell Stem Cell. 2007; 1:101–12. [PubMed: 18371339]

Mohrin M, Shin J, Liu Y, Brown K, Luo H, et al. A mitochondrial UPR-mediated metabolic checkpoint regulates hematopoietic stem cell aging. Science. 2015; 347:1374–77. [PubMed: 25792330]

Mohyeldin A, Garzon-Muvdi T, Quinones-Hinojosa A. Oxygen in stem cell biology: a critical component of the stem cell niche. Cell Stem Cell. 2010; 7:150–61. [PubMed: 20682444]

Morrison SJ, Kimble J. Asymmetric and symmetric stem-cell divisions in development and cancer. Nature. 2006; 441:1068–74. [PubMed: 16810241]

Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. Nature. 2014; 505:327–34. [PubMed: 24429631]

Morrison SJ, Shah NM, Anderson DJ. Regulatory mechanisms in stem cell biology. Cell. 1997; 88:287–98. [PubMed: 9039255]

Nakada D, Saunders TL, Morrison SJ. Lkb1 regulates cell cycle and energy metabolism in haematopoietic stem cells. Nature. 2010; 468:653–58. [PubMed: 21124450]

Osawa M, Hanada K, Hamada H, Nakauchi H. Long-term lymphohematopoietic reconstitution by a single CD34-low/negative hematopoietic stem cell. Science. 1996; 273:242–45. [PubMed: 8662508]

Pagliarini DJ, Rutter J. Hallmarks of a new era in mitochondrial biochemistry. Genes Dev. 2013; 27:2615–27. [PubMed: 24352419]

Panchision DM. The role of oxygen in regulating neural stem cells in development and disease. J Cell Physiol. 2009; 220:562–68. [PubMed: 19441077]

Piccoli C, Agriesti F, Scrima R, Falzetti F, Di Ianni M, Capitanio N. To breathe or not to breathe: the haematopoietic stem/progenitor cells dilemma. Br J Pharmacol. 2013; 169:1652–71. [PubMed: 23714011]

Pietras EM, Warr MR, Passegue E. Cell cycle regulation in hematopoietic stem cells. J Cell Biol. 2011; 195:709–20. [PubMed: 22123859]

Quyn AJ, Appleton PL, Carey FA, Steele RJ, Barker N, et al. Spindle orientation bias in gut epithelial stem cell compartments is lost in precancerous tissue. Cell Stem Cell. 2010; 6:175–81. [PubMed: 20144789]

Ramalho-Santos M, Willenbring H. On the origin of the term “stem cell”. Cell Stem Cell. 2007; 1:35–38. [PubMed: 18371332]

Rossi DJ, Jamieson CH, Weissman IL. Stems cells and the pathways to aging and cancer. Cell. 2008; 132:681–96. [PubMed: 18295583]

Scadden DT. The stem-cell niche as an entity of action. Nature. 2006; 441:1075–79. [PubMed: 16810242]

Shinin V, Gayraud-Morel B, Gomes D, Tajbakhsh S. Asymmetric division and cosegregation of template DNA strands in adult muscle satellite cells. Nat Cell Biol. 2006; 8:677–87. [PubMed: 16799552]

Shyh-Chang N, Daley GQ, Cantley LC. Stem cell metabolism in tissue development and aging. Development. 2013a; 140:2535–47. [PubMed: 23715547]

Shyh-Chang N, Zhu H, Yvanka de Soysa T, Shinoda G, Seligson MT, et al. *Lin28* enhances tissue repair by reprogramming cellular metabolism. Cell. 2013b; 155:778–92. [PubMed: 24209617]

Simon MC, Keith B. The role of oxygen availability in embryonic development and stem cell function. Nat Rev Mol Cell Biol. 2008; 9:285–96. [PubMed: 18285802]

Snippert HJ, van der Flier LG, Sato T, van Es JH, van den Born M, et al. Intestinal crypt homeostasis results from neutral competition between symmetrically dividing Lgr5 stem cells. Cell. 2010; 143:134–44. [PubMed: 20887898]

Suda T, Suda J, Ogawa M. Disparate differentiation in mouse hemopoietic colonies derived from paired progenitors. PNAS. 1984; 81:2520–24. [PubMed: 6585813]

Suda T, Takubo K, Semenza GL. Metabolic regulation of hematopoietic stem cells in the hypoxic niche. Cell Stem Cell. 2011; 9:298–310. [PubMed: 21982230]

Sun J, Ramos A, Chapman B, Johnnidis JB, Le L, et al. Clonal dynamics of native haematopoiesis. Nature. 2014; 514:322–27. [PubMed: 25296256]

Takubo K, Goda N, Yamada W, Iriuchishima H, Ikeda E, et al. Regulation of the HIF-1α level is essential for hematopoietic stem cells. Cell Stem Cell. 2010; 7:391–402. [PubMed: 20804974]

Takubo K, Nagamatsu G, Kobayashi CI, Nakamura-Ishizu A, Kobayashi H, et al. Regulation of glycolysis by Pdk functions as a metabolic checkpoint for cell cycle quiescence in hematopoietic stem cells. Cell Stem Cell. 2013; 12:49–61. [PubMed: 23290136]

Tothova Z, Kollipara R, Huntly BJ, Lee BH, Castrillon DH, et al. FoxOs are critical mediators of hematopoietic stem cell resistance to physiologic oxidative stress. Cell. 2007; 128:325–39. [PubMed: 17254970]

Trumpp A, Essers M, Wilson A. Awakening dormant haematopoietic stem cells. Nat Rev Immunol. 2010; 10:201–9. [PubMed: 20182459]

Wagers AJ, Sherwood RI, Christensen JL, Weissman IL. Little evidence for developmental plasticity of adult hematopoietic stem cells. Science. 2002; 297:2256–59. [PubMed: 12215650]

Walter D, Lier A, Geiselhart A, Thalheimer FB, Huntscha S, et al. Exit from dormancy provokes DNA-damage-induced attrition in haematopoietic stem cells. Nature. 2015; 520:549–52. [PubMed: 25707806]

Watt FM, Hogan BL. Out of Eden: stem cells and their niches. Science. 2000; 287:1427–30. [PubMed: 10688781]

Weissman IL, Anderson DJ, Gage F. Stem and progenitor cells: origins, phenotypes, lineage commitments, and transdifferentiations. Annu Rev Cell Dev Biol. 2001; 17:387–403. [PubMed: 11687494]

Wilson A, Laurenti E, Oser G, van der Wath RC, Blanco-Bose W, et al. Hematopoietic stem cells reversibly switch from dormancy to self-renewal during homeostasis and repair. Cell. 2008; 135:1118–29. [PubMed: 19062086]

Wu M, Kwon HY, Rattis F, Blum J, Zhao C, et al. Imaging hematopoietic precursor division in real time. Cell Stem Cell. 2007; 1:541–54. [PubMed: 18345353]

Yamamoto R, Morita Y, Ooehara J, Hamanaka S, Onodera M, et al. Clonal analysis unveils self-renewing lineage-restricted progenitors generated directly from hematopoietic stem cells. Cell. 2013; 154:1112–26. [PubMed: 23993099]

Yamazaki S, Iwama A, Takayanagi S, Morita Y, Eto K, et al. Cytokine signals modulated via lipid rafts mimic niche signals and induce hibernation in hematopoietic stem cells. EMBO J. 2006; 25:3515–23. [PubMed: 16858398]

Yu WM, Liu X, Shen J, Jovanovic O, Pohl EE, et al. Metabolic regulation by the mitochondrial phosphatase PTPMT1 is required for hematopoietic stem cell differentiation. Cell Stem Cell. 2013; 12:62–74. [PubMed: 23290137]

Zaugg K, Yao Y, Reilly PT, Kannan K, Kiarash R, et al. Carnitine palmitoyltransferase 1C promotes cell survival and tumor growth under conditions of metabolic stress. Genes Dev. 2011; 25:1041–51. [PubMed: 21576264]

Zon LI. Intrinsic and extrinsic control of haematopoietic stem-cell self-renewal. Nature. 2008; 453:306–13. [PubMed: 18480811]

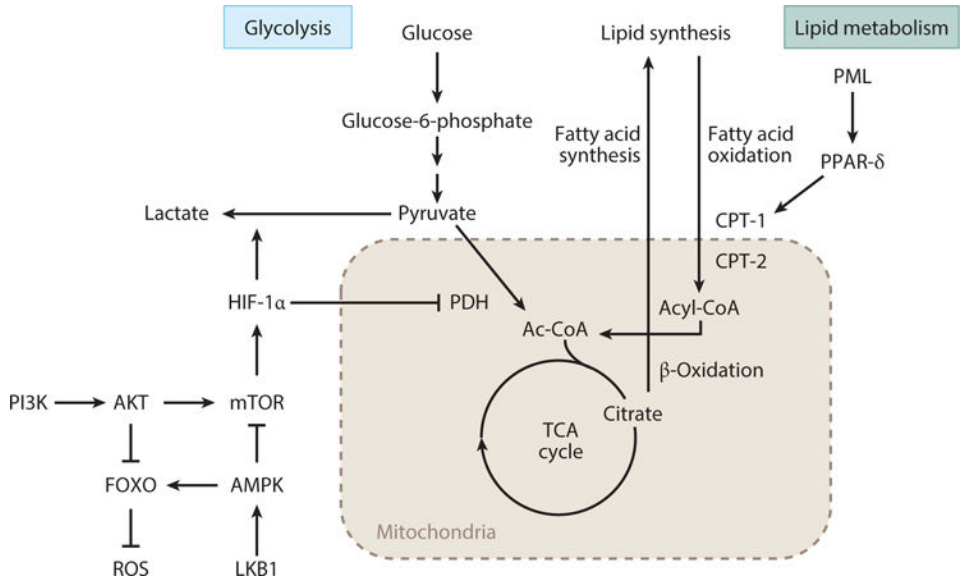

Figure 1.

Stem cell metabolism. Stem cells in various tissues rely on glycolysis, and HIF-1α promotes glycolysis, which prevents pyruvate oxidation by suppressing the PDH complex. The PI3K-AKT pathway promotes ROS production by repressing FOXO. LKB1/AMPK regulates stem cell function. Fatty acid synthase, the main biosynthetic enzyme, performs the condensation of Ac-CoA and malonyl-CoA to produce the saturated fatty acid palmitate and other long-chain fatty acids. The PML-PPAR pathway promotes fatty acid oxidation through positively regulating the activity of CPT-1, which is the rate-limiting enzyme for fatty acid oxidation. The PML-PPAR pathway for fatty acid oxidation is required for hematopoietic stem cell self-renewal by controlling the fate decision. Abbreviations: Ac-CoA, acetyl-coenzyme A; Acyl-CoA, acyl-coenzyme A; AMPK, AMP-activated protein kinase; CPT, carnitine-*O*-palmitoyltransferase; FOXO, forkhead box O; HIF-1α, hypoxia-inducible factor 1α; LKB1, liver kinase B1; PDH, pyruvate dehydrogenase; PML, promyelocytic leukemia; PPAR-δ, peroxisome proliferator–activated receptor δ; ROS, reactive oxygen species.

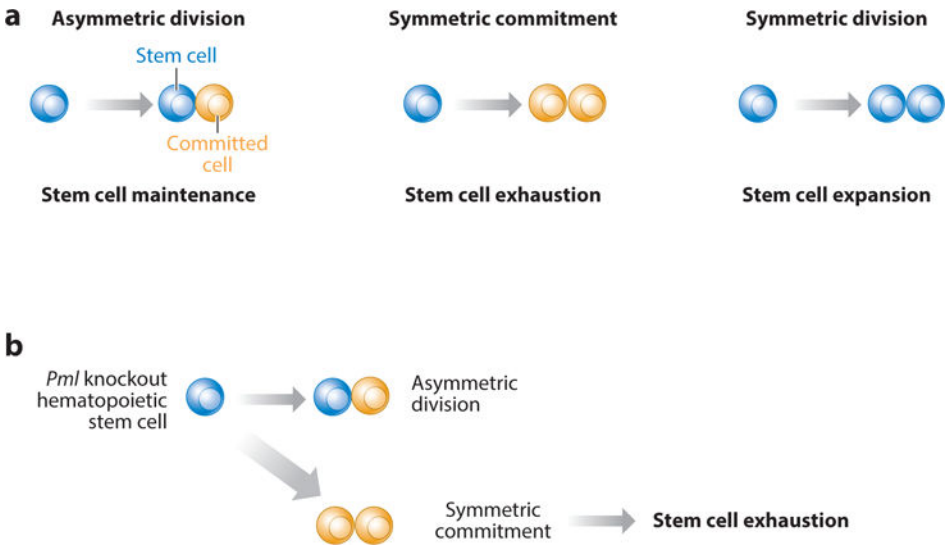

Figure 2.

The metabolic pathway regulates the division pattern of stem cells. (*a*) Division patterns of stem cells. A stem cell divides to provide one stem cell and one committed cell (asymmetric division: stem cell maintenance), two committed cells (symmetric commitment: stem cell exhaustion), or two stem cells (symmetric division: stem cell expansion). (*b*) The critical roles of the PML–PPAR-δ–FAO pathway in proper regulation of stem cell fate. Functional loss along this pathway reduces self-renewal of stem cells and triggers excessive commitment of stem cells, resulting in stem cell exhaustion. Abbreviations: FAO, fatty acid oxidation; PML, promyelocytic leukemia; PPAR-δ; peroxisome proliferator–activated receptor δ.

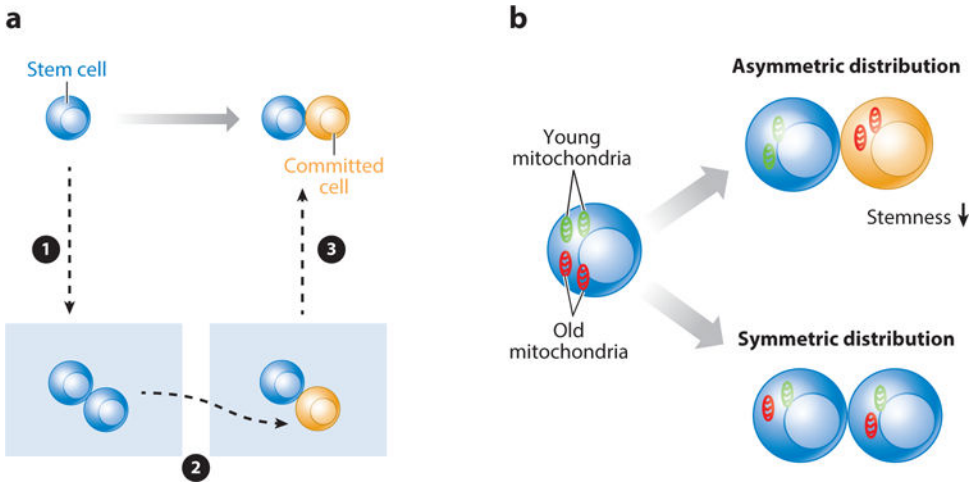

Figure 3.

Asymmetric stem cell division by unequal apportionment of older mitochondria. (*a*) A possible model for producing two distinct daughter cells. (❶) A stem cell first produces two stem cells through symmetric division. (❷) After that, one of these daughter cells loses its stem cell properties. (❸) Similar to asymmetric division, two daughter cells with distinct fates, one stem cell and one differentiated cell, are produced after this stem cell division. (*b*) Asymmetric distribution of old and young mitochondria influences the cell fate of the daughter cells of a stem cell. In some mammary stem-like-cell divisions, mitochondria are split unevenly between the two daughters, and old mitochondria are apportioned primarily to the tissue-progenitor daughter, whereas newly synthesized mitochondria are apportioned to the stem cell–like daughter.

Table 1

Metabolic pathways in stem and progenitor cells

Stem/progenitor cell	Surrounding environment	Key regulators	Metabolic pathway
Mesenchymal stem cell	Hypoxia	Hif-1α	Glycolysis
Chondroblast	Hypoxia		Glycolysis
Osteoblast	Not available		OXPHOS
Neural stem cell	Hypoxia	Foxo3	Low glycolysis
Neural progenitor	Normoxia	Acetyl-CoA transferase	Fatty acid synthesis
Hematopoietic stem cell	Hypoxia	Hif-1α	Glycolysis
		mTOR	Mitochondrial metabolism, ROS
		Pml-Pparδ	Fatty acid oxidation
		Foxo	Glycolysis, ROS
		Lkb1	Mitochondrial biogenesis
Embryonic stem cell	Not applicable	Pentose phosphate pathway	Glycolysis, low OXPHOS