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Transcriptional Regulation of Stem Cell and Cancer Stem Cell Metabolism

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Abstract

Purpose of review—Metabolism is increasingly recognized as a major player in control of stem cell function and fate. How stem cell metabolism is established, maintained, and regulated is a fundamental question of biology and medicine. In this review, we discuss major metabolic programs in stem cells and cancer stem cells, with a focus on key transcription factors that shape the stem cell metabolic phenotype.

Recent findings—Cancer stem cells primarily use oxidative phosphorylation for energy generation, in contrast to normal stem cells, which rely on glycolytic metabolism with the exception of mouse embryonic stem cells. Transcription factors control the metabolic phenotype of stem cells by modulating the expression of enzymes and thus the activity of metabolic pathways. It is evident that HIF1 α and PGC1 α function as master regulators of glycolytic and mitochondrial metabolism, respectively.

Summary—Transcriptional regulation is a key mechanism for establishing specific metabolic programs in stem cells and cancer stem cells.

Keywords

Stem cells; cancer stem cells; metabolism; glycolysis; oxidative phosphorylation; mitochondria; transcription

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Compliance with Ethics Guidelines

Conflict of Interest

Ahmet Alptekin, Bingwei Ye, and Han-Fei Ding declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

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

Introduction

Stem cells are functionally defined as cells with dual properties of self-renewal and multilineage differentiation potential [1, 2]. Self-renewal is the ability to generate progeny cells with the same developmental capacities as their parent cell, and multilineage differentiation potential is the capacity to generate multiple types of mature cells through differentiation. Pluripotent stem cells (PSCs), including embryonic stem cells (ESCs) [3–5] and induced pluripotent stem cells (iPSCs) [6, 7] are able to differentiate into any cell type in the body, whereas adult tissue stem cells, such as hematopoietic stem cells (HSCs) [8] and neural stem cells (NSCs) [9], can differentiate into various types of specialized cells in a particular tissue, thereby helping maintain tissue homeostasis.

In many aspects, cancer development recapitulates the processes of self-renewal and multipotent differentiation of stem cells. Most tumors have a clonal origin [10]. A single transformed cell requires about 30 to 33 cycles of cell divisions to progress to a clinically detectable mass ($\sim 10^9$ – 10^{10} cells) and tumorigenic cells can also initiate new tumor growth at distant sites (metastasis), which requires similar numbers of cell doublings [11]. This proliferation process also leads to the generation of tumor cells with heterogeneous phenotypes and biochemical activities, mimicking the differentiation process that normally occurs in the tissue [12, 13]. Thus, tumorigenic cells possess extensive proliferative potential (self-renewal) and the ability to give rise to phenotypically and biochemically diverse progeny cells (differentiation), which are the defining features of stem cells. The cancer stem cell model postulates that tumors are hierarchically organized with a subset of cancer stem cells located at the apex of a pyramid. These cancer stem cells are responsible for sustaining or initiating tumor growth through their self-renewal potential and for generating heterogeneous progeny tumor cells through aberrant differentiation [13]. While it remains controversial whether all cancers follow the cancer stem cell model [14], there is compelling evidence for the existence of cancer stem cells as defined by their ability to give rise to hierarchically organized tumors, which has been demonstrated in leukemia [15, 16], breast cancer [17], glioblastoma [18], colorectal cancer [19–21], pancreatic cancer [22], and ovarian cancer [23, 24]. Of note, it has long been recognized that embryonic carcinoma cells, which are the undifferentiated cells isolated from teratomas, possess the ability to generate tumors that contain all three germ layers [25, 26]. Teratoma formation remains a standard assay for assessing pluripotency of PSCs [27].

Metabolism is essential for sustaining the bioenergetic and biosynthetic needs of all living cells. Recent studies have revealed a central role of metabolism in control of the function and state of stem cells [28–31] and cancer stem cells [32, 33]. Studies of stem cell and cancer stem cell metabolism have been focused on two major metabolic processes for energy production (Figure 1), glycolysis in the cytosol and the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) in the mitochondrion [34]. Glycolysis is a series of enzymatic reactions that convert glucose to pyruvate, generating 2 net ATP molecules per molecule of glucose. Though relatively inefficient in ATP production, the glycolytic pathway has a key role in providing essential biosynthetic intermediates for the synthesis of amino acids, nucleotides, fatty acids, and NADH. In cells under hypoxic conditions, pyruvate is further converted to lactate, which is then excreted. However, cancer cells

predominantly convert pyruvate to lactate even in the presence of sufficient oxygen, a phenomenon known as aerobic glycolysis or the Warburg effect [35]. It is now recognized that aerobic glycolysis is a common feature of the metabolism of proliferating cells [36, 37]. For cells in oxygen-rich environments, the mitochondrial TCA cycle coupled to OXPHOS is a more efficient way for ATP production. Pyruvate derived from glycolysis is oxidized to acetyl coenzyme A (acetyl-CoA). Acetyl-CoA then enters the TCA cycle for the generation of NADH and FADH₂, which in turn transfer electrons to the electron transport chain to support OXPHOS, generating up to 34 more ATP molecules per glucose. The TCA cycle is also a major source of biosynthetic intermediates for the production of amino acids and lipids.

In this review, we first summarize our current understanding of metabolic phenotypes of stem cells and cancer stem cells. We then discuss recent findings on the transcriptional control of stem cell and cancer stem cell metabolism.

Stem Cell Metabolism

PSCs derived from the inner cell mass of pre-implantation embryos, as represented by mouse ESCs, are morphologically and molecularly distinct from those derived from post-implantation epiblasts (epiblast stem cells, EpiSCs). Mouse ESCs are considered to be in a ground or naïve state with unbiased developmental potential when compared with primed mouse EpiSCs, which cannot contribute to chimerism [27]. Mouse ESCs are metabolically bivalent, generating energy from either glycolysis or mitochondrial respiration depending on culture conditions. By contrast, mouse EpiSCs are highly glycolytic with reduced mitochondrial respiratory capacity because of lower expression of cytochrome *c* oxidase subunits in comparison with mouse ESCs [38].

Human ESCs are also derived from the inner cell mass. However, human ESCs morphologically and molecularly resemble mouse EpiSCs [39], and rely on glycolytic metabolism for energy production and pluripotency maintenance [38, 40]. Similar to mouse EpiSCs, human ESCs express lower levels of cytochrome *c* oxidase subunits in comparison with mouse ESCs [38]. In addition, compared with differentiated cells, human ESCs have increased expression of uncoupling protein 2 (UCP2), which promotes glycolysis by diverting pyruvate away from the mitochondria [40]. However, when human ESCs are converted to a naïve pluripotent state, mitochondrial metabolism is activated [41–43].

The reprogramming of somatic cells to iPSCs is marked by a shift from OXPHOS to a state of high glycolysis as a result of increased expression of glycolytic enzymes and reduced levels of electron transport chain components [40,44,45]. Importantly, the expression of glycolytic genes occurs prior to the expression of pluripotent markers, and stimulation and inhibition of glycolysis increases and reduces reprogramming efficiency, respectively [44]. These findings suggest an active role of metabolic reprogramming in pluripotency generation. However, the metabolic changes that occur during the reprogramming process are probably more complex than a simple switch from OXPHOS to glycolysis. Recent studies have revealed an initial transient increase in OXPHOS early in the reprogramming

process, which appears to be essential for the eventual glycolysis switch and successful reprogramming [46, 47].

All adult tissue stem cells that have been examined so far appear to rely on glycolysis for energy production, including HSCs, NSCs, muscle stem cells and mesenchymal stem cells. Tissue stem cells are quiescent, which prevents stem cells from exhaustion and allows for dynamic induction of tissue regeneration. Also, adult tissue stem cells reside in a hypoxic niche, which is critical for their maintenance in an undifferentiated and quiescent state [28–30, 48]. There is evidence suggesting that hypoxic signaling and glycolytic metabolism cooperate in reinforcing cell quiescence and promoting self-renewal [49].

Cancer Stem Cell Metabolism

Cancer cells reprogram cellular metabolism to meet the energetic and synthetic demands of growth and proliferation [50]. Cancer metabolism is characterized by aerobic glycolysis with a high rate of glucose consumption and lactate production [35], which diverts glycolic intermediates from mitochondrial ATP production to the biosynthesis of macromolecules needed for cell growth and proliferation [51–53]. There is evidence suggesting that cancer stem cells are also glycolytic, at least for some cancer types. Cancer stem cells from breast cancer [54], ovarian cancer [55], and colon cancer [56] show a significant increase in glucose uptake and lactate production, as well as in glycolytic enzyme expression, when compared to the bulk of tumor. These cancer stem cells also have a decrease in mitochondrial oxidative metabolism.

However, a growing body of evidence supports the notion that cancer stem cells preferentially use mitochondrial oxidative metabolism to meet their energy and biosynthesis requirements [57–59]. It has been shown that glioblastoma stem cells depend on mitochondrial respiratory chain and OXPHOS, but not on glycolysis, for their energy production, survival and tumorigenicity [60, 61]. In another study, it was found that leukemia stem cells derived from primary specimens of acute myelogenous leukemia (AML) patients are deficient in utilizing glycolysis but rely on mitochondrial OXPHOS for energy generation, and inhibition of BCL2-dependent mitochondrial respiration effectively eliminates AML stem cells [62]. Similarly, metabolic profiling of cancer stem cells from patients with epithelial ovarian cancer has revealed increased ability to utilize pyruvate via the TCA cycle. These ovarian cancer stem cells also show overexpression of genes associated with mitochondrial OXPHOS and fatty acid β -oxidation (FAO), increased mitochondrial reactive oxygen species (ROS) and membrane potential, and resistance to glucose deprivation [63]. Increased mitochondrial mass has also been found in cancer stem cells isolated from patients with metastatic breast cancer [64].

Another line of investigation focusing on drug-resistant tumor cells has led to the discovery of a common metabolic program in quiescent tumorigenic cells from different tumors that is characterized by increased OXPHOS and decreased glycolysis [57, 65]. For example, multidrug-resistant melanoma cells with high-level expression of the H3K4 demethylase JARID1B are slow-cycling, self-renewing tumorigenic cells essential for sustaining melanoma in vitro and in vivo [66]. These JARID1B-positive cells display marked

upregulation of enzymes involved in OXPHOS, with increased oxygen consumption and mitochondrial ATP production. Moreover, functional OXPHOS is required for the emergence of this subpopulation of slow-cycling tumorigenic cells following drug treatment [67]. Similarly, it has been shown that KRAS ablation leads to the emergence of a subpopulation of slow-cycling cells with cancer stem cell properties in a mouse model of pancreatic cancer. Transcriptome analysis indicates significant upregulation of genes involved in mitochondrial electron transport, FAO, and mitochondrial biogenesis. Importantly, KRAS ablation-resistant cells rely more on mitochondrial respiration than on glycolysis for energy production and survival [68]. It has been suggested that the selection of OXPHOS as a major energy supply route might confer slow-cycling cancer stem cells the ability to survive in hypoxic and nutrient-depleted environments [57].

Interestingly, a recent study has suggested that cancer stem cells could use either OXPHOS or glycolysis for their energy supply. Pancreatic cancer stem cells have a metabolic phenotype marked by increased mitochondrial respiration and reduced glycolytic activity, and are vulnerable to OXPHOS inhibition by metformin, which blocks the electron transport chain. However, the cancer stem cells that survived metformin treatment have acquired an intermediate metabolic phenotype with enhanced glycolytic capacity, thereby becoming resistant to OXPHOS inhibition [69]. Thus, cancer stem cells are metabolically heterogeneous, which may offer survival advantages under various microenvironmental conditions.

Transcriptional Regulation of Stem Cell and Cancer Stem Cell Metabolism

The observation that core pluripotency transcription factors can reprogram somatic cells to pluripotency [6], which is marked by a rewiring of metabolic pathways [31], suggests that transcriptional regulation is a key mechanism in establishing and maintaining stem cell metabolism. This notion is supported by an ever-increasing body of evidence as discussed below.

HIF1 α

Hypoxia-inducible factor 1 (HIF1) is a transcription factor essential for the hypoxic response, and is composed of two subunits, HIF1 α and HIF1 β . HIF1 levels increased under hypoxic conditions and decreased under normoxic conditions as a result of oxygen-dependent prolyl hydroxylation of HIF1 α by prolyl hydroxylases, which targets HIF1 α for degradation by the von Hippel-Lindau ubiquitin ligase complex [70]. It is well established that a primary function of HIF1 is to promote glycolysis through its transcriptional activation of glycolytic genes from glucose transporters (e.g., GLUT1) to lactate dehydrogenase A (LDHA), as well as metabolic regulators such as pyruvate dehydrogenase kinases (PDKs) [71–74]. LDHA converts pyruvate to lactate, and PDKs inhibit mitochondrial respiration by inactivating PDH, which converts pyruvate to acetyl-CoA for entry into the TCA cycle (Figure 1).

Recent studies have provided evidence for an essential role of HIF1 in the maintenance of adult tissue stem cells by promoting glycolysis [28, 72, 75]. Human mesenchymal stem cells express high levels of HIF1 α , leading to upregulation of GLUT1, HK2, LDHA, and PDKs,

and a marked increase in glycolysis [71]. Experiments with mouse HSCs demonstrated that HSCs require a HIF1 α -dependent glycolic program for their maintenance and function. *Hif1a*-deficient mouse HSCs fail to maintain their quiescent state, leading to HSC exhaustion, and these HSCs also have decreased glycolysis and increased mitochondrial metabolism. Importantly, overexpression of either *Pdk2* or *Pdk4* in *Hif1a*-deficient HSCs restores glycolysis, cell cycle quiescence, and stem cell function [76, 77].

HIF1 α also has a crucial role in regulation of PSC metabolism. Mouse EpiSCs are glycolysis dependent and express significantly higher levels of HIF1 α target genes compared with mouse ESCs. Moreover, overexpression of HIF1 α in mouse ESCs is sufficient to induce a switch from bivalent metabolism (ESCs) to glycolysis (EpiSCs), demonstrating a causal role of high HIF1 α expression in conferring the glycolytic phenotype of EpiSCs [38]. Similarly, HIF1 α is required for the metabolic shift from OXPHOS in somatic cells to glycolysis in iPSCs during reprogramming by transcriptional upregulation of PDKs and pyruvate kinase isoform M2 (PKM2) [78, 79].

MEIS1

Myeloid ecotropic insertion site 1 (MEIS1) is a homeodomain-containing transcription factor with a well-established role in normal hematopoiesis and leukemia pathogenesis [80]. Recent studies have identified an important role of Meis1 in promoting glycolysis in HSCs by transcriptional activation of Hif1 α expression [81, 82]. Adult mouse HSCs with inducible Meis1 deletion exhibit loss of quiescence and the ability to repopulate the bone marrow after transplantation. Meis1-deficient HSCs also show downregulation of Hif1 α and Hif2 α , leading to metabolic reprogramming from glycolysis to mitochondrial respiration with increased production of ROS. Moreover, the phenotype of Meis1-deficient HSCs can be rescued by treatment of Meis1 knockout mice with the antioxidant N-acetylcysteine [82]. These findings reveal an essential role of MEIS1 in the maintenance of HSC metabolism and function.

MYC

The MYC family of oncoproteins (MYC, MYCN, and MYCL) are master transcription regulators of cell proliferation and their genes are targeted by genomic amplification in many types of cancer [83]. It is well established that MYC has a key role in metabolic reprogramming during cell proliferation and tumorigenesis [53, 74, 84]. MYC stimulates glucose uptake, glycolysis, and lactate generation by directly activating the transcription of the glucose transporter gene GLUT1 and many glycolytic genes including enolase 1 (ENO1), HK2, LDHA, and PKM2 (Figure 1) [74, 85, 86].

The MYC-mediated glycolytic program may have a key role in the maintenance of the undifferentiated state of neural stem cells or progenitor cells. MYC and MYCN directly activate the expression of HK2 and LDHA in neural progenitor cells, which rely on aerobic glycolysis for energy production and survival. Neuronal differentiation of neural progenitor cells is marked by a switch from aerobic glycolysis to OXPHOS. This metabolic reprogramming is essential for the survival of differentiated neurons. Mechanistically, the

differentiation process induces downregulation of MYC and MYCN, leading to a reduction in HK2 and LDHA levels [87].

In pancreatic cancer stem cells, MYC has a major role in switching the metabolism from OXPHOS to glycolysis [33, 69]. These cancer stem cells depend on OXPHOS for energy production as a result of suppression of MYC, which directly represses the transcription of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PPARGC1A, also known as PGC1 α), a master regulator of mitochondrial biogenesis [88]. Treatment with the electron transport chain inhibitor metformin triggers energy crisis and apoptosis in pancreatic cancer stem cells, leading to the emergence of metformin-resistant pancreatic cancer stem cells that display increased glycolytic metabolism. The metabolic reprogramming in metformin-resistant CSCs is mediated by increased expression of MYC, which promotes glycolysis while represses OXPHOS at the same time. Genetic or pharmacological inhibition of MYC is able to reverse the resistance of pancreatic cancer stem cells to metformin [69]. Thus, MYC has an important function in driving glycolytic metabolism in stem cells and cancer stem cells.

NANOG

NANOG is a homeodomain transcription factor essential for establishing and maintaining pluripotency [89]. A recent study also suggested a critical role of NANOG in maintaining liver cancer stem cells. Working with several mouse models of liver cancer, Chen et al. showed that NANOG is critical for liver cancer development, promoting tumor progression by reprogramming mitochondrial metabolism in liver cancer stem-like cells [90]. NANOG binds to the promoter of OXPHOS genes and represses their expression, resulting in a reduction in mitochondrial respiration and ROS generation. In addition, NANOG transcriptionally activates genes involved in FAO, leading to an increase in FAO activity. Overexpression of OXPHOS genes or silencing FAO genes inhibits the self-renewal capacity of liver cancer stem cells, providing further evidence that NANOG sustains liver cancer stem cells by inhibiting OXPHOS and by activating FAO [90].

OCT4

Octamer-binding transcription factor 4 (OCT4) is a POU-domain transcription factor that functions as a master regulator of PSC self-renewal and pluripotency [91]. OCT4 is also one of the four factors used to generate iPSCs [6]. A recent study provided evidence for Oct4 in transcriptional activation of glycolysis in mouse ESCs [92]. It was shown that Oct4 can directly activate the transcription of Hk2 and Pkm2. Moreover, overexpression of Hk2 and Pkm2 in mouse ESCs is sufficient to increase glycolysis and to inhibit ESC differentiation triggered by withdrawal of leukemia inhibitory factor or by silencing the expression of Oct4 [92]. These findings link Oct4, a core pluripotency factor, to direct control of ESC glycolytic metabolism.

PGC1/PPARGC1

The PGC1 family of transcription coactivators, PGC1 α and PGC1 β , play a major role in transcriptional activation of mitochondrial biogenesis and functional capacity. Forced expression of PGC1 α is sufficient to drive mitochondrial biogenesis and upregulation of

genes encoding enzymes and protein components of the electron transport chain, FAO, and the TCA cycle. The function of PGC1 α and PGC1 β is dependent on their activity as co-activators of transcription factors that activate the expression of nuclear genes encoding mitochondrial enzymes and proteins. These transcription factors include nuclear respiratory factors (NRF1 and NRF2), peroxisome proliferator-activated receptor α (PPAR α), and estrogen-related receptors (ERR α , ERR β , and ERR γ) [88].

Although it is well documented that reprogramming of somatic cells to iPSCs requires a metabolic switch from OXPHOS to glycolysis [31,93], recent evidence indicated that OXPHOS may have a critical role in the reprogramming process. Kida et al. reported recently that early in the reprogramming process, ERR α and ERR γ , along with their co-activators PGC1 α and PGC1 β , are transiently induced, leading to a burst in OXPHOS activity. Importantly, this temporary increase in OXPHOS is necessary for iPSC generation, indicating a crucial function of mitochondrial metabolism in pluripotency induction [47]. Interestingly, a more recent study suggested that the early burst in OXPHOS and ROS induces nuclear factor (erythroid-derived 2)-like 2 (NFE2L2, also known as NRF2), a master regulator of the stress response. NFE2L2 then transcriptionally activates HIF1 α expression, which in turn drives the metabolic switch toward glycolysis. Moreover, destabilization of NFE2L2 significantly inhibits the metabolic reprogramming and decreases reprogramming efficiency [46].

There is also evidence indicating an important role of PGC1 α in the maintenance of drug-resistant tumorigenic melanoma cells [94, 95]. Melanoma tumors with high expression of PGC1 α exhibit increased mitochondrial respiration and decreased glycolytic activity. This metabolic program is essential for the tumorigenic potential of PGC1 α -positive melanoma cells. Further investigation revealed that PGC1 α expression is under the control of microphthalmia-associated transcription factor (MITF), a melanocyte-lineage transcription factor that functions as a lineage survival oncogene in melanoma [96]. MITF binds to the promoter of *PGC1 α* and activates its transcription [95]. Interestingly, treatment of melanoma cells with inhibitors of BRAF, an oncogene important in melanoma development, induces MITF and PGC1 α , leading to an increase in OXPHOS activity. Moreover, forced expression of PGC1 α protects melanoma cells from BRAF inhibition [94]. These findings suggest that a shift to mitochondrial OXPHOS is an important mechanism for the emergence of drug-resistant melanoma cells.

STAT3

Signal transducer and activator of transcription 3 (STAT3) is a key downstream mediator of action of leukemia inhibitory factor (LIF) in supporting long-term self-renewal of mouse ESCs [97], which are metabolically bivalent, using either OXPHOS or glycolysis for energy generation [38]. A recent study provides evidence for Stat3 in promoting mitochondrial metabolism in mouse ESCs by transcriptional activation of mitochondrial genes [98]. It was found that Stat3 binds to the mitochondrial genome and upregulates genes encoding subunits of the mitochondrial respiratory chain, leading to increased mitochondrial respiration. This increase in OXPHOS is crucial for optimal proliferation of mouse ESCs. Forced expression of a fusion Stat3 with mitochondrial localization signal is sufficient to promote self-

renewing proliferation of mouse ESCs. Importantly, Stat3 was also found to upregulate mitochondrial genes and to increase mitochondrial respiration during reprogramming of primed EpiSCs to naïve pluripotent iPSCs, suggesting an important function of LIF-Stat3 signaling in establishing the metabolic phenotype of naïve pluripotent cells [98].

Conclusions

It is now well recognized that metabolism is not only crucial for the maintenance of stem cells, including cancer stem cells, but also have an important role in determining their functions and fates. It is therefore interesting to note that whereas normal stem cells are mostly glycolytic, cancer stem cells rely predominantly on mitochondrial respiration for energy production. The underlying molecular mechanism remains poorly understood. Although it has been suggested that quiescent state might be intrinsically associated with the dependence on mitochondrial respiration [57], this model cannot readily explain the glycolytic phenotype of quiescent adult tissue stem cells. Transcription factors apparently promote either glycolysis or mitochondrial respiration, but not both, suggesting that normal and cancer stem cells might use distinct transcriptional programs for control of their metabolic states. Identification of intrinsic and environmental factors that influence the choice may suggest new therapeutic strategies for targeting cancer stem cells while sparing normal stem cells.

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References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. De Los Angeles A, Ferrari F, Xi R, Fujiwara Y, Benvenisty N, Deng H, et al. Hallmarks of pluripotency. *Nature*. 2015; 525(7570):469–78. DOI: 10.1038/nature15515 [PubMed: 26399828]
2. 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. DOI: 10.1146/annurev.cellbio.17.1.387 [PubMed: 11687494]
3. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, et al. Embryonic stem cell lines derived from human blastocysts. *Science*. 1998; 282(5391):1145–7. [PubMed: 9804556]
4. Evans MJ, Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. *Nature*. 1981; 292(5819):154–6. [PubMed: 7242681]
5. Martin GR. Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *Proc Natl Acad Sci U S A*. 1981; 78(12):7634–8. [PubMed: 6950406]
6. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006; 126(4):663–76. DOI: 10.1016/j.cell.2006.07.024 [PubMed: 16904174]

7. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell*. 2007; 131(5):861–72. DOI: 10.1016/j.cell.2007.11.019 [PubMed: 18035408]
8. Copley MR, Beer PA, Eaves CJ. Hematopoietic stem cell heterogeneity takes center stage. *Cell Stem Cell*. 2012; 10(6):690–7. DOI: 10.1016/j.stem.2012.05.006 [PubMed: 22704509]
9. Bond AM, Ming GL, Song H. Adult Mammalian Neural Stem Cells and Neurogenesis: Five Decades Later. *Cell Stem Cell*. 2015; 17(4):385–95. DOI: 10.1016/j.stem.2015.09.003 [PubMed: 26431181]
10. Fialkow PJ. Clonal origin of human tumors. *Biochim Biophys Acta*. 1976; 458(3):283–321. [PubMed: 1067873]
11. Tannock, IF. Principles of cell proliferation: cell kinetics. In: DeVita, VT, Hellman, S., Rosenberg, SA., editors. *Cancer: Principles and Practice of Oncology*. 3. Philadelphia: J.B. Lippincott; 1989. p. 3-13.
12. Heppner GH. Tumor heterogeneity. *Cancer Res*. 1984; 44(6):2259–65. [PubMed: 6372991]
13. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. *Nature*. 2001; 414(6859):105–11. [PubMed: 11689955]
14. Meacham CE, Morrison SJ. Tumour heterogeneity and cancer cell plasticity. *Nature*. 2013; 501(7467):328–37. DOI: 10.1038/nature12624 [PubMed: 24048065]
15. Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, et al. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. *Nature*. 1994; 367(6464): 645–8. DOI: 10.1038/367645a0 [PubMed: 7509044]
16. Wang JC, Lapidot T, Cashman JD, Doedens M, Addy L, Sutherland DR, et al. High level engraftment of NOD/SCID mice by primitive normal and leukemic hematopoietic cells from patients with chronic myeloid leukemia in chronic phase. *Blood*. 1998; 91(7):2406–14. [PubMed: 9516140]
17. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. *Proc Natl Acad Sci U S A*. 2003; 100(7):3983–8. DOI: 10.1073/pnas.0530291100 [PubMed: 12629218]
18. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, et al. Identification of human brain tumour initiating cells. *Nature*. 2004; 432(7015):396–401. [PubMed: 15549107]
19. Dalerba P, Dylla SJ, Park IK, Liu R, Wang X, Cho RW, et al. Phenotypic characterization of human colorectal cancer stem cells. *Proc Natl Acad Sci U S A*. 2007; 104(24):10158–63. DOI: 10.1073/pnas.0703478104 [PubMed: 17548814]
20. O'Brien CA, Pollett A, Gallinger S, Dick JE. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. *Nature*. 2007; 445(7123):106–10. DOI: 10.1038/nature05372 [PubMed: 17122772]
21. Ricci-Vitiani L, Lombardi DG, Pilozzi E, Biffoni M, Todaro M, Peschle C, et al. Identification and expansion of human colon-cancer-initiating cells. *Nature*. 2007; 445(7123):111–5. DOI: 10.1038/nature05384 [PubMed: 17122771]
22. Li C, Heidt DG, Dalerba P, Burant CF, Zhang L, Adsay V, et al. Identification of pancreatic cancer stem cells. *Cancer Res*. 2007; 67(3):1030–7. DOI: 10.1158/0008-5472.CAN-06-2030 [PubMed: 17283135]
23. Curley MD, Therrien VA, Cummings CL, Sergeant PA, Koulouris CR, Friel AM, et al. CD133 expression defines a tumor initiating cell population in primary human ovarian cancer. *Stem Cells*. 2009; 27(12):2875–83. DOI: 10.1002/stem.236 [PubMed: 19816957]
24. Zhang S, Balch C, Chan MW, Lai HC, Matei D, Schilder JM, et al. Identification and characterization of ovarian cancer-initiating cells from primary human tumors. *Cancer Res*. 2008; 68(11):4311–20. DOI: 10.1158/0008-5472.CAN-08-0364 [PubMed: 18519691]
25. Kleinsmith LJ, Pierce GB Jr. Multipotentiality of Single Embryonal Carcinoma Cells. *Cancer Res*. 1964; 24:1544–51. [PubMed: 14234000]
26. Martin GR. Teratocarcinomas and mammalian embryogenesis. *Science*. 1980; 209(4458):768–76. [PubMed: 6250214]
27. Nichols J, Smith A. Naive and primed pluripotent states. *Cell Stem Cell*. 2009; 4(6):487–92. DOI: 10.1016/j.stem.2009.05.015 [PubMed: 19497275]

- 28•. Ito K, Suda T. Metabolic requirements for the maintenance of self-renewing stem cells. *Nat Rev Mol Cell Biol.* 2014; 15(4):243–56. This review provides a thorough overview of metabolic pathways for the maintenance of adult tissue stem cells. DOI: 10.1038/nrm3772 [PubMed: 24651542]
29. Chandel NS, Jasper H, Ho TT, Passegue E. Metabolic regulation of stem cell function in tissue homeostasis and organismal ageing. *Nat Cell Biol.* 2016; 18(8):823–32. DOI: 10.1038/ncb3385 [PubMed: 27428307]
30. Shyh-Chang N, Daley GQ, Cantley LC. Stem cell metabolism in tissue development and aging. *Development.* 2013; 140(12):2535–47. DOI: 10.1242/dev.091777 [PubMed: 23715547]
31. Wu J, Ocampo A, Izpisua Belmonte JC. Cellular Metabolism and Induced Pluripotency. *Cell.* 2016; 166(6):1371–85. DOI: 10.1016/j.cell.2016.08.008 [PubMed: 27610564]
- 32•. Peiris-Pagès M, Martinez-Outschoorn UE, Pestell RG, Sotgia F, Lisanti MP. Cancer stem cell metabolism. *Breast Cancer Research.* 2016; 18(1):1–10. This review provides the most updated information on metabolic phenotypes of cancer stem cells. DOI: 10.1186/s13058-016-0712-6 [PubMed: 26728744]
33. Viale A, Draetta Giulio F. Sugar? No Thank You, Just a Deep Breath of Oxygen for Cancer Stem Cells. *Cell Metab.* 2015; 22(4):543–5. <http://dx.doi.org/10.1016/j.cmet.2015.09.020>. [PubMed: 26445511]
34. O'Neill LAJ, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. *Nat Rev Immunol.* 2016; 16(9):553–65. DOI: 10.1038/nri.2016.70 [PubMed: 27396447]
35. Warburg O. On respiratory impairment in cancer cells. *Science.* 1956; 124:269–70. [PubMed: 13351639]
36. MacIver NJ, Michalek RD, Rathmell JC. Metabolic regulation of T lymphocytes. *Annu Rev Immunol.* 2013; 31:259–83. DOI: 10.1146/annurev-immunol-032712-095956 [PubMed: 23298210]
37. Agathocleous M, Harris WA. Metabolism in physiological cell proliferation and differentiation. *Trends Cell Biol.* 2013; 23(10):484–92. DOI: 10.1016/j.tcb.2013.05.004 [PubMed: 23756093]
38. Zhou W, Choi M, Margineantu D, Margaretha L, Hesson J, Cavanaugh C, et al. HIF1 α induced switch from bivalent to exclusively glycolytic metabolism during ESC-to-EpiSC/hESC transition. *EMBO J.* 2012; 31(9):2103–16. DOI: 10.1038/emboj.2012.71 [PubMed: 22446391]
39. Tesar PJ, Chenoweth JG, Brook FA, Davies TJ, Evans EP, Mack DL, et al. New cell lines from mouse epiblast share defining features with human embryonic stem cells. *Nature.* 2007; 448(7150):196–9. DOI: 10.1038/nature05972 [PubMed: 17597760]
40. Zhang J, Khvorostov I, Hong JS, Oktay Y, Vergnes L, Nuebel E, et al. UCP2 regulates energy metabolism and differentiation potential of human pluripotent stem cells. *EMBO J.* 2011; 30(24):4860–73. DOI: 10.1038/emboj.2011.401 [PubMed: 22085932]
41. Ware CB, Nelson AM, Mecham B, Hesson J, Zhou W, Jonlin EC, et al. Derivation of naive human embryonic stem cells. *Proc Natl Acad Sci U S A.* 2014; 111(12):4484–9. DOI: 10.1073/pnas.1319738111 [PubMed: 24623855]
42. Takashima Y, Guo G, Loos R, Nichols J, Ficiz G, Krueger F, et al. Resetting Transcription Factor Control Circuitry toward Ground-State Pluripotency in Human. *Cell.* 2014; 158(6):1254–69. DOI: 10.1016/j.cell.2014.08.029 [PubMed: 25215486]
43. Huang K, Maruyama T, Fan G. The Naive State of Human Pluripotent Stem Cells: A Synthesis of Stem Cell and Preimplantation Embryo Transcriptome Analyses. *Cell Stem Cell.* 2014; 15(4):410–5. DOI: 10.1016/j.stem.2014.09.014 [PubMed: 25280217]
44. Folmes CD, Nelson TJ, Martinez-Fernandez A, Arrell DK, Lindor JZ, Dzeja PP, et al. Somatic oxidative bioenergetics transitions into pluripotency-dependent glycolysis to facilitate nuclear reprogramming. *Cell Metab.* 2011; 14(2):264–71. DOI: 10.1016/j.cmet.2011.06.011 [PubMed: 21803296]
45. Panopoulos AD, Yanes O, Ruiz S, Kida YS, Diep D, Tautenhahn R, et al. The metabolome of induced pluripotent stem cells reveals metabolic changes occurring in somatic cell reprogramming. *Cell Res.* 2012; 22(1):168–77. DOI: 10.1038/cr.2011.177 [PubMed: 22064701]

46. Hawkins KE, Joy S, Delhove JM, Kotiadis VN, Fernandez E, Fitzpatrick LM, et al. NRF2 Orchestrates the Metabolic Shift during Induced Pluripotent Stem Cell Reprogramming. *Cell Rep.* 2016; 14(8):1883–91. DOI: 10.1016/j.celrep.2016.02.003 [PubMed: 26904936]
47. Kida Yasuyuki S, Kawamura T, Wei Z, Sogo T, Jacinto S, Shigeno A, et al. ERRs Mediate a Metabolic Switch Required for Somatic Cell Reprogramming to Pluripotency. *Cell Stem Cell.* 2015; 16(5):547–55. <http://dx.doi.org/10.1016/j.stem.2015.03.001>. [PubMed: 25865501]
48. Cheung TH, Rando TA. Molecular regulation of stem cell quiescence. *Nat Rev Mol Cell Biol.* 2013; 14(6):329–40. DOI: 10.1038/nrm3591 [PubMed: 23698583]
49. Cavallucci, V., Fidaleo, M., Pani, G. Neural Stem Cells and Nutrients: Poised Between Quiescence and Exhaustion. *Trends Endocrinol Metab.* 2016. <http://dx.doi.org/10.1016/j.tem.2016.06.007>
50. DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB. The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. *Cell Metab.* 2008; 7(1):11–20. DOI: 10.1016/j.cmet.2007.10.002 [PubMed: 18177721]
51. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science.* 2009; 324(5930):1029–33. DOI: 10.1126/science.1160809 [PubMed: 19460998]
52. Cairns RA, Harris IS, Mak TW. Regulation of cancer cell metabolism. *Nat Rev Cancer.* 2011; 11(2):85–95. DOI: 10.1038/nrc2981 [PubMed: 21258394]
53. Pavlova NN, Thompson CB. The Emerging Hallmarks of Cancer Metabolism. *Cell Metab.* 2016; 23(1):27–47. This comprehensive review catalogs cancer-related metabolic changes with discussion of their contributions to tumorigenesis. DOI: 10.1016/j.cmet.2015.12.006 [PubMed: 26771115]
54. Ciavardelli D, Rossi C, Barcaroli D, Volpe S, Consalvo A, Zucchelli M, et al. Breast cancer stem cells rely on fermentative glycolysis and are sensitive to 2-deoxyglucose treatment. *Cell Death Dis.* 2014; 5:e1336.doi: 10.1038/cddis.2014.285 [PubMed: 25032859]
55. Liao J, Qian F, Tchabo N, Mhawech-Fauceglia P, Beck A, Qian Z, et al. Ovarian cancer spheroid cells with stem cell-like properties contribute to tumor generation, metastasis and chemotherapy resistance through hypoxia-resistant metabolism. *PLoS One.* 2014; 9(1):e84941.doi: 10.1371/journal.pone.0084941 [PubMed: 24409314]
56. Emmink BL, Verheem A, Van Houdt WJ, Steller EJA, Govaert KM, Pham TV, et al. The secretome of colon cancer stem cells contains drug-metabolizing enzymes. *Journal of proteomics.* 2013; 91:84–96. <http://dx.doi.org/10.1016/j.jprot.2013.06.027>. [PubMed: 23835434]
57. Viale A, Corti D, Draetta GF. Tumors and Mitochondrial Respiration: A Neglected Connection. *Cancer Research.* 2015; 75(18):3687–91. DOI: 10.1158/0008-5472.can-15-0491
58. Vlasi E, Pajonk F. The metabolic state of cancer stem cells—a valid target for cancer therapy? *Free Radical Biology and Medicine.* 2015; 79:264–8. <http://dx.doi.org/10.1016/j.freeradbiomed.2014.10.732>. [PubMed: 25450330]
59. Dando I, Dalla Pozza E, Biondani G, Cordani M, Palmieri M, Donadelli M. The metabolic landscape of cancer stem cells. *IUBMB Life.* 2015; 67(9):687–93. DOI: 10.1002/iub.1426 [PubMed: 26337609]
60. Janiszewska M, Suvà ML, Riggi N, Houtkooper RH, Auwerx J, Clément-Schatlo V, et al. Imp2 controls oxidative phosphorylation and is crucial for preserving glioblastoma cancer stem cells. *Genes Dev.* 2012; 26(17):1926–44. DOI: 10.1101/gad.188292.112 [PubMed: 22899010]
61. Vlasi E, Lagadec C, Vergnes L, Matsutani T, Masui K, Poulou M, et al. Metabolic state of glioma stem cells and nontumorigenic cells. *Proceedings of the National Academy of Sciences.* 2011; 108(38):16062–7. DOI: 10.1073/pnas.1106704108
62. Lagadinou Eleni D, Sach A, Callahan K, Rossi Randall M, Neering Sarah J, Minhajuddin M, et al. BCL-2 Inhibition Targets Oxidative Phosphorylation and Selectively Eradicates Quiescent Human Leukemia Stem Cells. *Cell Stem Cell.* 2013; 12(3):329–41. <http://dx.doi.org/10.1016/j.stem.2012.12.013>. [PubMed: 23333149]
63. Pasto A, Bellio C, Pilotto G, Ciminale V, Silic-Benussi M, Guzzo G, et al. Cancer stem cells from epithelial ovarian cancer patients privilege oxidative phosphorylation, and resist glucose deprivation. *Oncotarget.* 2014; 5(12):4305–19. DOI: 10.18632/oncotarget.2010 [PubMed: 24946808]

64. Farnie G, Sotgia F, Lisanti MP. High mitochondrial mass identifies a sub-population of stem-like cancer cells that are chemo-resistant. *Oncotarget*. 2015; 6(31):30472–86. DOI: 10.18632/oncotarget.5401 [PubMed: 26421710]
65. Wolf Dieter A. Is Reliance on Mitochondrial Respiration a “Chink in the Armor” of Therapy-Resistant Cancer? *Cancer Cell*. 2014; 26(6):788–95. <http://dx.doi.org/10.1016/j.ccell.2014.10.001>. [PubMed: 25490445]
66. Roesch A, Fukunaga-Kalabis M, Schmidt EC, Zabierowski SE, Brafford PA, Vultur A, et al. A Temporarily Distinct Subpopulation of Slow-Cycling Melanoma Cells Is Required for Continuous Tumor Growth. *Cell*. 2010; 141(4):583–94. <http://dx.doi.org/10.1016/j.cell.2010.04.020>. [PubMed: 20478252]
67. Roesch A, Vultur A, Bogeski I, Wang H, Zimmermann Katharina M, Speicher D, et al. Overcoming Intrinsic Multidrug Resistance in Melanoma by Blocking the Mitochondrial Respiratory Chain of Slow-Cycling JARID1B high Cells. *Cancer Cell*. 2013; 23(6):811–25. <http://dx.doi.org/10.1016/j.ccr.2013.05.003>. [PubMed: 23764003]
- 68•. Viale A, Pettazzoni P, Lyssiotis CA, Ying H, Sanchez N, Marchesini M, et al. Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function. *Nature*. 2014; 514(7524): 628–32. This study provides experimental evidence for targeting oxidative phosphorylation as a therapeutic strategy for eliminating pancreatic cancer stem cells. DOI: 10.1038/nature13611 [PubMed: 25119024]
- 69•. Sancho P, Burgos-Ramos E, Tavera A, Bou Kheir T, Jagust P, Schoenhals M, et al. MYC/PGC-1 α Balance Determines the Metabolic Phenotype and Plasticity of Pancreatic Cancer Stem Cells. *Cell Metab*. 2015; 22(4):590–605. <http://dx.doi.org/10.1016/j.cmet.2015.08.015> *This study describes a molecular mechanism for the metabolic plasticity of pancreatic cancer stem cells.* [PubMed: 26365176]
70. Semenza Gregg L. Hypoxia-Inducible Factors in Physiology and Medicine. *Cell*. 2012; 148(3): 399–408. <http://dx.doi.org/10.1016/j.cell.2012.01.021>. [PubMed: 22304911]
71. Palomäki S, Pietilä M, Laitinen S, Pesälä J, Sormunen R, Lehenkari P, et al. HIF-1 α is upregulated in human mesenchymal stem cells. *STEM CELLS*. 2013; 31(9):1902–9. DOI: 10.1002/stem.1435 [PubMed: 23744828]
72. Suda T, Takubo K, Semenza Gregg L. Metabolic Regulation of Hematopoietic Stem Cells in the Hypoxic Niche. *Cell Stem Cell*. 2011; 9(4):298–310. <http://dx.doi.org/10.1016/j.stem.2011.09.010>. [PubMed: 21982230]
73. Hu CJ, Wang LY, Chodosh LA, Keith B, Simon MC. Differential roles of hypoxia-inducible factor 1 α (HIF-1 α) and HIF-2 α in hypoxic gene regulation. *Mol Cell Biol*. 2003; 23(24): 9361–74. [PubMed: 14645546]
74. Gordan JD, Thompson CB, Simon MC. HIF and c-Myc: sibling rivals for control of cancer cell metabolism and proliferation. *Cancer Cell*. 2007; 12(2):108–13. DOI: 10.1016/j.ccr.2007.07.006 [PubMed: 17692803]
75. Teslaa T, Teitell MA. Pluripotent stem cell energy metabolism: an update. *EMBO J*. 2015; 34(2): 138–53. DOI: 10.15252/embj.201490446 [PubMed: 25476451]
76. Takubo K, Goda N, Yamada W, Iriuchishima H, Ikeda E, Kubota Y, et al. Regulation of the HIF-1 α level is essential for hematopoietic stem cells. *Cell Stem Cell*. 2010; 7(3):391–402. DOI: 10.1016/j.stem.2010.06.020 [PubMed: 20804974]
77. Takubo K, Nagamatsu G, Kobayashi CI, Nakamura-Ishizu A, Kobayashi H, Ikeda E, 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(1):49–61. DOI: 10.1016/j.stem.2012.10.011 [PubMed: 23290136]
78. Mathieu J, Zhou W, Xing Y, Sperber H, Ferreccio A, Agoston Z, et al. Hypoxia-inducible factors have distinct and stage-specific roles during reprogramming of human cells to pluripotency. *Cell Stem Cell*. 2014; 14(5):592–605. DOI: 10.1016/j.stem.2014.02.012 [PubMed: 24656769]
79. Prigione A, Rohwer N, Hoffmann S, Mlody B, Drews K, Bukowiecki R, et al. HIF1 α modulates cell fate reprogramming through early glycolytic shift and upregulation of PDK1-3 and PKM2. *Stem Cells*. 2014; 32(2):364–76. DOI: 10.1002/stem.1552 [PubMed: 24123565]

80. Argiopoulos B, Yung E, Humphries RK. Unraveling the crucial roles of Meis1 in leukemogenesis and normal hematopoiesis. *Genes Dev.* 2007; 21(22):2845–9. DOI: 10.1101/gad.1619407 [PubMed: 18006680]
81. Simsek T, Kocabas F, Zheng J, Deberardinis RJ, Mahmoud AI, Olson EN, et al. The distinct metabolic profile of hematopoietic stem cells reflects their location in a hypoxic niche. *Cell Stem Cell.* 2010; 7(3):380–90. DOI: 10.1016/j.stem.2010.07.011 [PubMed: 20804973]
82. Kocabas F, Zheng J, Thet S, Copeland NG, Jenkins NA, DeBerardinis RJ, et al. Meis1 regulates the metabolic phenotype and oxidant defense of hematopoietic stem cells. *Blood.* 2012; 120(25):4963–72. DOI: 10.1182/blood-2012-05-432260 [PubMed: 22995899]
83. Dang CV. MYC on the path to cancer. *Cell.* 2012; 149(1):22–35. DOI: 10.1016/j.cell.2012.03.003 [PubMed: 22464321]
84. Dang CV. MYC, metabolism, cell growth, and tumorigenesis. *Cold Spring Harbor perspectives in medicine.* 2013; 3(8):a014217.doi: 10.1101/cshperspect.a014217 [PubMed: 23906881]
85. Kim JW, Zeller KI, Wang Y, Jegga AG, Aronow BJ, O'Donnell KA, et al. Evaluation of myc E-box phylogenetic footprints in glycolytic genes by chromatin immunoprecipitation assays. *Mol Cell Biol.* 2004; 24(13):5923–36. DOI: 10.1128/MCB.24.13.5923-5936.2004 [PubMed: 15199147]
86. Osthus RC, Shim H, Kim S, Li Q, Reddy R, Mukherjee M, et al. Deregulation of glucose transporter 1 and glycolytic gene expression by c-Myc. *J Biol Chem.* 2000; 275(29):21797–800. DOI: 10.1074/jbc.C000023200 [PubMed: 10823814]
87. Zheng X, Boyer L, Jin M, Mertens J, Kim Y, Ma L, et al. Metabolic reprogramming during neuronal differentiation from aerobic glycolysis to neuronal oxidative phosphorylation. *eLife.* 2016; 5:e13374.doi: 10.7554/eLife.13374 [PubMed: 27282387]
88. Scarpulla RC, Vega RB, Kelly DP. Transcriptional integration of mitochondrial biogenesis. *Trends in Endocrinology & Metabolism.* 2012; 23(9):459–66. <http://dx.doi.org/10.1016/j.tem.2012.06.006>. [PubMed: 22817841]
89. Torres-Padilla ME, Chambers I. Transcription factor heterogeneity in pluripotent stem cells: a stochastic advantage. *Development.* 2014; 141(11):2173–81. DOI: 10.1242/dev.102624 [PubMed: 24866112]
90. Chen CL, Uthaya Kumar DB, Punj V, Xu J, Sher L, Tahara SM, et al. NANOG Metabolically Reprograms Tumor-Initiating Stem-like Cells through Tumorigenic Changes in Oxidative Phosphorylation and Fatty Acid Metabolism. *Cell Metab.* 2016; 23(1):206–19. DOI: 10.1016/j.cmet.2015.12.004 [PubMed: 26724859]
91. Boiani M, Scholer HR. Regulatory networks in embryo-derived pluripotent stem cells. *Nat Rev Mol Cell Biol.* 2005; 6(11):872–84. DOI: 10.1038/nrm1744 [PubMed: 16227977]
92. Kim H, Jang H, Kim TW, Kang B-H, Lee SE, Jeon YK, et al. Core Pluripotency Factors Directly Regulate Metabolism in Embryonic Stem Cell to Maintain Pluripotency. *STEM CELLS.* 2015; 33(9):2699–711. DOI: 10.1002/stem.2073 [PubMed: 26059508]
93. Zhang J, Nuebel E, Daley George Q, Koehler Carla M, Teitell Michael A. Metabolic Regulation in Pluripotent Stem Cells during Reprogramming and Self-Renewal. *Cell Stem Cell.* 2012; 11(5):589–95. DOI: 10.1016/j.stem.2012.10.005 [PubMed: 23122286]
94. Haq R, Shoag J, Andreu-Perez P, Yokoyama S, Edelman H, Rowe Glenn C, et al. Oncogenic BRAF Regulates Oxidative Metabolism via PGC1 α and MITF. *Cancer Cell.* 2013; 23(3):302–15. <http://dx.doi.org/10.1016/j.ccr.2013.02.003>. [PubMed: 23477830]
95. Vazquez F, Lim J-H, Chim H, Bhalla K, Girnun G, Pierce K, et al. PGC1 α Expression Defines a Subset of Human Melanoma Tumors with Increased Mitochondrial Capacity and Resistance to Oxidative Stress. *Cancer Cell.* 2013; 23(3):287–301. <http://dx.doi.org/10.1016/j.ccr.2012.11.020>. [PubMed: 23416000]
96. Garraway LA, Widlund HR, Rubin MA, Getz G, Berger AJ, Ramaswamy S, et al. Integrative genomic analyses identify MITF as a lineage survival oncogene amplified in malignant melanoma. *Nature.* 2005; 436(7047):117–22. http://www.nature.com/nature/journal/v436/n7047/supinfo/nature03664_S1.html. [PubMed: 16001072]
97. Wray J, Kalkan T, Smith AG. The ground state of pluripotency. *Biochem Soc Trans.* 2010; 38(4):1027–32. DOI: 10.1042/BST0381027 [PubMed: 20658998]

98. Carbognin E, Betto RM, Soriano ME, Smith AG, Martello G. Stat3 promotes mitochondrial transcription and oxidative respiration during maintenance and induction of naive pluripotency. *EMBO J.* 2016; 35(6):618–34. DOI: 10.15252/embj.201592629 [PubMed: 26903601]

Fig. 1.

Transcriptional regulation of glycolytic and mitochondrial metabolism. HIF1 α , MYC, and OCT4 transcriptionally activate glycolytic enzymes and regulators, whereas PGC1, ERR, and STAT3 stimulate OXPHOS by upregulating mitochondrial enzymes and proteins. ALDOA, fructose-bisphosphate aldolase A; ENO, enolase; ETC, electron transport chain; HK, hexokinase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GPI, glucose-6-phosphate isomerase; LDHA, lactate dehydrogenase; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PFK1, phosphofructokinase-1; PGAM; phosphoglycerate mutase; PGK, phosphoglycerate kinase; PK, pyruvate kinase; PPP, pentose phosphate pathway.