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REVIEW

Metabolism in embryonic and cancer stemness

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Abstract Cells constantly adjust their metabolic state in response to extracellular signals and nutrient availability to meet their demand for energy and building blocks. Recently, there has been significant research into the metabolic aspects of embryonic stem cells/pluripotent stem cells (ESCs/PSCs) and cancer stem cells (CSCs), which has revealed the unique metabolic status of different stem cell lineages. While ESCs and CSCs were largely thought to harbor similar metabolic states, recent evidence demonstrates that their metabolic dependency is distinctly different. The glucose metabolism of ESCs largely depends on glycolysis, including a one-carbon pathway during differentiation. While proliferating cancer cells share the glycolytic phenotype of ESCs, the mitochondria-centric oxidative phosphorylation constitutes an important metabolic circuit of CSCs under metabolic stress, indicating the dynamic nature of metabolic plasticity. In this review, we catalogued metabolic signatures of cellular "stemness" to provide insights into the therapeutic potential of ESCs and CSCs.

Keywords Cancer metabolism · Stem cell metabolism · Cancer stem cell metabolism · *O*-GlcNAc · Oxidative phosphorylation · Cancer stemness

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Introduction

The cancer stem cell (CSC) hypothesis postulates that only a fraction of the cancer cells within certain tumors have the ability to self-renew and generate the diverse cells that comprise a tumor (Visvader and Lindeman 2008; Pardal et al. 2003; Reya et al. 2001). CSCs are likely to share many of the features of normal stem cells that provide for a long lifespan, including relative quiescence, upregulated expression of several drug transporters to evade chemotherapeutic effect, active capacity for DNA-repair, and a resistance to apoptosis (Shigdar et al. 2014; Dean et al. 2005).

Traditionally, metabolism was seen as a passive process that produced energy and building blocks to meet the demands of the specialized cell hierarchy according to the intra- and/or extra- cellular signals. Nowadays, however, the active roles of metabolism are under intensive investigation. Cells constantly adjust their metabolic state in response to extracellular signaling and nutrient availability. Inversely, the metabolic state of cells can affect signal transductions and cell hierarchy. Metabolic pathways provide substrates for post-translational modifications that influence cell signaling and epigenetic modifications of histones and DNA (Vander Heiden et al. 2009; Lu and Thompson 2012).

With the recent focus on cancer metabolism research, metabolic reprogramming as a hallmark of cancer has been increasingly appreciated (Vander Heiden et al. 2009). The

metabolic rewiring observed in cancer not only serves to fulfill the proliferative demand of tumor cells, but also plays a significant role in driving cancer development and progression (Metallo and Vander Heiden 2010; Lu and Thompson 2012). Thus, the knowledge on how metabolism is rewired in CSCs may provide significant insight in developing anti-cancer drugs targeting CSCs.

Non-CSCs in the tumor have been shown to proliferate at a faster rate than CSCs, but have little tumor-initiating potential (Kreso and Dick 2014). The diversion of key metabolites into cellular pathways and metabolic changes in rapid proliferating cancer cells may play a crucial role in inducing different phenotypic states of cancer cells (Ciavardelli et al. 2014). These findings have significant implications for studies examining cancer metabolism and the Warburg effect. The vast majority of studies in this area have focused on the bulk populations of cancer cells, thus, obscuring the potential heterogeneity of cancer cell metabolism (Feng et al. 2014). For this reason, relatively little is known about the metabolic properties of CSCs, also called tumor initiating cells (TICs) (Feng et al. 2014).

In this review, we first summarized the metabolic signatures of stem cells to gain insights into those of CSCs. Secondly, we examined recent findings that support the hypothesis that non-stem-like cancer cells (or non-CSCs) can be reprogrammed to stem-like cancer cells (or CSCs). Finally, we tried to update recent views on the metabolic transition during reprogramming of non-stem-like cancer cells to stem-like cancer cells. The results from very recent experimental data suggest that oxidative phosphorylation (OxPhos) is especially important for stem-like cancer cells (or CSCs).

Metabolic signatures of PSCs

PSCs rely heavily on glycolysis compared to their differentiated counterparts

A study by Van Blerkom (2009) found that the pluripotent inner cell mass (ICM) that resides in the blastocyst have a lower inner mitochondrial membrane potential ($\Delta\Psi_m$). Consistent with this, a study found that pluripotent embryonic stem cells (ESCs) derived from an in vitro culture of the ICM show high rates of glycolysis compared to their differentiated counterparts (Shyh-Chang et al. 2013a). Human embryonic stem cells (hESCs) show lower mitochondrial content and depend on anaerobic glycolysis more than hESC-derived fibroblasts (Prigione et al. 2010; Rafalski et al. 2012). hESCs also highly express glycolysis-related genes with elevated lactate production compared to differentiated cells (Varum et al. 2011). A study conducted by Shyh-Chang et al. (2013a) demonstrated that a switch from OxPhos back to glycolysis is also seen when differentiated cells are converted into induced pluripotent stem cells (iPSCs). During the reprogramming of mouse and human somatic cells to iPSCs, oxygen consumption is decreased while lactate production is increased (Folmes et al. 2012; Mathieu et al. 2014; Shyh-Chang and Daley 2013). Indeed, a metabolomics analysis demonstrated that somatic cells convert from an oxidative to a glycolytic state in pluripotency (Panopoulos et al. 2012).

Metabolic differences between stem cells and differentiated cells might even promote the 'stemness' state (Rafalski et al. 2012). Stimulation of glycolysis promoted reprogramming efficiency, while the blockade of glycolytic enzymes activity blunted it (Folmes et al. 2011). Similarly, high glucose culture medium reprogrammed mouse somatic cells to iPSCs more efficiently than low glucose medium (Jang et al. 2012; Zhu et al. 2010). Although it is now clear that glycolytic metabolism critically regulates 'stemness', there is controversy as to whether metabolic shifts precede pluripotency acquisition or a stem cell state promotes changes in metabolism (Rafalski et al. 2012). During reprogramming, the upregulation of glycolysis precedes the reactivation of pluripotent markers (Hansson et al. 2012; Shyh-Chang and Daley 2013). However, the reprogramming factor, Oct4, directly upregulates glycolysis in mESCs (Jang et al. paper in process). The reprograming factor Lin28 primarily regulates metabolism in stem cells (Shyh-Chang and Daley 2013; Ito and Suda 2014). Therefore, it is possible that reprogramming factors first elicit a metabolic shift that is necessary to induce additional endogenous pluripotency factors to complete the reprogramming into a stem cell state (Rafalski et al. 2012). In the Warburg effect, cancer cells are thought to shunt glycolytic intermediates into amino acid, lipid and nucleotide synthesis for cell proliferation (Vander Heiden et al. 2009). Similarly, mouse ESCs show increased activity in the pentose phosphate pathway (PPP), demonstrating that anabolic glycolysis is a common feature of metabolism in both ESCs and cancer cells (Shyh-Chang et al. 2013a).

One-carbon pathway is essential for PSC maintenance

ESCs use a unique mode of amino acid metabolism to maintain their pluripotent epigenetic state (Shyh-Chang et al. 2013a). mESCs were screened for their dependence on each of the 20 amino acids, and it was found that restricting threonine alone uniquely abolished their growth (Wang et al. 2009). Recently, in hESCs, methionine metabolism has been proven to be important for stemness maintenance (Shiraki et al. 2014). Both threonine and methionine metabolism converge on one-carbon metabolism. One-carbon metabolism involves the folate and methionine cycles, and integrates the nutritional status from amino acids, glucose, and vitamins to generate diverse outputs, such as the biosynthesis of lipids,

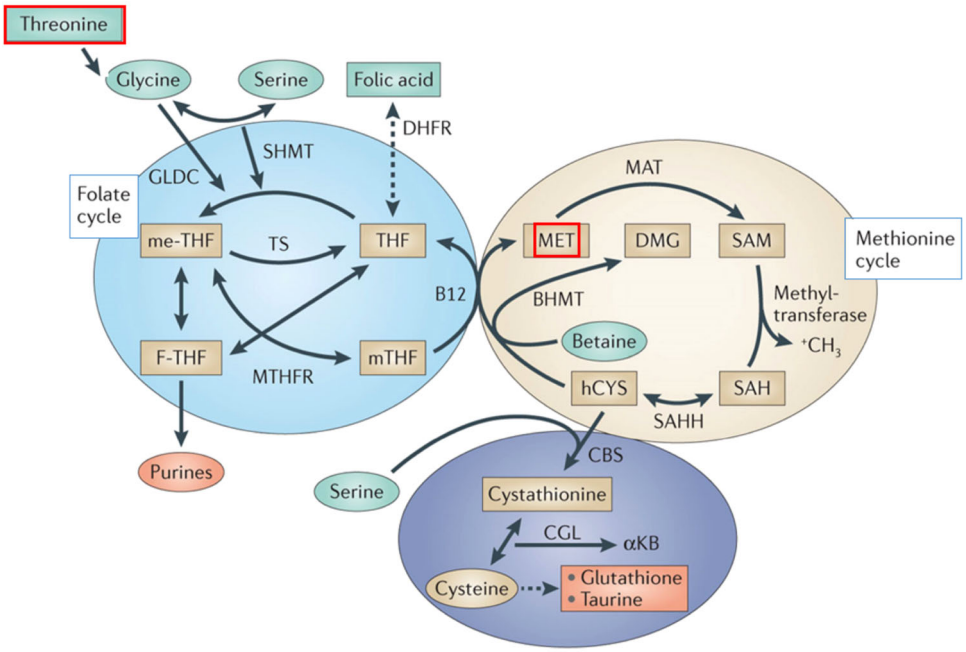

Fig. 1 One-carbon pathway. One-carbon metabolism involves the folate and methionine cycles and integrates nutritional status. Typically, threonine and methionine are essential for maintenance of stem cells in mouse and human ESCs, respectively

nucleotides and proteins, the maintenance of redox status, and the substrates for methylation reactions which are shown in Fig. 1 (Locasale 2013). Threonine is converted to glycine by threonine dehydrogenase (TDH), and glycine is used by glycine decarboxylase (GLDC) to generate one-carbon equivalents for the folate pool. In mESCs, TDH and GLDC regulate the synthesis of 5-methyl-tetrahydrofolate, thereby modulating S-adenosylmethionine (SAM) metabolism and histone H3K4 tri-methylation (Shyh-Chang et al. 2013b). Methionine is converted to SAM by adenylation. In hESCs, methionine deprivation results in a rapid decrease of intracellular SAM, triggering the activation of p53–p38 MAPK signaling, reducing NANOG expression, and posing hESCs for differentiation, followed by potentiated differentiation into all three germ layers (Shiraki et al. 2014). Recently, the serine-driven one-carbon metabolism is found to be essential to cancer biology (Zhang et al. 2012; DeBerardinis 2011) and contributes a major portion to NADPH generation (Fan et al. 2014). Dysregulation of the folate pathway results in decreased cellular NADPH/NADP(+) levels and diminished reducing power, which increases cell sensitivity to oxidative stress (Fan et al. 2014). The study of the one-carbon pathway in stem cells may broaden our understating of the role of nutrients on cancer metabolism.

PSCs rely on *O*-GlcNAc pathway

Single attachment of *N*-acetylglucosamine (GlcNAc) on serine and threonine residues of nucleoplasmic proteins, which is called *O*-GlcNAcylation, controls diverse aspects of cellular physiology, including nutrient and growth factor sensing, cell cycle progression, and stress response (Jang et al. 2012; Hart and Copeland 2010; Slawson and Hart 2011; Hart et al. 2011; Ma and Vosseller 2013). In cancer cells, increasing increments of glucose uptake drives the augmentation of glycolytic flux, and upregulates the flux into the metabolic branch pathways of glycolysis.

The first step in glycolysis is the phosphorylation of cellular glucose to generate glucose 6-phosphate, which can be shunted into the PPP or converted into fructose-6-phosphate. While the majority of fructose-6-phosphate continues through glycolysis to produce pyruvate, some of it is directed into the hexosamine biosynthetic pathway (HBP). The amino group from glutamine is transferred to fructose-6-phosphate to generate glucosamine-6-phosphate. Glucosamine-6-phosphate is ultimately converted to UDP-GlcNAc, which is used as a GlcNAc donor in *O*-GlcNAcylation which is shown in Fig. 2 (Ma and Vosseller 2013). Only two enzymes catalyze the addition and removal of *O*-GlcNAc in mammals: *O*-GlcNAc transferase (OGT) adds the modification and *O*-GlcNAcase (OGA) removes it (Hanover et al. 2010; Love et al. 2010).

The important role of *O*-GlcNAcylation in ESCs has been determined by experiments that demonstrate that the complete elimination of OGT expression is lethal to mESCs (Shafi et al. 2000). Recently, we showed that a mild knockdown in cellular *O*-GlcNAc levels decreases mESC self-renewal capacity and somatic cell reprogramming efficiency of PSCs (Jang et al. 2012). Several transcriptional

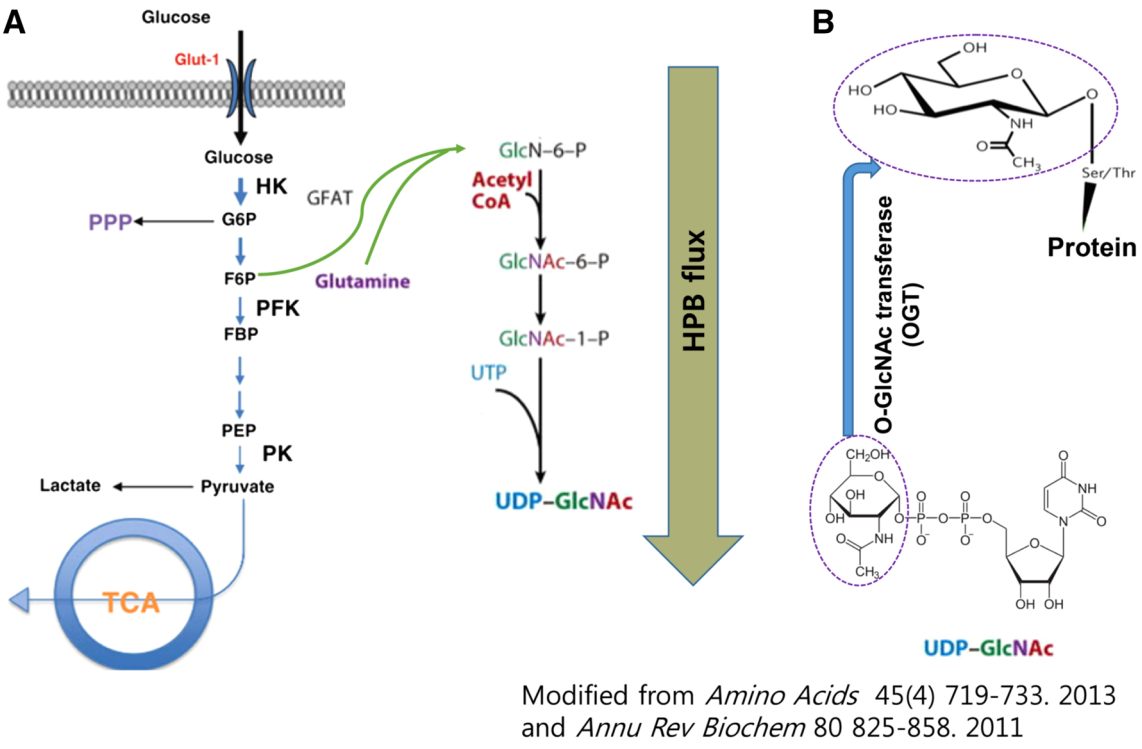

Fig. 2 *O*-GlcNAc signaling. **a**. Some of the glucose enters into the hexosamine biosynthetic pathway (HBP) and is converted to UDP-GlcNAc. **b**. OGT uses UDP-GlcNAc as a substrate and modifies serine or threonine residues of nucleoplasmic proteins

factors such as c-Myc, Oct4, and Sox2 implicated in the regulation of pluripotency and reprogramming are shown to be modified by *O*-GlcNAc (Myers et al. 2011; Jang et al. 2012; Chou et al. 1995). Especially *O*-GlcNAc modification at threonine 228 residue of Oct4, a core ESC factor, is important in maintaining ESC self-renewal, to reprogram somatic cells and induce several pluripotency-related genes (Jang et al. 2012). In mESCs, OGT is preferentially associated with ten-eleven translocation 1 (TET1) to genes promoters in close proximity of unmethylated CpG-rich transcription start sites and regulates the expression of metabolic genes (Vella et al. 2013). Because increased *O*-GlcNAcylation is observed in various cancer types, these results indicate that hyper-*O*-GlcNAcylation in cancer may contributes to CSC self-renewal and pluripotency (Ma and Vosseller 2013).

Reprogramming of non-stem-like cancer cells to stem-like cancer cells

The acquisition of stem cell-like features of cancer cells, their malignant behavior, and the alterations in their metabolic pathways may occur during cancer progression, and contribute to their adaptation and survival under oxidative stress, hypoxia, and nutrient deprivation (Mimeault and Batra 2014). Alterations in adult stem cells' homeostasis induced by genetic and epigenetics defaults could reprogram these cells to acquire more advantageous features in response to the tumor microenvironment requirements, thus, leading to CSCs generation (Munoz et al. 2012). The most recent studies are beginning to support a new development paradigm, in which the molecular logic behind the conversion of non-CSCs into CSCs can be better understood in terms of the "metabolic facilitators" and "metabolic impediments" that operate as proximate openings and roadblocks, respectively, for the transcriptional events and signal transduction programs ultimately orchestrating the intrinsic and/or microenvironmental paths to CSC cellular states (Menendez et al. 2013). Oncogenic transformation frequently involves de novo acquisition of developmental programs, analogous to cellular reprograming, and yields cells with unlimited self-renewal potential, a feature shared with CSC and other directly reprogrammed stem cells. A number of signaling pathways unique to normal stem cells may be operating in CSCs. Molecular markers identified as master regulators of pluripotency are Oct4, Nanog, C-myc, Klf4, Sox2, TCF3, HMGA2, BMI1, and LIN28. The signaling, which governs stem cell biology, can be summarized by three pathways; Shh, Notch, and Wnt signaling. It is known that alterations in these molecular pathways provide an unlimited proliferative capacity to CSCs (Leal and Lleonart 2013; Suva et al. 2013). Furthermore, just as normal stem cells are regulated by their microenvironment,

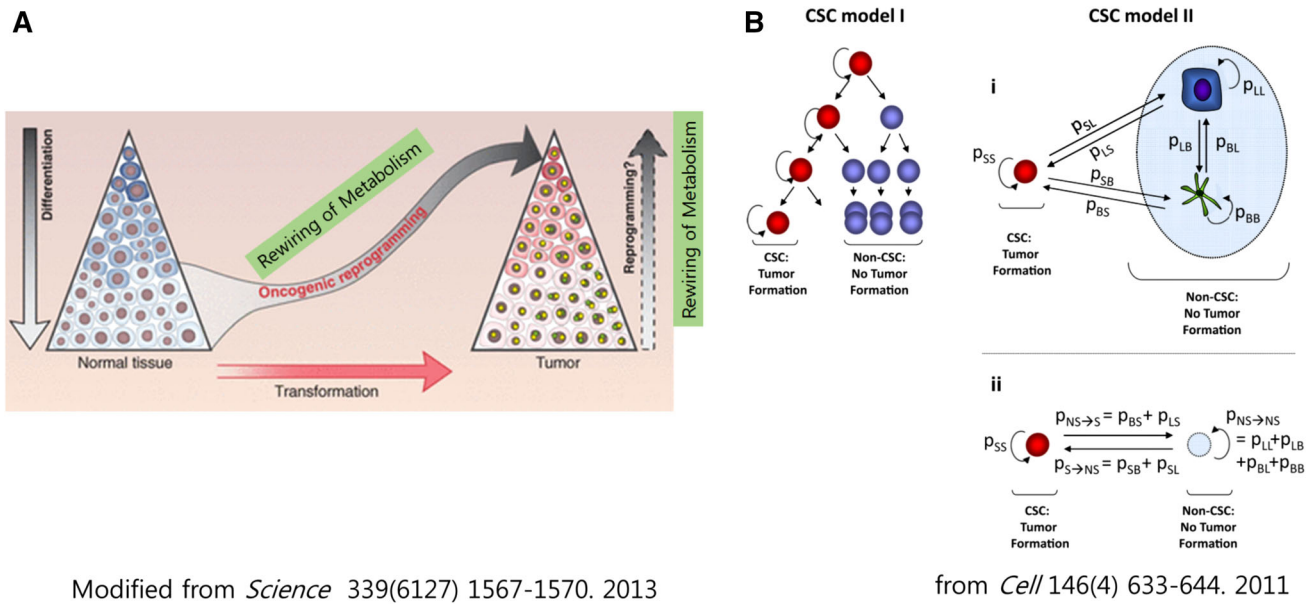

Fig. 3 Interconversion between CSC and non-CSC states. **a**. Oncogenic and metabolic rewiring occur when normal cells transition to tumor cells. Similarly non-CSCs might be able to be reprogrammed to CSCs. **b**. Recently proposed CSC models. In the traditional model (*model I*), CSCs give rise to non-CSCs, but not vice versa, resulting in a hierarchical cell-lineage structure reflective of normal tissue biology. De novo scenario (*model II*) in which there is bidirectional interconversion between CSC and non-CSC states

or niche, CSCs interact with and are regulated by cells in their own tumor microenvironment. Cytokines IL-1, IL-6 and IL-8 activate the Stat3/NF-κB pathways in both tumor and stromal cells. Activation of these pathways stimulates further cytokine production, generating positive feedback loops that favor CSC self-renewal. In certain cancers, stem-like cells are critical for tumor initiation and growth, and they occupy the apex of this hierarchy. Although speculative, such dynamic bidirectional transitions could provide a unifying view of cellular organization within tumors, compatible with both the CSC and the stochastic model (Suva et al. 2013) (Fig. 3). It may be also useful to develop combination therapies based on agents with selective action against CSCs together with agents that specifically target non-CSCs populations within tumors, as recently demonstrated with therapies employing novel selective CSC inhibitors combined with conventional chemotherapeutic drugs (Bertolini et al. 2014).

Metabolic transition during reprogramming of non-stem-like cancer cells to stem-like cancer cells

Aforementioned, ESC/PSCs are heavily reliant on glycolysis. In iPSCs, a transition from mitochondrial oxidative metabolism to glycolysis is required for successful reprogramming. In sharp contrast, when non-CSCs transition into a stem-like state, which is instigated by environmental metabolic stress, it is required that glycolysis energy metabolism shifts towards phosphorylation energy metabolism and become dependent on mitochondria (Vlashi et al. 2011). It is not clear why the "stemness" state of cancer cells demands metabolic requirements that are opposite from those of ESC/PSCs. Unlike normal programmed development of ESCs in an ordered context and chronological sequence, tumor progression is largely disordered and heterogeneous. Based on this notion, it is speculated that a tumor cell's metabolic plasticity should be required to efficiently adapt to fluctuating microenvironmental provisions. This metabolic property would allow tumor cells to conform into more appropriate metabolic modules depending on the corresponding milieu. Thus, in the context of nutrient deprivation, OxPhos could provide a more survival-prone niche for CSCs. Indeed, the dual blockade of glycolysis and OxPhos using clinically available 2-deoxy-glucose and metformin is effective in inhibiting tumor growth and suppressing metastasis, suggesting that CSCs are vulnerable in conditions of nutrient depletion and mitochondrial OxPhos inhibition (Cheong et al. 2011).

It is suggested that CSCs or TICs, the latter is coined recently to avoid unnecessary conceptual confusions with ESC, are supposed to emerge through state transition at least in some solid cancers as shown in Fig. 3 (Gupta et al. 2011; Chaffer et al. 2011). In comparison to hematological malignancies, in which hematopoietic cells are hierarchically organized and stem cell subclones are responsible for cancer initiation and progression, the mainstream idea about cancer development and progression lies within the

current paradigm of clonal evolution (Merlo et al. 2006; Nowell 1976). In clonal evolution theory, tumor cells typically are diverse populations consisting of heterogenic genetic traits. Among these, the fittest clone harboring genetic variations that are advantageous to selective pressure from the environment would become dominant and drive cancer progression. In contrast, CSC or TIC theory is derived from the hierarchic model in which tumor cells are organized as normal tissues with stem cells maintaining the tissue hierarchy (Dick 2003; Vermeulen et al. 2008). The CSCs were first identified in liquid cancers and then in solid cancers, suggesting that a small subpopulation of stem cells drive tumor initiation and progression. Of note, recent studies on the metabolic state of these CSCs revealed that CSCs rely mainly on OxPhos, contrary to the Warburg effect evident in most tumors.

Normal cells have a bivalent metabolism—glycolytic or phosphorylative module depending on the cells' requirements. It is not unreasonable to speculate that CSCs could exhibit such a malleable metabolic phenotype. Given that CSCs are responsible for drug resistance, tumor recurrence, and metastasis, CSCs must overcome intrinsic and extrinsic stresses that arise during tumor progression. Indeed, a hypoxic environment activates genes associated with "stemness" such as notch, Oct4, and c-myc, as well as genes associated with glycolysis (Folmes et al. 2012). Although hypoxia typifies the tumor microenvironment, nutrient depletion and acidosis also comprise a heterogeneous tumor microenvironment. We suggest that "stemness" is not a determined cell type but rather a cell state that is inter-transitional between two states; non-CSC and CSC. The metabolic phenotype of the former state, non-CSCs are mainly glycolytic since these cells are highly proliferative. In contrast, the metabolic phenotype of CSCs is mainly phosphorylative since CSCs are rather quiescent in terms of proliferation.

Consistent with our tenet, a recent study provides provocative results regarding the CSCs metabolism and therapeutic implications. Using inducible mouse tumor model of mutated KRas, Viale et al. (2014) demonstrated that oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function. Further, these resistant cells share characteristics of CSCs compatible with known pancreatic CSCs of CD133 + CD44Hi (Viale et al. 2014). These oncogene ablation-resistance CSCs exhibit more active electron transport chain (ETC) compared to non-CSCs. Also, autophagy and microlipophagy are as critical as ETC activity for the survival of CSCs. The strong dependence on ETC activity of CSCs on autophagic and catabolic processes makes them more resistant to nutrient deprivation and environmental stressors. In line with this report, a recent report showed that the reduction of OxPhos inhibits tumor formation. In mouse colorectal cancer cells and a skin tumor model, knocking down LONP1 reduced the OxPhos and inhibited tumor formation. In human colon cancers, upregulation of LONP1 was associated with increased tumor growth and a poor survival rate (Quiros et al. 2014). Clinically, these observations convey significant implications for the development cancer therapeutics that target tumor bioenergetics as an indispensable "adjuvant" which allows oncogenic pathway inhibitors to preemptively eradicate CSCs.

Conclusion and future perspectives

Cellular metabolism is emerging as one of the key regulatory elements of stem cell maintenance and differentiation induction. In particular, a niche driven glycolytic metabolic phenotype is crucial in the maintaining stemness while switching to oxidative metabolism is associated with stem cell differentiation. In cancer, CSCs or TICs also exhibit a similar metabolic profile, indicating glycolytic metabolism is crucial to stemness property. Intriguingly, a recent report suggests that oncogene ablation can select for CSCs in pancreatic tumor mouse models, and demonstrate these CSCs show enhanced mitochondrial ETC activity. This result implies that OxPhos inhibition could eliminate CSCs. While these recent advances begun to provide deeper insight into a more comprehensive understanding of metabolic characteristics of stem cells, both ESC/PSCs and CSC/TICs, many questions remain unanswered. Future challenges include delineating the metabolic phenotype of CSCs in a context dependent way so as to clarify some controversial observations regarding CSCs-specific metabolism and understanding the physiological implications of such metabolic profiles in CSCs and ESC/PSCs. Yet to be answered, we cautiously envision that mutual interactions between the intrinsic factors of cells (either CSCs or ESC/PSCs) and the heterogeneity of the tumor microenvironment determine the cell's metabolic and physiological state. Further studies on stem cell metabolism should also reveal how these metabolic changes affect the switch from a quiescent to an active proliferative state.

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