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Concise review: Cancer cell reprogramming and therapeutic implications

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ABSTRACT

The cancer stem cell (CSC) hypothesis postulates that cancer originates from the malignant transformation of stem cells and is considered to apply to a variety of cancers. Additionally, cancer cells alter metabolic processes to sustain their characteristic uncontrolled growth and proliferation. Further, microRNAs (miRNAs) are found to be involved in acquisition of stem cell-like properties, regulation and reprogramming of cancer cells during cancer progression through its post-transcriptional-regulatory activity. In this concise review, we aim to integrate the current knowledge and recent advances to elucidate the mechanisms involved in the regulation of cell reprogramming and highlights the potential therapeutic implications for the future.

Introduction

Cancer remains the most lethal disease although high response rates to initial treatments including chemotherapy, radiotherapy or sometimes even after combinational chemotherapies. Despite immunotherapy and targeted therapy have emerged as effective strategies in the past few years, their effects have been partially impeded due to cancer heterogeneity and the existence of CSCs. CSCs represent a small and elusive subpopulation of cancer cells within a tumor mass with stem cell properties. The concept of CSCs indicates that transformed stem cells within a tumor are able to self-renew, promote growth capabilities of cancer and are responsible for drug/treatment resistance, tumor recurrence and metastasis, and differentiate into a heterogeneous tumor population [1]. This small subset of cancer cells acts as tumor initiating cells.

Even in the presence of ample oxygen, cancer cells demonstrate a distinctive form of cellular metabolism characterized by high levels of glucose uptake and increased conversion of glucose to lactose (fermentation) via the glycolytic pathway. This phenomenon, called the "Warburg effect" and also known as aerobic glycolysis, has been recognized for many years [2]. "Warburg effect" and lipid metabolism (β-oxidation) are characteristic features of CSCs [3], and determine the fate of their progression and self-renewal. Therefore, this altered metabolism has emerged as an important hallmark of CSCs and targeting cancer metabolism is considered as a crucial therapy.

MiRNAs belong to the family of non-coding RNAs with a length of 21–25 nucleotides, and emerged as a new class of small RNAs with a critical role in the regulation of gene expression ever since their discovery in 1993 [4,5]. It is well known that miRNAs are cell regulators capable of controlling the expression of several genes at the same time [6]. MiRNAs are dysregulated in almost all solid and hematological malignancies, and specific miRNA expression signatures allow the characterization of different tumors and stages. MiRNAs have been reported play a critical role in a wide range of biological and cellular processes, such as development, proliferation, and apoptosis. Recently, studies indicate that miRNAs may also control other properties of CSCs [7].

Here, we will discuss the cancer cells reprogramming into CSCs, metabolic reprogramming and miRNA mediated cancer cell reprogramming in this concise review (Fig. 1). We will focus on the biological landscape and consider therapeutic implications and challenges of cancer.

Reprogramming into CSCs

CSC is a type of malignant cell endowed with limitless self-renewal and tumorigenicity which shares many features with normal stem cells, such as pluripotency, tumor formation and drug resistance [8,9]. It

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is responsible for tumor maintenance and propagation. Since J. Dick's initial CSC hypothesis proposed for leukemia, thousands of studies have shed light on CSCs [10,11]. The CSC hypothesis postulates that cancer originates from the malignant transformation of stem/progenitor cells. Increasing evidences have claimed that many tumors rely on subpopulations of CSCs with the ability to propagate malignant clones indefinitely and to produce an overt cancer. CSCs can originate from normal committed cells which undergo tumor-reprogramming processes and reacquire a stem cell-like phenotype. Accumulating evidences also show how tumor homeostasis and progression strongly rely on the capacity of nontumorigenic cancer cells to dedifferentiate to CSCs. CSCs have also been indicated to adopt several mechanisms, driven by cellular plasticity, senescence and quiescence, to maintain their self-renewal capability and to resist tumor microenvironmental stress and treatments. CSCs have been shown to be the main cause of therapy resistance and cancer recurrence. It has been revealed that CSCs have a particular metabolism that differs from non-CSCs to maintain their stemness properties.

However, CSCs normally constitute a small subset of the cancer cells in a heterogeneous tumor, and they are difficult to be isolated and characterized [12]. Thus, the molecular mechanisms of how CSCs cause varied malignancies remains poorly understood [13]. Cancer cell reprogramming can provide a useful platform to comprehensively explore CSC-associated mechanisms, including the origin and molecular functions [14].

The primary strategy is to enrich classical stem cell markers such as CD13, CD24, CD44, CD47, CD90 and CD133, in the cells, and follow other techniques including side-population analysis, sphere formation, and so on, to induce CSCs [15–18]. It has been confirmed that mouse and human fibroblasts could be reprogrammed into induced pluripotent stem cells (iPSCs) by virus-mediated transduction of Kruppel-like factor 4 (KLF4), Octamer-binding transcription factor 3/4 (Oct-3/4), Sex-determining region Y-box 2 (SOX2) and c-Myc, which are often called the OSKM Yamanaka factors [19,20]. The invention of methods for the induction of human iPSCs derived from somatic cells opened a new era of research.

The successful process of somatic reprogramming into a stem cell-like state has paved the way to reprogram malignant cells back to their original state well before oncogenic transformation occurs. The generation of pluripotent cancer cells (iPCCs) from cancer cells may provide tools for exploring the mechanisms of tumor initiation and progression *in vitro* to investigate the plasticity of cancer cells and origin of CSCs, and achieve cancer type-specific drug discovery. Cancer cells derived from almost all tissues can be transferred with an identical set of reprogramming factors, Yamanaka factors, to generate induced iPCCs [21–23]. Such iPCCs appear to have a CSC-like state after the reprogramming process [22,24,25]. Recently, many studies have reported that other transcription factors can drive CSC generation. It has been verified that both an ovarian cancer cell line and fallopian tube epithelial cells can be reprogrammed and Glis family zinc finger 1 (GLIS1) can successfully replace MYC as a transcription factor [26]. Furthermore, it has been indicated that Methyl-CpG binding domain protein 3 (MBD3) inhibits the formation of liver CSCs. The results also suggest that expression and activity of the transcription factor c-JUN are increased in induced CSCs, and are essential for stemness and CSCs properties, indicating that c-JUN might serve as a target for liver cancer therapy [27].

The selective targeting CSCs is a promising therapeutic strategy to prevent or slow cancer growth of human cancer and reduce the risk of recurrence [28]. Therapeutic strategies include disrupting the central regulating signaling pathways important for the cell type, targeting specific markers, inhibition of the ATP-binding cassette (ABC) transporters, manipulating miRNA expression, or inducing the differentiation and apoptosis of CSCs.

Signaling pathways that underlie CSC biology and have been identified as potential targets, such as Notch/Delta-like ligand (DLL), CXC chemokine receptor 1–2/CXCL8/FAK, and Wnt pathways [29]. Since CSCs and normal stem cells share the expression of many genes and signaling pathways, the redundancy of the regulatory pathways may effectively limit the efficacy and clinical impact of the therapeutic approaches. Meanwhile, the high-throughput drug screening using patient-specific iPCCs has been receiving growing attention. For instance, chemotherapy takes a huge toll on patients with cancer because of its undesirable side-effects. In addition, a differentiated cytotoxicity screen could lead to the development of drugs that are more specific to their target cells [29].

However, these reprogramming methods remain challenges, such as to break through the efficiency threshold due to insufficient gene delivery and limitations in cellular uptake, the cancer-specific epigenetic state and chromosomal aberrations of cancer cells [30–32].

Metabolic reprogramming

Metabolic reprogramming is a hallmark of malignancy and refers to

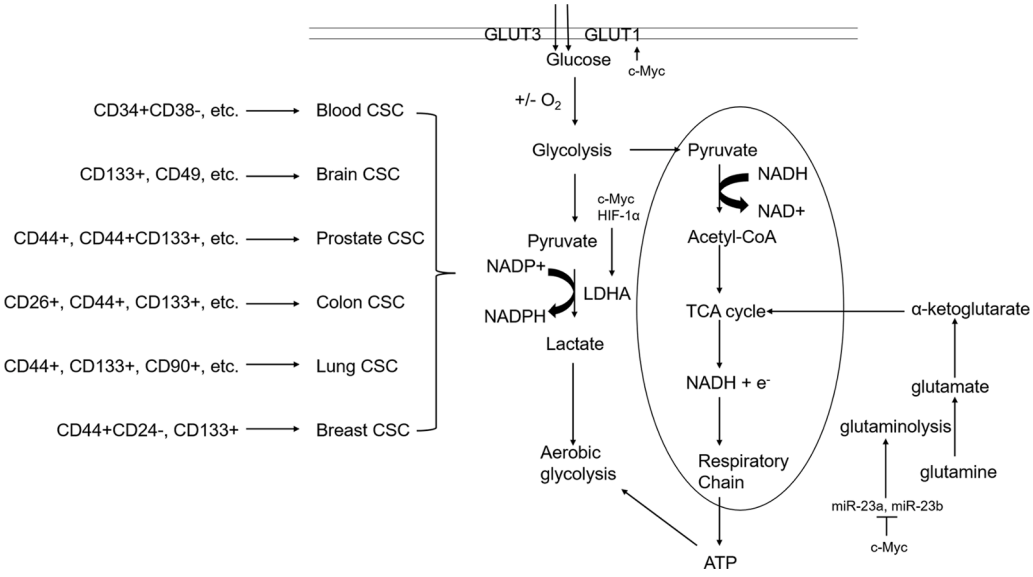

Fig. 1. A simplified overview of cancer cells reprogramming into CSCs, metabolic reprogramming and miRNA mediated cancer cell reprogramming.

the ability of cancer cells to alter their metabolism in order to support the increased energy request due to continuous growth, rapid proliferation, and other characteristics typical of neoplastic cells. The altered cancer cell metabolism hypothesis initially proposed by Dr. Otto Warburg's discovery in 1930 is now accepted. Cancer cells rewire their metabolism to promote growth, survival, proliferation, and long-term maintenance. The common characteristic of this altered metabolism is that cancer cells preferentially utilize glucose through aerobic glycolysis, which is an increase in glycolysis with concomitant lactate production. This phenomenon is observed even in the presence of completely functioning mitochondria and together is so-called Warburg Effect. The Warburg Effect has been documented for over 90 years and extensively studied over the past 10 years with numerous papers reporting to have established either its causes or its functions [33]. While metabolic reprogramming of cancer cells has long been considered from the standpoint of how and why cancer cells preferentially Warburg Effect, the progress during the past several years has substantially advanced our understanding of the rewired metabolic network in cancer cells that is intertwined with oncogenic signaling and metastatic cascade.

The glycolytic pathway and its regulation have been detailed explained in previous description [34]. In other words, altered metabolism is the fundamental difference between normal and cancer cells that to sustain their characteristic uncontrolled growth and proliferation. These metabolic alterations include (1) a shift from oxidative phosphorylation to aerobic glycolysis to support the increased need for ATP, (2) increased glutaminolysis for nicotinamide adenine dinucleotide phosphate (NADPH) regeneration, (3) altered flux through the pentose phosphate pathway and the tricarboxylic acid cycle for macromolecule generation, (4) increased lipid uptake, lipogenesis, and cholesterol synthesis, (5) upregulation of one-carbon metabolism for the production of ATP, nicotinamide adenine dinucleotide (NADH) /NADPH, nucleotides, and glutathione, (6) altered amino acid metabolism, (7) metabolism-based regulation of apoptosis, and (8) the utilization of alternative substrates, such as lactate and acetate [35].

Meanwhile, the constitutive activation of signaling pathways involved in cell growth because of most tumor cells reprogram their glucose metabolism as a result of mutations in oncogenes and tumor suppressors. Glucose metabolism can be modulated through both oncogenes and tumor-suppressor genes which are downstream of many signaling pathways. For instance, the extracellular signal-regulated kinase (ERK)- mitogen activated protein kinase (MAPK) signaling pathway, which is activated by the RAS oncoproteins (HRAS, KRAS, and NRAS) and positively associated with cell proliferation and survival [36, 37], has been shown to promote the Warburg effect [38]. Constitutive activation of ERK and MAPK signaling is frequently observed in human cancers. ERK1/2-dependent phosphorylation and nuclear translocation of pyruvate kinase isoenzyme type M2 PKM2 has been confirmed to promote the Warburg effect [38]. TGIF2 has been found to promote the progression of lung adenocarcinoma by bridging EGFR/RAS/ERK signaling to cancer cell stemness [39]. The transcription factor, c-Myc, has been found to increase the expression of GLUT1, LDHA, and a number of enzymes in the glycolytic pathway, as well as hypoxia-inducible factor 1α (HIF-1α), which also upregulates LDHA and cooperates with c-Myc in the induction of HK2 [40–42]. Stiffer Matrix has also been found to accelerate migration of hepatocellular carcinoma cells through enhanced aerobic glycolysis via the MAPK-YAP signaling [43]. Recently, glycans and glycosylation have also been found to be involved in cancer cell reprogramming[44].

Numerous directions are being investigated to harness energetic processes as therapeutic strategies for cancer. Attempts to target the glucose metabolism, especially on Warburg effect, for cancer diagnosis and therapy emerges in the past decades and is still in developing, including application of glucose metabolism in cancer diagnosis and treatment. For example, one of the most impressively clinical utility of the Warburg effect is positron emission tomography (PET) with a radiolabeled analog of glucose (18F-fluorodeoxyglucose, FDG) performed to non-invasively visualize glucose uptake in human body since 1976 [45,46]. PET scanner detects the radioactive decay of 18F-FDG-6-p and the body images were generated to show distribution of 18F-FDG. Therefore, the accumulated amounts of 18F-FDG-6-p the presence of living malignance [47,48]. Currently, various agents involved in glucose metabolism are actively investigated as novel targets with therapeutic potential, such as glucose transporter (GLUT)−1 inhibitory agents, Galloflavin, the analogs of Gossypol, and so on [2]. Despite the emerging of metabolic enzymes or transporters inhibitors, the efficiency of targeting tumor glucose metabolism is still under challenge. If we will uncover many other unknown aspects of glucose metabolism in cancer, then we can use them to benefit patient care more in the future.

MiRNA mediated cancer cell reprogramming: emerging alternatives

MiRNAs are a class of endogenous small non-coding RNAs with 19–25 nucleotide in length. MiRNAs function as major players in post-transcriptional regulation and numerous biological processes such as proliferation, survival, apoptosis and stem cell physiology [49–51], through base pairing between seed sequences in miRNA and complementary sequences within the open reading frame or an untranslated region of the target messenger RNAs (mRNAs), thereby destabilizing mRNA and/or inhibiting protein synthesis [6,52]. Each miRNA can target hundreds of transcripts and proteins directly or indirectly, and more than one miRNA can converge on a single transcript target. Therefore, the potential regulatory circuitry afforded by miRNA is enormous. Recent studies indicate that miRNAs undergo a complex, but finely tuned regulation in cell reprogramming [53].

MiR-302 s, miR-200c, miR-369, miR-34a, and miR-30b have been reported to be crucial in enhancing the expression of pluripotency-associated genes [22,54-61]. MiR-302 has been found to reprogram human skin cancer cells into pluripotent ES-cell-like state [59]. The miR-302 family (miR-302 s) is expressed most abundantly in slow-growing human embryonic stem (ES) cells, and quickly decreases after cell differentiation and proliferation. Thus, miR-302 s was investigated as one of the key factors essential for maintenance of ES cell renewal and pluripotency in this study [59]. Previous study has demonstrated that miRNAs let-7, miR-125, miR-9, and miR-30 directly repress LIN28 expression in embryonic stem and cancer cells. LIN28 is a homologue of the Caenorhabditis elegans lin-28 gene. In human tumors, LIN28 is a reprogramming factor and up-regulated and functions as an oncogene promoting malignant transformation and tumor progression [62]. It has also been validated that miR-34a inhibits liver cancer cell growth by reprogramming glucose metabolism [63]. In addition, it has been confirmed that miR-33b is an anti-oncogenic miRNA, which inhibits non-small cell lung cancer (NSCLC) cell growth by targeting LDHA through reprogramming glucose metabolism [64]. Moreover, down-regulated miR-125a-5p has been revealed to promote the reprogramming of glucose metabolism and cell malignancy by increasing levels of cd147 in thyroid cancer [65]. Furthermore, Let-7a has been found to induce metabolic reprogramming in breast cancer cells via targeting mitochondrial encoded NADH dehydrogenase subunit 4 (ND4) [66].

Therefore, miRNA can be used for cancer reprogramming based therapeutic agents, such as miR-22 to target TET2 in leukemia (AML and MDS) in breast cancer, Let-7 to target RAS and HMGA2 in breast cancer, miR-128 to target BMI-1 in brain cancer, miR-200 to target ZEB1/ZEB2, BMI-1, and SUZ12 in breast cancer, and some other miRNA in the colon cancer and prostate cancer have been reported to reduce cancer malignancy [67–77].

HIF1α and c-Myc are onco-proteins which are main regulators responsible for metabolic reprogramming in cancers. The miRNAs may also regulate glutamine metabolic enzymes in cancer cells. For instance, 30–50% of invasive breast tumors have reported increased c-Myc [78].

High expression of c-Myc caused increased requirements of glutamine for proliferation in breast cancer cells. It has been verified that c-Myc enhanced glutamine metabolism through increased mitochondrial glutaminase expression through repression of miR-23 in P-493 B cells [79]. Inhibition of c-Myc can decrease glutaminase activity, reduce uptake of both glucose and glutamine, and reduce cell growth [80]. Upregulation of c-Myc could induce mammary cancer in transgenic mice. MiR-20a, miR-20b, miR-9, and miR-222 have been validated to contribute to c-Myc-induced mammary carcinogenesis [81]. In the recent studies, miR-210 have been reported to interact with HIF-1α whose correlation with hypoxia is a biological phenomenon associated with tumor aggressiveness. MiR-210 is an oncogenic miRNA and a target of HIF-1 and −2 [82]. It has also been observed that miR-210 targets the mRNA that encodes the mitochondrial electron transport chain component protein succinate dehydrogenase complex subunit D (SDHD). Decreased expression of SDHD results in an increased stabilization of HIF1α and cancer cell survival [83,84].

In brief, miRNAs have been identified to act as tumor suppressor miRNAs and oncogenic miRNAs based on their modulating effect on the expression of their target genes. It has been summarized that miR-34a can be functional as potent tumor suppressor, CSC cell inhibitor, and potential anticancer therapeutic [85]. MiR-138 has also been reported to suppress glioblastoma proliferation through downregulation of CD44 [86]. While miR-21 is one of the mRNAs displaying oncogenic property and is upregulated in most of the cancers. MiR-21 can be down-regulated to prevent oncogenic transformation of normal gingival fibroblasts in oral cancer malignancy [87]. MiR-9–5p has been observed as an oncogenic miRNA associated with poor prognosis in many malignancies. For instance, NUMB suppression by miR-9–5p enhances $CD44^{+}$ prostate cancer stem cell growth and metastasis [88].

Although there are many studies and improvement, the drug design and efficacy are still complicated because of the features of RNA oligonucleotides. Challenging characteristics include: (i) degradation by nucleases upon addition into biological systems. (ii) poor cell membrane penetration. (iii) entrappment in the endosome (iv) poor binding affinity for complementary sequences. (v) poor delivery to desired target tissues. (vi) off-target and unwanted toxicities and (vii) activation of innate immune responses [89–92]. Once these potential obstacles discussed here are resolved, miRNA therapeutics should show continuing promise as therapeutic molecules for various types of cancers.

Conclusions

Despite the extensive study on CSCs, cancer metabolism and miRNAs with interesting results accumulated in the last decades, questions are still arising. Nevertheless, with technological advances, it is expected that we will uncover many other unknown aspects of CSCs, glucose metabolism and miRNA mediated cancer cell reprogramming in cancer and use them to benefit patient care in the future.

Data availability

All the data during the current study are included in the article or uploaded as supplementary information.

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Ethics approval and consent to participate

The experimental protocols were approved by the Ethics Committee of the Xingouqiao Street Community Health Service Center. This paper has not been published elsewhere in whole or in part. All authors have read and approved the content, and agree to submit it for consideration for publication in your journal.

CRediT authorship contribution statement

Xue Xiao: Writing – original draft, Writing – review & editing, Methodology. **Hua Chen:** Writing – original draft, Writing – review & editing. **Lili Yang:** Writing – original draft, Writing – review & editing. **Guoping Xie:** Visualization, Data curation. **Risa Shimuzu:** Writing – original draft, Writing – review & editing, Methodology, Funding acquisition, Supervision. **Akiko Murai:** Writing – original draft, Writing – review & editing, Methodology, Funding acquisition, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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