Journal of
Stem Cell Research & Therapy
ISSN: 2157-7633

Chen et al., J Stem Cell Res Ther 2014, 4:4
DOI: 10.4172/2157-7633.1000197

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Metabolic Enzymes: The Novel Targets for Cancer Stem Cells

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Keywords: Metabolic enzymes; Cancer stem cells

Introduction

In many types of hematologic malignancies and solid tumors, cancer stem cells (CSCs) represent small cell populations with capacities for self-renewal and differentiation [1]. Therapies targeting CSCs hold the promise of effective treatment of human cancer [2-4]. A successful anti-CSCs strategy should inhibit specific genes whose expression are required for the maintenance of CSCs [1]. The fact that many key genes are involved in both CSCs proliferation and normal stem cells regulation through various pathways such as Wnt/β-catenin [5], Hedgehog [6], Bim-1 [7,8], p53, $p16^{INK4a}$ and $p19^{ARF}$ [9], has made it more important to identify genes that are functionally required by CSCs but not by normal stem cell counterparts.

Metabolic Genes in Cancer Stem Cells

Although cancer metabolism has long been thought to be equal to aerobic glycolysis, studies in the field in the past decade have strengthened the conclusion that not only aerobic glycolysis, but also other metabolic genes or pathway are important in supporting cancer cell growth and proliferation [10,11]. A couple of metabolic genes or pathways are specifically activated in human cancer cells and those metabolic genes or pathways are more functionally required by CSCs [1,3]. The major mechanisms of metabolic genes activation in CSCs include direct or indirect activation by onco-protein, recurrent mutation and amplification/overexpression (Figure 1).

One class of metabolic genes or pathways is directly changed by cancer-initiating genetic changes such as acquiring an oncogene or accumulating a DNA mutation in CSCs. Those genetic changes may cause aberrant expression of these metabolic genes, which are required for self-renewal and differentiation of CSCs. Chronic myeloid leukemia (CML) is a good model to study CSCs as the BCR-ABL onco-protein is the only difference between the CSCs and their normal stem cell counterparts [12]. Using a BCR-ABL transduction/transplantation CML mouse model, DNA microarray analysis was used to compare gene expression between BCR-ABL-expressing and non-BCR-ABL-expressing $Lin^{-}c\text{-}Kit^{+}Sca\text{-}1^{+}$ cells. A couple metabolic genes were found to be upregulated by BCR-ABL oncogene, and this upregulation cannot be reversed by BCR-ABL kinase inhibition [12]. Among those genes, Arachidonate 5-lipoxygenase (*Alox5*) is a member of the lipoxygenase family of enzymes and transforms essential fatty acids into leukotrienes [13]. Alox5 has been shown to be involved in numerous physiological and pathological processes, including oxidative stress response, inflammation, and cancer [13]. The expression of *Alox5*gene was elevated by BCR-ABL. However, this elevation cannot be abolished by imatinib treatment. The studies further showed that in the absence of *Alox5*, BCR-ABL failed to induce CML in mice [12]. This *Alox5* deficiency caused impairment of the function of leukemia stem cells(LSCs) but not normal hematopoietic stem cells (HSCs) through its effects on differentiation, cell division and survival of long-term LSCs (LT-LSCs), which consequently caused a depletion of LSCs and a failure of CML development [12].

Alox5 was also identified as a novel target in glioma stem-like cells (GSLCs) [14]. Nordy, an Alox5 inhibitor, was shown to be able to attenuate the growth of GSLCs *in vitro*. Inhibition of Alox5 reduced the GSLC pool through a decrease in the $CD133^{+}$ population and abrogated clonogenicity [14]. Inhibition of Alox5 also appeared to exert its effect via astrocytic differentiation by upregulating GFAP and downregulating stemness related genes, rather than by inducing apoptosis of GSLCs [14].

A metabolic gene inactivated by BCR-ABL in LSCs from CML mouse model is stearoyl-CoA desaturase 1 (*Scd1*). *Scd1* was down regulated by BCR-ABL onco-protein in LSCs and played a tumor-suppressive role in LSCs but not in HSCs [15]. Deletion of *Scd1*caused acceleration of CML development and conversely overexpression of *Scd1* delayed CML development in a CML mouse model [15].

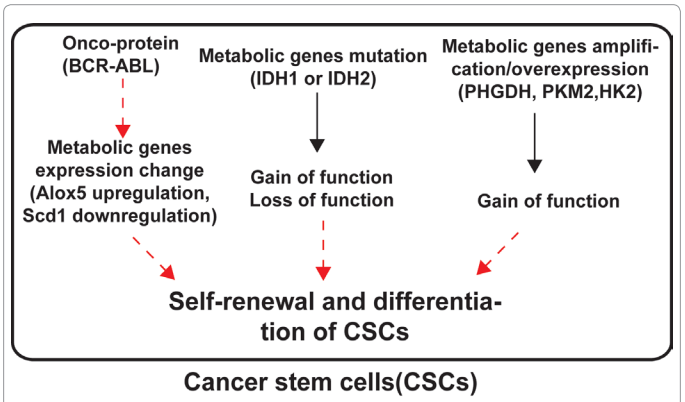

Figure 1: A couple of metabolic genes or pathways are activated through direct or indirect activation by onco-protein, recurrently mutation and amplification/overexpression.

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Received March 29, 2014; **Accepted** April 17, 2014; **Published** April 19, 2014

Citation: Chen Y, Li P, Li J (2014) Metabolic Enzymes: The Novel Targets for Cancer Stem Cells. J Stem Cell Res Ther 4: 197. doi:10.4172/2157-7633.1000197

Although Pten, p53, and Bcl2 pathways were shown to be affected by SCD1 in LSCs, the mechanism of SCD1 regulating LSCs remains unclear [15]. These CSCs related pathways may be regulated by SCD1 through its metabolic functions or other novel functions independent of its metabolic role. It will be important to dissect the function of SCD1 in LSCs.

The transcriptional regulatory properties of the oncogene Myc also regulated the expression of genes necessary for CSCs/cancer cells to engage in glutamine catabolism [16]. The Myc-dependent glutaminolysis adjusted the mitochondrial metabolism to glutamine catabolism to sustain cellular viability [16]. The stimulation of mitochondrial glutamine metabolism resulted in reduced glucose carbon entering the TCA cycle and a decreased contribution of glucose to the mitochondrial-dependent synthesis of phospholipids [16]. Similarly, the promyelocytic leukemia protein (PML) tumor-suppressor gene had a crucial role in the self-renewal of CSCs by controlling cell fate decisions [17]. PML acted as both a negative regulator of PPARγ co-activator 1A (*PGC1A*) acetylation and a potent activator of PPAR signaling and fatty acid oxidation [17,18].

The expression change of metabolic pathways was also observed in other types of CSCs.

The distinct metabolic properties change has been shown in breast CSCs in comparison to non-CSC cancer cells [19]. The metabolic analyses revealed that CSCs preferentially perform glycolysis over oxidative phosphorylation compared to non-CSCs [19]. In the lethal therapy-related myelodysplasia syndrome or acute myeloid leukemia (t-MDS/AML), the dysfunctions of the alanine and aspartate metabolism, glyoxylate and dicarboxylate metabolism, phenylalanine metabolism, citrate acid cycle, and aminoacyl-t-RNA biosynthesis were shown in blood stem cells, which may result in decreased ability to detoxify reactive oxygen species generated by chemo and radiation therapy, therefore leading to cancer-causing mutations [20].

The secondary class of metabolic genes is mutated in CSCs in different cancer types. Those mutations in metabolic enzymes may cause gain of function or loss of function. The normal function of isocitrate dehydrogenase-1 (IDH1) and IDH2 is to metabolize isocitrate and $NADP^+$ to yield α-ketoglutarate (αKG) and NADPH [21,22]. Mutations in IDH1 and IDH2 have recently been identified in 20% of AML, as well as other malignancies including glioblastoma, chondrosarcoma, and prostate cancer [22,23]. These alterations are gain of function mutations because they drive the synthesis of the 'oncometabolite' R-2-hydroxyglutarate (2HG). 2HG-producing IDH mutants prevent the histone demethylation that is required for lineage-specific progenitor cells to differentiate into terminally differentiated cells [24]. Recently, the conditional knock-in mice in which the most common IDH1 mutation, IDH1 (R132H) showed increased numbers of early hematopoietic progenitors. These mice developed splenomegaly and anemia with extramedullary hematopoiesis [21]. Inhibition of IDH1 blocked glioma in differentiation and promotes tumor control [25,26]. Similarly, by using a transgenic mouse model that expresses the IDH2 (R140Q), mutant IDH2 was shown to contribute to AML initiation [27]. Targeted inhibition of mutant IDH2 resulted in reduced leukemia cell proliferation and induced differentiation of leukemic blasts in AML [27,28].

Another class of metabolic genes is amplified or overexpressed in CSCs. Phosphoglycerate dehydrogenase (PHDGH) catalyzes the first step of the serine biosynthetic pathway downstream of glycolysis, which is a metabolic gatekeeper both for macromolecular biosynthesis and serine-dependent DNA synthesis [29]. In primary breast tumors, PHGDH localizes to a genomic region of recurrent copy number gain and its protein levels are elevated in 70% of estrogen receptor (ER)-negative breast cancers [30,31]. Suppression of PHGDH in PHGDH high-expression cancer cell lines caused a strong decrease in cell proliferation, as well as a reduction in serine synthesis [30,31]. Besides breast cancer, PHGDH is also amplified in human melanoma and PHGDH knockdown impairs proliferation of those melanoma cells and breast tumor initiation [30,31]. However, in the established human tumor, PHGDH depletion did not impair tumor maintenance or growth *in vivo* [32]. In addition to PHGDH, other glucose metabolic genes have also been shown important in tumor initiation. The glycolytic pyruvate kinase isoenzyme M2 (PKM2) determines the energy regeneration by converting glucose to lactate (active form, Warburg effect). It is strongly expressed in human cancers [33]. Overexpression of mutant PKM2 reduced glycolysis and led to decreased tumor initiation and growth [33]. However, PKM2 was also shown not to be necessary for tumor maintenance or growth in xenograft mouse models [34]. Another possible metabolic gene affecting CSCs is Hexokinase 2 (HK2), which catalyzes the first committed step of glucose metabolism and is expressed at higher levels in cancer cells than is observed in normal adult tissues [35]. Using *Hk2* conditional knockout mice, HK2 was shown to be required for tumor initiation and maintenance in mouse models of lung cancer and breast cancer [35]. PHGDH, PKM2 and HK2 were all observed to affect tumor initiation, suggesting that those genes may play an important and specific role in CSCs.

The Strategy for Developing Anti-Metabolic Target Inhibitor

How to target those metabolic genes is a critical question in developing effective anti-tumor drugs to inhibit CSCs and human cancer. A couple of metabolic genes affect the CSCs through their metabolic function. Targeting their metabolic functions and inhibiting their metabolites will be necessary to block the self-renewal and induce the differentiation of CSCs. IDH1 and IDH2 mutants produce 'oncometabolite' 2HG, which prevents the histone demethylation and blocks the differentiation of lineage-specific progenitor cells [24]. The inhibitors of IDH1 or IDH2 mutants reduced the levels of 2HG and induced cell differentiation [26,28]. Some metabolic genes such as *SCD1, PHGDH, PKM2* and *HK2* were shown to be important in CSCs or tumor initiation, but the detailed function roles of those metabolic genes in CSCs or human cancer are still not clear [15,32,34,35]. For example, the function of PHGDH in cancer cell setting is independent of its role in serine biosynthesis, instead this gene acts as a modulator of FOXM1 protein stability [36]. PKM2 recently was found playing a non-metabolic role in tumorigenicity by regulating β-catenin transactivation upon EGFR activation in cancer cells [33]. These results suggest that metabolic enzymes, like PHDGH and PKM2, might have a novel function independent of their roles in metabolism and more studies are needed to further understand the novel function of those metabolic genes in CSCs before developing the potent compounds to target those genes.

As CSCs represent a very small population of cancer cells in cancer patients, choosing a suitable preclinical CSCs model will be important for testing the efficacy of those anti-metabolic target inhibitors. Human cancer cell line, patient derived cancer cells, 3D cancer cell culture,cancer mouse model, cancer cell line xenograft mouse model and patient derived xenograft mouse model are commonly used

preclinical models to test the efficacy of anti-tumor drugs [37,38]. For those metabolic genes functioning in CSCs or associated with tumor initiation, the anti-tumor efficacy may not be observed in human cancer cell line or human cancer cell line xenograft mouse model [32,34]. Therefore, 3D cell culture, cancer mouse model and patient derived xenograft mouse model will be very helpful to estimate the efficacy of those metabolic target inhibitors in CSCs and human cancer. For example, 3D gel culture systems have been used to identify and study cell line-derived CSCs and their patterns of differentiation *in vitro* [39]. BCR-ABL transduction/ transplantation CML mouse is a good model to study the biology of CSCs of CML and test the effects of anti-tumor drugs on CSCs [12]. It is necessary to choose the "right" preclinical cancer model for different anti-metabolic target drugs.

The strategy for targeting CSCs

While accumulated experimental evidence have shown the presence of CSCs and their critical roles in cancer growth, metastasis, drug resistance and disease relapse, more efforts have been initiated to identify novel compounds to target CSCs and advance cancer treatment. Several anti-CSCs small molecule compounds including BBI-608 and VS-6063 are being investigated by clinical trials. BBI-608 blocked CSCs self-renewal and induced cell death in CSCs as well as non-stem cancer cells and showed a broad-spectrum anti-tumor and anti-metastatic activity in preclinical studies [40]. BBI-608 has entered a Phase III randomized study in patients with pretreated advanced colorectal cancer [40]. VS-6063, a small molecule FAK inhibitor preferentially targets CSCs and reduces tumor-initiating capacity, as FAK signaling has been shown to be important for the development and survival of CSCs [41]. Although those compounds showed certain encouraging and promising effects on CSC and tumor growth in preclinical studies and small-scale clinical trials, it is currently not known whether those compounds may eradicate the CSCs in cancer patients.

As metabolic changes are crucial for the self-renewal and differentiation of CSCs, it may be a good strategy to combine the chemotherapy drugs, target therapy drugs, the potential anti-CSCs inhibitors and metabolic enzymes inhibitors together. Multiple metabolic targets inhibitors are being developed, such as IDH1/2 inhibitor and PHGDH inhibitor. Recently, the first IDH1 inhibitor AG-120 entered a Phase I clinic trial to evaluate its safety, pharmacokinetics, pharmacodynamics, and clinical activity in advanced hematologic malignancies that harbor an IDH1 mutation. Moreover, the effect of IDH1 inhibition in combination with current cancer drugs and other CSC inhibitors are expected to be investigated in the near future [42]. Intriguingly, AG-221, a novel, oral, potent IDH2 mutant inhibitor was just reported to be well tolerated and show promising initial clinical and pharmacodynamic activity in patients with relapsed and refractory IDH2 mutant hematologic malignancies [43].

The rational for the combination therapy is tumor cell heterogeneity and its implication for drug resistance, and the success of combination chemotherapy in the clinic [44]. In CML, BCR-ABL kinase inhibitor can kill myeloid leukemia cells but not the LSCs [45]. BCR-ABL kinase inhibitor combined with ALOX pathway inhibitor and other anti-CSCs compounds may open up a new avenue for curing CML [12]. Similarly, in IDH2 mutant AML, chemotherapy drugs could rapidly kill most proliferated AML cells. IDH2 inhibitor combined with anti-CSCs drug may kill AML CSCs and prevent the relapsed disease [43]. Those chemotherapy drugs, target therapy drugs, anti-CSCs drugs and anti-metabolic target drugs will give us multiple combination therapy strategies, which may provide the best choice to kill CSCs and cure human cancer (Figure 2).

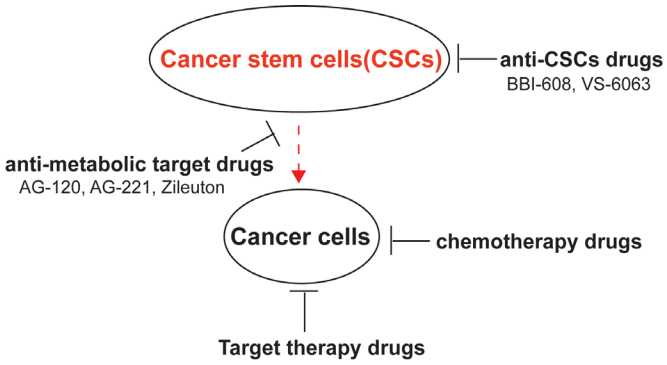

Figure 2: The combination therapy for CSCs and human cancer.

Conclusion

Taken together, altered cell metabolism is considered an essential hallmark of cancer and many metabolic genes or pathways have been shown to be associated with tumor initiation and growth, metastasis and disease relapse [10]. Those metabolic genes are also linked to self-renewal and differentiation of CSCs [12,21,27,34]. Inhibition of those metabolic pathways in combination with current cancer drugs or other anti-CSC inhibitors may provide a curative therapeutic strategy for cancer patients.

Acknowledgment

We thank Con Sullivan for suggestion on the manuscript.

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