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Review Article

Cancer Stem Cell (CSC) Metabolism: A Boon to Cancer Research

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Abstract

Cancer stem cell (CSC) research is one of the main targeted area of research in the present world scenario. CSCs are a small population of cells within the heterogenous tumor mass with self-renewing capacity that can be differentiated into cancer cells. Different avenues of CSC research are looked into to find ways for it's elimination. A very new emerging field of CSC research has been discussed in this review. This review provides an insight into the metabolic phenotypes developed by CSCs and how they are different from the other cancer cells and normal stem cells. The probable reasons behind the maintenance and recurrence of cancer in association with CSC metabolism is vividly discussed. The role of the tumor microenvironment in developing CSCs as well as the heterogeneity of CSC is one of the important areas contributing to CSC cell metabolism. CSC metabolism being an emerging topic of research, possible targets of CSC metabolism has been brought into light. Targeting CSC metabolism can pave the way for CSC eradication as metabolism is the potential cause of CSC heterogeneity and plasticity.

Keywords: Cancer Stem Cells (CSCs); CSC Metabolism; CSC Plasticity; Tumor Microenvironment; Metabostemness; Oncometabolites

Abbreviations

CSC: Cancer Stem Cell; TME: Tumor Microenvironment; OXPHOS: Oxidative Phosphorylation; ALDH: Aldehyde Dehydrogenase; AML: Acute Myeloid Leukaemia; NSCLC: Non-Small Cell Lung Cancer; PDAC: Pancreatic Ductal Adenocarcinoma; ATP: Adenosine Triphosphate; GLUT1: Glucose Transporter 1; STAT3: Signal Transducer And Activator Of Transcription3; HIF1α: Hypoxia Inducible Factor 1 Alpha; HIF2α: Hypoxia Inducible Factor 2 Alpha; DRP1: Dynamin Related Protein1; IMP: Insulin-Like Growth Factor 2 Mrna Binding Protein; PGC-1α: Peroxisome Proliferator-Activated Receptor-Γ Coactivator-1α; Hscs: Haematopoietic Stem Cells; TCA: Tricarboxylic Acid; DNA: Deoxyribo Nucleic Acid; ROS: Reactive Oxygen Species; PML: Promyelocytic Leukaemia Protein; Pparδ: Peroxisome Proliferator-Activated Receptor Δ; ASCT 2: Cysteine-Preferring Transporter 2; LKB1: Liver Kinase B1; LRP6: LDL Receptor-Related Protein 6; EMT: Epithelial Mesenchymal Transition; NF-Kb: Nuclear Factor Kappa-Light-Chain-Enhancer Of Activated B Cells; TGF-B: Transforming Growth Factor-Beta; GOT: Glutamate-Oxaloacetate Transaminases; CAF: Cancer-Associated Fibroblast; BCL2: B-Cell Lymphoma 2; GLS: Glutaminase

Introduction

The varied scientific and technological advances over the past few decades have enabled researchers to inculcate enormous knowledge in the field of cancer biology thus, excavating numerous avenues that lead to the initiation and advancement of cancer. Despite of the progress, cancer still remains the leading cause of death worldwide which has been documented due to the limited availability of the current treatments and the obstinacy of metastatic cells towards such treatment [1]. Tumorigenesis has long been a posed problem of attention [2]. With the advent of cancer stem cell (CSC) theory, scientists have indulged more into establishing the association of tumor initiation, progression and resistance to therapy in relation to CSCs. Developing CSC-specific therapeutics might concomitantly be used with the conventional treatments like, chemotherapy and radiotherapy thus, eradicating cancer (Fulawka, Donizy and Halon, 2014). The experimental evidence of the presence of CSC dates back to 1990s with the dawn of an era in cancer research (Fulawka, Donizy and Halon, 2014). It was hypothesized by Durante in 1874 that, tumors arise from a rare subset of cells having features of stem cell (LR, 2011).

CSCs or tumor - initiating cells are minor population of the heterogeneous tumor mass which are endowed with the capability of producing a primary tumor. CSCs are contemplated as quiescent with the ability to enter the cell cycle at a slow rate [3]. Evidence in support of this idea is determined by the fact that conventional anticancer treatments which preferably target rapidly dividing cells are unsuccessful in destroying CSCs. This subset of tumor cells are responsible for the uncontrolled and sustained growth of malignant tumors even after treatment with consequential role in metastasis and resurgence [1,4]. Thus, removal of CSCs represents one of the crucial treatment blueprint. In addition, CSCs possess the ability of self-renewal and differentiate into non-CSCs, express cell surface markers like, CD34, CD44, CD133 or aldehyde dehydro-

genase (ALDH) enzyme, activate specific signaling pathways such as, Hedgehog, Wnt or Notch, acquire quiescence and contains a vigorous DNA repair system - the characteristics very similar to normal stem cells [5,6]. Either mutagenic changes in the normal stem cells help to initiate oncogenic development and hence CSC formation or differentiated cells acquiring stemness can generate CSCs without requiring mutation of somatic stem cells [7,8]. Evidence of a minor population of cancer initiating cells with stem-like properties were identified by Bonnet and Dick in acute myeloid leukaemia (AML). Later, diverse group of scientists have marked the presence of CSCs in solid tumors, inclusive of melanoma, head and neck, thyroid, breast, lung, liver, stomach, pancreatic, colon, ovarian and prostate cancer [5,9]. Considering CSCs as the source of cancer cells with characteristics of metastatic dissemination and resistance to therapy, eliminating them will be a marked discovery in attaining a permanent solution to patient cure. Due to it's similarity with the normal stem cells, accurate identification and elimination entitles the most important challenge in cancer research at present.

Cellular heterogeneity within tumor masses have been proposed via two models - the stochastic theory, proposed by Peter Nowell in 1976 explains the loss of certain tissue phenotype due to subsequent assembly of mutations is an evolutionary process thus, leading to cancer initiation and development by selection of the most favourable trait. This clonal evolution model states that each cancer cell has the same capability to develop a tumor. Whereas, the cancer stem cell model hypothesizes that, a small group of cells having stem-like property are accountable for disease development. Correspondingly, organization of tumors are hierarchical and sustainable by a defined class of self-renewable cancer cells. These tumor-initiating cells being located at the top of the hierarchy attribute stemness and are responsible for the formation of diverse progeny of extremely proliferative cells constituting the tumor mass [10]. Based on these two concepts, an integration of clonal evolution model and cancer stem cell hypothesis might appoint an assured strategy to eliminate cancer [11]. Another concept that emerged from recent studies is, that CSCs show exceptional degree of plasticity. Certainly, it is a fact that CSCs may appear from varied types of cells like, differentiated cancer cells or normal adult stem cells [10,12]. Evolved from the abovementioned concepts, the potent changes prevailing in the bioenergetics gadgetry of the cancer cells firmly adds to heterogeneity of tumors [13]. To cope with the high bioenergetics demand, tumor mass mostly depends on the extremely plastic character of both cancer cells and the stroma surrounding the tumor. Indeed, this helps in adjusting the CSC metabolism in order to support the increased rate of proliferation which is required for cancer growth and spread [14]. A general accord on the metabolic behaviour of cancer cells have found to be variable which have let them to adapt temporary bioenergetics tragedy triggered by deficiency of nutrients or hypoxia. In support of this view, metabolic heterogeneity has been identified between different types of tumor as well as within the same tumor – thus, validating that resident factors such as, glucose, oxygen, pH and levels of metabolites contribute to form metabolic chambers [14]. Metabolic dysregulation directs oncometabolism, an emerging prominent hallmark of cancer, regarded as an opportunity to target selectively deviant characteristics of the transformed cells [15].

The involvement of different cell types and cellular compartments is ought to occur as cancer cells may derive energy from various sources like, glucose, pyruvate, lactate, acetate, hydroxybutyrate, glutamine, ketones and fatty acids [14]. Furthermore, coexistence of varied metabolic activities within tumors of the same cell type contributes to heterogeneous metabolism [14]. Intratumor metabolic heterogeneity in non-small cell lung cancers (NSCLCs) was recently demonstrated by Hensley., *et al.* which particularly showed that less perfused areas mainly received energy from glucose and highly vascularized areas used other source of fuels such as, amino acids, ketones, fatty acids, and lactate via oxidative phosphorylation, a way of utilizing several different substrates, depending upon their closeness to the blood vessels (Hensley., *et al.* 2016). Distinctive oncometabolic characters of NSCLCs depend on divergent genetic make-up, verifying the involvement of multiple oncogenes affecting tumor metabolism. Further, Kerr., et al. explained the addition of an extra KRASG12D mutant allele is related with a glycolytic transition and a more insistent NSCLC phenotype in mouse model [16]. Accompanied with this is a better understanding of the tumor microenvironment which contributes to metabolic plasticity. The interaction between the catabolic surrounding tumor microenvironment and anabolic cancer cell is well summarized by Reverse Warburg effect, paves the way for incredible therapeutic targets to restrict proliferation of cancer cells, invasion, angiogenesis, drug resistance and recurrence of disease [17,18]. According to this concept, to maintain high proliferative rate, cancer cells attain energy from metabolic intermediates delivered by the neighbouring cells. Notably, lactate, ketones and free fatty acids obtained from activated autophagic and glycolytic processes in the tumor stromal cells have been a fuel source to mitochondrial metabolism [17,19]. The overall framework is indicative of the fact that in tumor microenvironment and in cancer cells, bioenergetics plasticity accomplishes several biochemical demands in simultaneously working tissue compartments. Thus, cancer cell proliferation is attached to the metabolic plasticity and heterogeneity which has emerged as a tool to terminate cell progression [15]. Several researchers have recommended that CSC metabolic features are unique as compared to rest of the differentiated tumor bulk and the normal stem cells (Dando., *et al.* 2015). A metabolic shift from glycolysis to oxidative phosphorylation represent the transition from dormant to a proliferative state. This finding was supported by less mitochondrial respiration and inferior production of ROS which are important in stem cell quiescence maintenance [20]. It is a contrary scenario where few evidences show glucose as the vital nutrient for CSCs [21] and there are few other recent reports stating the use of mitochondrial oxidative metabolic pathway as the energy source [22]. Interpreting these findings in a therapeutic context have revealed two approaches to restrict tumor recurrence through inhibition

of CSC quiescence: (i) CSC induction to enter cell cycle and subsequent removal via conventional cancer therapies and (ii) maintain cells in the dormant state. Both these approaches may be targeted by the use of metabolic procedures [5]. A very recent study in lung and ovarian cancer stem cells showed that upregulated expression of telomerase which is exclusively perceived in normal and cancer stem cells - a trademark of stemness linked to increased glucose and mitochondrial-dependent metabolic pathway [23]. Direct inspection of CSC metabolism has been carried out in a handful of studies, making it an emerging and unexplored area of cancer stem cell research.

Cancer stem cell metabolism

Unlimited growth and high proliferative status is one of the principal characteristics of cancer. To assist unusual sustenance and growth, cancer cells require an increased uptake of nutrients to carry out the metabolic pathways (Hensley., *et al.* 2016). Cancer cells achieve this by regulating various biosynthetic pathways in turn to generate metabolic progenitors to persuade anabolic and energetic urge and perpetuate redox balance (Vazquez., *et al.* 2016). The major pathway utilized by CSCs in order to acquire energy for their survival is the glycolytic pathway with several evidence of using OXPHOS as well. The generation of ATP though is less but, production rate is higher, providing ATP immediately as required hugely by cancer cells [18]. Moreover, glucose catabolism via glycolysis renders metabolic intermediates for amino acid and nucleotide biosynthesis. Thus, the shift from oxidative to glycolytic metabolism effectively helps cancer cells to sustain intolerant conditions like, hypoxia and permit cancer cells to grow, migrate and invade to distant secondary sites [18]. It is not necessary that both glycolysis and oxidative phosphorylation (OXPHOS) are mutually exclusive. For instance, a study of breast CSCs reported high glucose intake simultaneous with low lactate production and higher ATP generation – with continuous mitochondrial increase in potential and capacity in comparison with the differentiated cell population [24].

Glycolysis (Aerobic)

Non-proliferating normal cells under aerobic conditions in the cytoplasm use glycolysis to produce pyruvate which in turn is oxidized to generate energy in the form of adenosine triphosphate (ATP) by the mitochondrial oxidative phosphorylation (OXPHOS) pathway. Whereas, the pyruvate from glycolysis, under anaerobic conditions is governed to produce lactate. In contrast, cancer cells in presence of oxygen are seen to depend much more on glycolysis for producing energy, a phenomenon known as 'Warburg effect' or 'aerobic glycolysis' [25]. This particular metabolic adjustment, although generates ATP much faster is less effective than OXPHOS thus, emanating atypically high uptake of glucose to help ATP production. The keenness of cancer cells towards glucose is arbitrated by the elevated expression of glucose transporter 1 (GLUT1) [26]. Contrasting the glycolytic ability of CSCs and non-CSCs, CSCs show an increased glucose utilization, lactate production and ATP synthesis than non-CSCs and of similar origin, confering magnified glycolysis in CSCs [27]. Elevated rate of glycolysis enables the production of diverse metabolic intermediates which can supply substituted biosynthetic routes to produce macromolecules like, amino acids, nucleosides and lipids - the generated products are then utilized as materials to support high cell division rates and hence, proliferation of cancer cells [26].

Evidence of having glycolytic phenotype in CSCs

In some types of breast cancer, hepatocellular and nasopharyngeal carcinoma, an increased level of Myc oncogene expression is the prime factor of stemness and glycolytic shift [27]. A metabolic transformation from OXPHOS to glycolysis was the reason for amplified CSC characters along with stemness by the redution of ROS in $CD44^{+}$ $CD24^{low}$ $EPCAM^{+}$ breast CSCs [27]. It was demonstrated that the CSC phenotype relies on glycolysis in pancreatic ductal carcinoma (PDAC) as a glycolytic inhibitor, 3 -bromopyruvate diminish self-renewal of aldehyde dehydrogenase 1^{+} ($ALDH^{+}$) - refined CSCs and even reversed resistance by gemcitabine [28]. Additionally, $CD133^{+}$ $CD49f^{+}$ CSCs in hepatocellular carcinoma [29] and radioresistant sphere forming nasopharyngeal CSCs favoured glycolysis as the metabolic formula [27]. Constitutive activation of STAT3 has been noticed in the several types of CSC survival [30]. This constitutive expression of STAT3 in recent studies showed that it triggers a metabolic transformation to aerobic glycolysis downregulating mitochondrial function in primary fibroblasts and STAT3 tumor cell lines [31]. HIF1α upregulation is related with STAT3 - induced glycolysis whereas, downregulated mitochondrial oxidation is independent of HIF1α [31]. It is evident via *in vitro* and *in vivo* mouse model that STAT3 activity is significant for aerobic glycolysis induction and STAT3 inhibition downregulated glycolysis thus, carrying out cell death [31]. Isolated CSCs from xenograft of human glioblastoma have elevated rate of glycolysis due to the expression of HIF1α and HIF2α, upregulating glucose transporter, GLUT1 and decreased level of succinate dehydrogenase, causing mitochondrial dysfunction, producing ROS - enabling low mitochondrial respiration [26].

Oxidative phosphorylation

Several studies overwhelmingly showed the acceptance of mitochondrial respiration and oxidative metabolism in contrast to the old paradigm of glycolysis being the major fuel source. Mitochondrial respiration incorporates a sequence of several chemical reactions occuring in presence of oxygen within the mitochondria for producing ATP. This biosynthetic pathway is much more effective in producing energy than glycolysis, forming 36 ATP molecules per glucose molecule in comparison to two molecules of ATP in glycolysis. Studies recently have proved that a definite sub-population of CSCs show an increase in mitochondrial mass and membrane potential thus, leading to a comprehensive rise in the mitochondrial function [32]. There are evidences that state CSCs utilize less glucose, produce less lactate and are dependent on OXPHOS with low glycolytic flux than their differentiated equivalents. Several tumors with OXPHOS rather than glycolysis as their metabolic energy pathway has been evident -human glioblastomas, melanoma [56]. The mitochondrial mass plays a pivotal role as a biomarker for the CSCs [32].

Evidence of having OXPHOS phenotype in CSCs

Increase in mitochondrial mass within a breast cancer subset have shown induced stem-like features that resulted in elevated metastatic power and are resistant to DNA damage [32]. It is a known fact that redox balance is crucial for maintaining the equilibrium between self-renewal and differentiation of CSCs and normal stem cells [26]. Moreover, maximum of the ROS produced in a cell is derived from the mitochondrial respiration. In order to eliminate ROS and protect cells from oxidative stress, stem cells show low levels of ROS and high antioxidant gene expression [26]. $CD33^{+}$ CSCs, CSCs from primary gliomas and pancreatic cancer prefers OXPHOS over glycolysis for generating energy [26]. The metabolic transition to OXPHOS in $CD133^{+}$ glioblastomas was arranged by Insulin-like growth factor 2 mRNA binding protein (IMP) which has direct interaction with many mitochondrial genes and modulates markers for stemness inclusive of, CD133, Sox2, Oct 4 and Nanog [26]. Whereas, OXPHOS is maintained in $CD133^{+}$ pancreatic cancer by expression of peroxisome proliferator-activated receptor-γ coactivator - 1α (PGC-1α) transcription factor leading to increased OXPHOS [26]. Although, Leukaemia stem cells depicts low ROS levels, an upregulated BCL-2-dependent OXPHOS has been shown and so, inhibiting BCL - 2 decreases OXPHOS thus, eliminating CSCs [33]. Similarly, those breast cancer cell lines with increased mitochondrial mass are augmented with CSC markers, has high tumor initiation ability in murine xenografts, are efficient in forming mammospheres and show resistance to paclitaxel drug treatment [26]. In ovarian cancer, a highly dominated OXPHOS with increased generation of ROS and membrane potential was observed [34]. Another example of OXPHOS - dependent metabolism has been documented in CD133 expressing CSCs of the pancreatic ductal adenocarcinoma [26]. A recent report has provided evidence of higher mitochondrial fission carried out by dynamin-related protein 1 (DRP1) in brain tumor – initiating cells [35].

Other metabolic pathways

Due to the persistence of CSCs in different microenvironment, depending on the availability of nutrients, CSCs derive energy for their survival from various metabolic sources. The utilization of glucose and mitochondrial oxidative metabolism is widely been persuaded. In addition, amino acids mainly glutamine and lysine are used as energy fuels and as well as fatty acids and ketones. Glycolysis and mitochondrial oxidation being the major pathways for CSC survival, secondary pathways such as, fatty acid oxidation, pentose phosphate pathway and glutaminolysis do have mention as well [22].

Metabolism of lipids is a major source of energy and intermediates that are include cellular transformation and cancer progression [26,36]. The strong avidity of cancer cells for lipid is fulfilled either by uptake of exogenous lipid or by generating endogenous via de novo synthesis (Peixoto and Lima, 2018). The synthesis of lipid necessitates several steps to convert citrate obtained from tricarboxylic acid (TCA) cycle into bioactive fatty acids. Haematopoietic stem cells (HSCs) are maintained via fatty acid oxidation pathway – promyelocytic leukaemia protein (PML) and peroxisome proliferator-activated receptor δ (PPARδ), controls the asymmetric division and fate of the HSCs [26,37]. It has been proved that pharmacological drugs or genetic inhibition of any compound of this pathway can exhaust stem cells thus, inferring, that fatty acid oxidation is critical for stemness [37]. Liver kinase B1 (LKB1), a fatty acid oxidation – associated protein is important for maintenance of HSCs [26]. Analysis of metabolism of fatty acid oxidation by $CD133^{+}/CD49f^{+}$ of liver CSCs have been demonstrated [38]. $CD133^{+}$ cells isolated from colorectal cancer patients showed an increase in Wnt/β-catenin activity and lipid content [39]. Fatty acid oxidation associated genes are found to be elevated in CSCs spooled from patients with ovarian cancer [34]. Blocking fatty acid oxidation by a carnitine palmitoyl transferase 1 inhibitor, etamoxir has been found to be exhibited to inhibit formation of spheroid in breast cancer *in vitro* and reduced tumor growth *in vivo* [40]. Likewise, fatty acid synthesis inhibition leading to decrease in CSC marker by Soraphen A, resveratrol and cerulenin has been documented (Corominas-Faja., *et al*. 2014). Recent reports have put forward a subset of leukaemia stem cells express a fatty acid transporter, CD36 can inhabit gonadal adipose tissue microenvironment to induce lipolysis and thus, posing resistance to chemotherapy [41]. Oral squamous cell carcinomas possessing $CD36^{+}$ cells denoted a slow proliferating population of cell expressing CD44, a stem cell marker and high expression of lipid metabolism genes associated with metastasis [42]. Additionally, $CD36^{+}$ cells with high metastatic power are found in other tumors like, melanoma and breast cancers [42]. To elucidate the role of lipid metabolism in CSC biology, further studies should be carried out mainly in respect to the tumor microenvironmental changes.

Metabolism of glutamine being an anabolic process, forms macromolecules with less energetic power [26]. From various tumours including, pancreatic, lung and ovarian cancers, glutamine metabolism plays an exceptional role in CSCs [43]. A pluripotent gene selects glutamine dependency in c-Myc overexpressing cells [44]. Glutamine is able to enter cells via the alanine, serine, cysteine-preferring transporter 2 (ASCT 2) which in turn is hydrolysed into ammonia and glutamate. Glutamate has two fates, either it combines with cysteine and glycine forming reduced glutathione, an antioxidant whereas, glutamate can even get converted into α-ketoglutarate to feed the TCA cycle with intermediates – thus, energy production. This process is effective for cells lacking citrate production and using insufficient glucose (De Berardinis and Cheng, 2010). Sensitivity of CSCs to metformin via AMPK-mTOR pathway was found to be regulated by glutamine metabolism in colorectal cancer cell lines [26]. It has been proposed by another study with PDAC cells that a noncanonical novel glutamine pathway is a requirement for stabilizing oxidative stress in CSCs and tumor expansion [43]. In addition, it has been shown that, glutamate-oxaloacetate transaminases (GOT1 and GOT2) and glutaminase (GLS) expression are elevated in CSCs, the former converts aspartate derived from glutamine to oxaloacetate - this pathway inhibition has developed response in CSCs against radiotherapy, a combination treatment of a glutamine metabolism inhibitor with radiotherapy can be a suitable to treat PDAC [43].

Metabolism of lysine has also been detected to be obligatory to enhance colorectal CSC self-renewal and influence metastasis of liver. CSCs expressing CD110 (thrombopoietin-binding receptor) activate lysine degradation via thrombopoietin signaling, generating acetyl CoA to acetylate LDL receptor-related protein 6 (LRP6). LRP6 activates Wnt signaling pathway as well as helps in self-renewal of $CD110^{+}$ CSCs. Thus, catabolic pathway of lysine regulates the redox state followed by drug resistance, self-renewal and liver metastasis [26].

Effect of tumor niche on CSC metabolism

While investigating the reason behind CSC maintenance and dissemination, a dynamic area of research has been identified-the tumor microenvironment which acts as a niche for CSCs. CSCs inhabits in a typical niche where multivariant interactions take place between the CSCs and the tumor microenvironment thus, promoting biochemical reactions as well as biological paracrine signalling important to maintain the population of CSCs [45]. The cancer stem cell niche is contributed by a plethora of several tumor-specific factors including, fibroblasts, endothelial cells, immune cells, macrophages and adipocytes which cross-connect among themselves as well as with the CSCs residing in the niche. Moreover, the local environmental factors such as, growth factors, cytokines, hypoxia and extracellular matrix, all of which contributes strongly to activate the self-renewing pathways of CSCs. The interaction between the CSCs and the surrounding tumor microenvironment affects cancer cell plasticity thus, emergence of stem-like character mainly due to epithelial-mesenchymal transition (EMT), a dedifferentiation procedure [46]. Tumor microenvironment showing high catabolism with HIF-1α, NF-κB and TGF-β activation concur with ketogenesis and glycolysis which renders features of the CSCs [47]. Glutamine, alanine and glutamate are found to be EMT-associated metabolites in a study which showed that these oncometabolites are related with poor survival in breast cancer [48]. Cancer-associated fibroblasts (CAFs) are the novel components of the tumor niche which undergoes a strict metabolic change to rely on glycolysis than on oxidative phosphorylation for bioenergetics [49]. The migratory capability of CAFs as well as to sustain their secretion of growth factors and cytokines, they use autophagic programs [50]. Indeed, substrates obtained from autophagic reactions, have been found to provide energy needs to PDAC [51]. The CAFs utilize glutamine to provide fuel to CSC niche and support tumor progression [52]. The cancer-associated endothelial cells have high proliferation and migration features and so possess glycolytic mechanism to their anabolic requirements (Ahmed, Escalona and Leung, 2018). CSCs can internalize nutrients rich in energy or mitochondrial compartments which generate energy from the extracellular atmosphere to utilize it in their own bioenergetic pathways. Hypoxia in the tumor microenvironment alters interactions between CSCs and the tumor milieu-interaction of breast CSCs and macrophages with changing macrophages to an immunosuppressive trait with increased expression of HIF - 1α and HIF - 2α has been noticed [48].

Targeting CSC metabolism

Identifying a population of cancer cells with stem-like properties based on a distinct cellular metabolism is an emerging idea of CSC research. Convincing evidence proposes that as a result of metabolic transition the stem-like characteristic has evolved that enables the differentiated cancer cells and the normal stem cells to become more likely susceptible to epigenetic changes. Thus, such cells actually move up the hierarchy due to their acquired pluripotency. With respect to pre-malignant tumor, the metabolic derogation induces changes in CSCs which are classified as 'metabostemness' [1]. Novel therapeutic approaches can be developed targeting the biochemical energy pathways which contributes to CSC maintenance and its diffusion into distant areas. Invariably, histone and DNA epigenetic alterations by tumorigenesis develops metabolic intermediates obtained from mutated metabolic enzymes that are part of glycolysis, OXPHOS and fatty acid oxidation are determined as 'oncometabolites' [1]. No such anticancer therapies till date could make up to the clinical use. So, metabolic networks that enable cancer cell stemness can be a potential target in order to remove the existence of CSCs. The use of surface markers in identifying and targeting CSCs did not serve the purpose of hitting CSCs as intra- and inter-tumor heterogeneity being a strong issue and thus, the origin of CSC plasticity-a fact that is hard to eradicate via the use of surface markers. In relation to this, the identification of metabolic markers can reliably help to identify the cancer cells possessing stem features. In this context, as per the evidence of mitochondrial mass increment, a surrogate marker for increased mitochondrial biogenesis can be utilized for identification of cells with elevated capacity of self-renewal has been provided for several cancers [40]. To track mitochondrial mass independent of their both glycolytic- and OXPHOS-dependent traits using fluorescent probes is an effective way to recognize CSCs [5]. It has been recently demonstrated using MCF7 breast cancer cells through Multitracker, a fluorescent probe that elevated mass of mitochondria enhances anabolic CSCs [5]. Identification of the rare minor group of cells from a heterogeneous tumor mass can be attained by measuring the mitochondrial functional state by the mitochondrial membrane potential - this is linked with the differentiation and malignant spread of the disease [53]. Since, CSC propagation is enhanced by glycolytic and mitochondrial oxidative metabolism, specific inhibitors targeting the metabolic pathways can be used [5]. VLX600, a mitochondria inhibitor that works by targeting mitochondrial respiration, has been found to target cancer cell population that shows quiescence thus, enables inhibition of tumor growth *in vivo* [5]. In addition, several other mitochondrial respiration inhibitors are identified that inhibit dissemination of CSCs which includes, nitazoxanide, closeted, nicodamid and pyrivinium pamoate. Whereas, atovaquone, the antimalarial drug has been proposed to inhibit OXPHOS by inducing Warburg-like effect and activates areobic glycolysis in breast cancer cells [5]. So collectively, either targeting metabolic enzymes directly or halting the mediators upstream in the metabolic pathways can eradicate CSCs in diverse tumor types in combination with the standard conventional therapies [54-56].

Conclusion

The fact that metabolism plays a major role in maintaining the CSCs is a novice field of research with emerging concepts and views to target innovative drugs. Since, CSC solely is an exponentially evolving field of research, still, few avenues are unanswered. Certainly, the role of TME in controlling metabolic plasticity of CSCs is to be deduced and at the same time it must be looked into whether, CSCs themselves show heterogeneity metabolically according to different tumor niche stimuli. The differences in metabolism of CSCs and non-CSCs as well as between CSCs and normal stem cells have to be distinguished clearly. Thus, several hurdles have yet to overcome in order to completely eliminate CSCs - a journey that is worth nurturing.

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Bibliography

1. Turdo Alice., *et al.* "Meeting The Challenge Of Targeting Cancer Stem Cells". *Frontiers in Cell and Developmental Biology* 7 (2019).

2. Ahmed N., *et al.* "Tumour microenvironment and metabolic plasticity in cancer and cancer stem cells: Perspectives on metabolic and immuneregulatory signature niche more resistant ovarian cancer stem cells". *Elsevier* 53 (2018): 265-281.

3. Chen Wanyin., *et al.* "Cancer Stem Cell Quiescence and Plasticity As Major Challenges In Cancer Therapy". *Stem Cells International* (2016): 1-16.

4. Luo Ming and Max S Wicha. "Targeting Cancer Stem Cell Redox Metabolism To Enhance Therapy Responses". *Seminars in Radiation Oncology* 29.1 (2019): 42-54.

5. De Francesco Ernestina M., *et al.* "Cancer Stem Cells (Cscs): Metabolic Strategies For Their Identification And Eradication". *Biochemical Journal* 475.9 (2018): 1611-1634.

6. Snyder V and L Arnold. "Cancer Stem Cell Metabolism and Potential Therapeutic Targets". *Frontiers in Oncology* 8 (2018): 203.

7. Jagust Petra., *et al.* "Metabolism-Based Therapeutic Strategies Targeting Cancer Stem Cells". *Frontiers in Pharmacology* 10 (2019): 203.

8. Rahman M., *et al.* "The Cancer Stem Cell Hypothesis: Failures and Pitfalls". C*ongress of Neurological Surgeons* 68 (2010): 531-545.

9. Al-Hajj M., *et al.* "Prospective Identification of Tumorigenic Breast Cancer Cells". *Proceedings of the National Academy of Sciences* 100.7 (2003): 3983-3988.

10. Pattabiraman Diwakar R and Robert A Weinberg. "Tackling The Cancer Stem Cells — What Challenges Do They Pose?". *Nature Reviews Drug Discovery* 13.7 (2014): 497-512.

11. Apostoli Anthony J and Laurie Ailles. "Clonal Evolution And Tumor-Initiating Cells: New Dimensions In Cancer Patient Treatment". *Critical Reviews in Clinical Laboratory Sciences* 53.1 (2016): 40-51.

12. Brooks Michael D., *et al.* "Therapeutic Implications of Cellular Heterogeneity and Plasticity in Breast Cancer". *Cell Stem Cell* 17.3 (2015): 260-271.

13. Pavlova Natalya N and Craig B Thompson. "The Emerging Hallmarks of Cancer Metabolism". *Cell Metabolism* 23.1 (2016): 27-47.

14. Reina-Campos Miguel., *et al.* "Metabolism Shapes The Tumor Microenvironment". *Current Opinion in Cell Biology* 48 (2017): 47-53.

15. Hanahan Douglas and Robert A Weinberg. "Hallmarks Of Cancer: The Next Generation". *Cell* 144. 5 (2011): 646-674.

16. Kerr Emma M., *et al.* "Mutant Kras Copy Number Defines Metabolic Reprogramming And Therapeutic Susceptibilities". *Nature* (2016).

17. Pavlides Stephanos., *et al.* "The Reverse Warburg Effect: Aerobic Glycolysis in Cancer Associated Fibroblasts and The Tumor Stroma". *Cell Cycle* 8.23 (2009): 3984-4001.

18. Martinez-Outschoorn Ubaldo E., *et al.* "Cancer Metabolism: A Therapeutic Perspective". *Nature Reviews Clinical Oncology* 14.1 (2017): 11-31.

19. Martinez-Outschoorn Ubaldo E., *et al.* "Stromal–Epithelial Metabolic Coupling in Cancer: Integrating Autophagy and Metabolism In The Tumor Microenvironment". *The International Journal of Biochemistry and Cell Biology* 43.7 (2011): 1045-1051.

20. Kobayashi Chiharu I and Toshio Suda. "Regulation of Reactive Oxygen Species In Stem Cells And Cancer Stem Cells". *Journal of Cellular Physiology* 227.2 (2012): 421-430.

21. Liu P-P., *et al.* "Metabolic Regulation of Cancer Cell Side Population By Glucose Through Activation Of The Akt Pathway". *Cell Death and Differentiation* 21.1 (2014): 124-135.

22. Peiris-Pages M., *et al.* "Cancer Stem Cell Metabolism". *Breast Cancer Res* 18 (2016): 55.

23. Lau Eunice Yuen-Ting., *et al.* "Cancer Stem Cells and Their Microenvironment: Biology and Therapeutic Implications". *Stem Cells International* (2017): 1-11.

24. Vlash Erina., *et al.* "Metabolic Differences In Breast Cancer Stem Cells And Differentiated Progeny". *Breast Cancer Research and Treatment* 146.3 (2014): 525-534.

25. Warburg O. "On The Origin Of Cancer Cells". *Science* 123.3191 (1956): 309-314.

26. Peixoto J and J Lima. "Metabolic Traits Of Cancer Stem Cells". *The Company of Biologists* (2018).

27. Sancho Patricia et al. "Hallmarks Of Cancer Stem Cell Metabolism". *British Journal of Cancer* 114.12 (2016): 1305-1312.

28. Isayev Orkhan., *et al.* "Inhibition Of Glucose Turnover By 3-Bromopyruvate Counteracts Pancreatic Cancer Stem Cell Features And Sensitizes Cells To Gemcitabine". *Oncotarget* 5.13 (2014): 5177-5189.

29. Shen Yao-An., *et al.* "Metabolic Reprogramming Orchestrates Cancer Stem Cell Properties in Nasopharyngeal carcinoma". *Cell Cycle* 14.1 (2015): 86-98.

30. Sherry Maureen M., *et al.* "STAT3 Is Required for Proliferation and Maintenance Of Multipotency In Glioblastoma Stem Cells". *Stem Cells* 27.10 (2009): 2383-2392.

31. Demaria Marco., *et al.* "A STAT3-Mediated Metabolic Switch Is Involved in Tumour Transformation and STAT3 Addiction". *Aging* 2.11 (2010): 823-842.

32. Farnie Gillian., *et al.* "High Mitochondrial Mass Identifies A Sub-Population Of Stem-Like Cancer Cells That Are Chemo-Resistant". *Oncotarget* 6.31 (2015): 30472-30486.

33. Lagadinou Eleni D., *et al.* "BCL-2 Inhibition Targets Oxidative Phosphorylation and Selectively Eradicates Quiescent Human Leukemia Stem Cells". *Cell Stem Cell* 12.3 (2013): 329-341.

34. Pastò Anna., *et al.* "Cancer Stem Cells from Epithelial Ovarian Cancer Patients Privilege Oxidative Phosphorylation, And Resist Glucose Deprivation". *Oncotarget* 5.12 (2014): 4305-4319.

35. Xie Qi., *et al.* "Mitochondrial Control by DRP1 In Brain Tumor Initiating Cells". *Nature Neuroscience* 18.4 (2015): 501-510.

36. Santos Claudio R and Almut Schulze. "Lipid Metabolism in Cancer". *FEBS Journal* 279.15 (2012): 2610-2623.

37. Ito Keisuke., *et al.* "A PML–PPAR-Δ Pathway for Fatty Acid Oxidation Regulates Hematopoietic Stem Cell Maintenance". *Nature Medicine* 18.9 (2012): 1350-1358.

38. Chen Chia-Lin., *et al.* "NANOG Metabolically Reprograms Tumor-Initiating Stem-Like Cells Through Tumorigenic Changes in Oxidative Phosphorylation and Fatty Acid Metabolism". *Cell Metabolism* 23.1 (2016): 206-219.

39. Tirinato Luca., *et al.* "Lipid Droplets: A New Player in Colorectal Cancer Stem Cells Unveiled By Spectroscopic Imaging". *Stem Cells* 33.1 (2015): 35-44.

40. De Francesco Ernestina Marianna., *et al.* "Targeting Hypoxic Cancer Stem Cells (Cscs) With Doxycycline: Implications for Optimizing Anti-Angiogenic Therapy". *Oncotarget* 8.34 (2017).

41. Ye Haobin., *et al.* "Leukemic Stem Cells Evade Chemotherapy By Metabolic Adaptation To An Adipose Tissue Niche". *Cell Stem Cell* 19.1 (2016): 23-37.

42. Pascual Gloria., *et al.* "Targeting Metastasis-Initiating Cells Through the Fatty Acid Receptor CD36". *Nature* 541.7635 (2016): 41-45.

43. Li Doudou., *et al.* "Inhibition of Glutamine Metabolism Counteracts Pancreatic Cancer Stem Cell Features And Sensitizes Cells To Radiotherapy". *Oncotarget* 6.31 (2015).

44. Lu Weiqin., *et al.* "Cancer Metabolism: Is Glutamine Sweeter Than Glucose?". *Cancer Cell* 18.3 (2010): 199-200.

45. Plaks Vicki., *et al.* "The Cancer Stem Cell Niche: How Essential Is the Niche in Regulating Stemness Of Tumor Cells?". *Cell Stem Cell* 16.3 (2015): 225-238.

46. Lau Eunice Yuen-Ting., *et al.* "Cancer Stem Cells and Their Microenvironment: Biology And Therapeutic Implications". *Stem Cells International* (2017): 1-11.

47. Fiorillo Marco., *et al.* ""Energetic" Cancer Stem Cells (E-Cscs): A New Hyper-Metabolic and Proliferative Tumor Cell Phenotype, Driven By Mitochondrial Energy". *Frontiers in Oncology* 8 (2019): 677.

48. Peiris-Pagès M. "Cancer Stem Cell Metabolism". *Breast Cancer Research* 18 (2019): 55.

49. Vander Heiden MG., *et al.* "Understanding the Warburg Effect: The Metabolic Requirements Of Cell Proliferation". *Science* 324.5930 (2009): 1029-1033.

50. Martinez-Outschoorn Ubaldo E., *et al.* "Autophagy In Cancer Associated Fibroblasts Promotes Tumor Cell Survival". *Cell Cycle* 9.17 (2010): 3515-3533.

51. Sousa Cristovão M., *et al.* "Pancreatic Stellate Cells Support Tumour Metabolism Through Autophagic Alanine Secretion". *Nature* 536.7617 (2016): 479-483.

52. Yang Lifeng., *et al.* "Targeting Stromal Glutamine Synthetase In Tumors Disrupts Tumor Microenvironment-Regulated Cancer Cell Growth". *Cell Metabolism* 24.5 (2016): 685-700.

53. Ye Xiao-Qun., *et al.* "Heterogeneity of Mitochondrial Membrane Potential: A Novel Tool To Isolate And Identify Cancer Stem Cells From A Tumor Mass?". *Stem Cell Reviews and Reports* 7.1 (2011): 153-160.

54. LRO. "Stem Cells and Cancer Stem Cells. Incancer Stem Cells - The Cutting Edge". In Tech 3-28.

55. Gottlieb E., *et al.* "Cancer Metabolism At A Glance". *Journal of Cell Science* 129 (2016): 3367-3373.

56. Simsek Tugba., *et al.* "The Distinct Metabolic Profile Of Hematopoietic Stem Cells Reflects Their Location In A Hypoxic Niche". *Cell Stem Cell* 7.3 (2010): 380-390.

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