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REVIEW

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The role of tumor microenvironment on cancer stem cell fate in solid tumors

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Abstract

In the last few decades, the role of cancer stem cells in initiating tumors, metastasis, invasion, and resistance to therapies has been recognized as a potential target for tumor therapy. Understanding the mechanisms by which CSCs contribute to cancer progression can help to provide novel therapeutic approaches against solid tumors. In this line, the effects of mechanical forces on CSCs such as epithelial-mesenchymal transition, cellular plasticity, etc., the metabolism pathways of CSCs, players of the tumor microenvironment, and their influence on the regulating of CSCs can lead to cancer progression. This review focused on some of these mechanisms of CSCs, paving the way for a better understanding of their regulatory mechanisms and developing platforms for targeted therapies. While progress has been made in research, more studies will be required in the future to explore more aspects of how CSCs contribute to cancer progression.

Keywords Cancer stem cells, Tumor microenvironment, Metabolism, Solid tumors, EMT, Cellular plasticity, Signaling pathways

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Introduction

Cancer is still one of the primary reasons of death all around the world with several complications such as metastasis, heterogeneity in cells, invasion, relapse, and therapy resistance [1]. In the last two decades, the discovery of the origin of cancer has led to a better understanding of the mechanism of malignancies. In this line, the model of cancer stem cells (CSCs) has been widely accepted in different malignancies as potential factors in charge of invasion and therapy resistance [2–5]. Despite advances in screening programs and the development of new immunotherapy methods, eradication or representation of a defined method to identify, recognize, and isolate the population of turmeric cells has not yet succeeded and remains unknown. One of the challenges ahead of the eradication of CSCs is reckoned to stem from the plasticity and heterogeneity that these cells show in the microenvironment of a tumor [6]. This plasticity could take root in the metabolism of these cells, which has been introduced to be one of the ways

through which this fraction of cells could support their feature of growth and tumorigenesis [7]. The metabolism of CSCs has received special attention as the key to adjusting to the severe condition of the tumor microenvironment (TME), which contributes to cancer cells thriving, expanding, and overcoming immune cells [8]. The plasticity and heterogeneity of CSCs in their metabolism pathways could be rooted in different factors. One of which is assumed to be the TME consisting of factors like tumor-associated macrophages (TAM), cancer-associated fibroblasts (CAF), endothelial cells (ECs), immune cells and the received signals from the presented cells in TME, playing a vital role in influencing and regulating the population of CSCs and their metabolism reprogramming [8, 9]. Therefore, considering the significance of TME in the regulation of the metabolism of CSCs, in this review, we will focus on the effects of mechanical forces on CSCs and the metabolism of CSCs, players of the TME and the influence of the TME on regulating the metabolism of CSCs.

The origin of cancer stem cells and their contribution to cancer progression

Tumor-initiating cells (TICs) also known as CSCs are subpopulations of tumor cells that initiate tumors and cause relapses. Cells that can self-renew are designated as cancer stem cells. These cells divide and give rise to other cells that give rise to different kinds of cancer [10–12]. CSCs develop from tumor progenitor cells, stem cells, or dedifferentiated cells that acquire CSC characteristics during tumor initiation. Transformation can occur during regeneration and as a result of infections, toxins, radiation, or metabolic influences causing mutations [13]. The transformation can also occur as a result of infections, toxins, radiation, or metabolic influences. At this time, tumor suppressors are inactivated promoting uncontrolled growth of the cells [14]. Consequently, stem cells acquire stem cell characteristics as a result of de-differentiation. For stem cells to transform, different genomic changes are needed that allow them to proliferate in uncontrolled, niche-independent ways [15]. It is believed that stem cells and their progeny can be transformed by only a few genomic changes since stem cells have unlimited growth potential. Even differentiated intestinal epithelial cells can become CSCs in mice, according to recent studies [16, 17]. The liver has also been shown to produce tumors from adult differentiated cells, tissue-resident stem cells, or their progeny [18, 19]. Only the CSC population can initiate tumor growth in tumors generated from CSCs, resulting in a unidirectional hierarchy. To maintain their pool of CSCs, CSCs divide asymmetrically at tumor initiation. Transient amplifying cells are generated from asymmetric divisions and undergo symmetric divisions, resulting in high proliferation rates [20, 21]. For the first time, the hypothesis of CSCs was proved by Lapidot et al. [22], who found out that a rare population isolated from myeloid leukemia (AML) can initiate tumorigenesis in severe combined immune-deficient (SCID) mice [22]. This minority subgroup whose footsteps have been found in numerous tumors, including melanoma [23], breast cancer [24], AML [25], gastrointestinal cancer [26], colorectal cancer [27], glioblastoma [28], pancreas cancer [29], and lung cancer [30] is believed to derive from normal tissue stem cells or the dedifferentiation of normal cancer cells. Resistance to therapy, recurrence, tumor growth, and metastasis have been attributed to the presence of this small fraction of the cells in their residence tumor [31, 32]. Properties like self-renewal, remaining in the G0 phase, and expression of molecules related to the drug efflux transport system in CSCs contribute to drug resistance, and the capacity to initiate tumorigenesis [28, 33]. Concerning the fact that the markers expressed by CSCs are also expressed by the other populations of stem cells like adult tissue residents and embryonic stem cells that can also vary among different tumor types lead to limiting the specifying biomarkers of CSCs [34]. However, over-expression of surface markers such as CD133, CD44, epithelial cell adhesion molecule (EpCAM, CD326) [35–42], homeobox protein NANOG, octamer-binding transcription factor 4 (OCT4), sex-determining region Y HMG-box 2 (SOX2) [43] sphere formation [44], aldehyde dehydrogenases 1A1 (ALDH1A1) activity [45] and ATP-binding cassette sub-family G member 2 (ABCG2) [46] have been detected and used for isolation of CSCs. It is not surprising that CSCs take advantage of signaling pathways like Wnt/β-catenin, c-MYC, Janus kinase /signal transducer and activator of transcription (JAK/STAT), Hedgehog/Notch, etc. [47, 48] to preserve some of their properties like mechanical forces and metabolism shifting and regulation, plasticity, self-renewal, etc. [49]. It is notable that metabolism alterations in these cells are closely related to the mentioned signaling pathways, which will be discussed in the next parts.

Metabolism feature of CSCs

To survive in the wide range of micro-environmental conditions they experience, CSCs are likely designed to obtain energy from various sources, depending on the available substrates. There is sufficient support for a glucose-based and oxidative-based metabolism [50]. Furthermore, CSCs may use different amino acids as fuel, such as glutamine and lysine. Acetyl-CoA is generated from glycolysis, and fatty acid oxidation is catabolized by the tricarboxylic acid cycle (TCA) cycle and oxidative phosphorylation (OXPHOS) in normal cells'

mitochondria to make ATP. Through the well-known Warburg effect, cancer cells, unlike normal cells, increase the glycolytic flux in aerobic conditions [50]. Additionally, the glycolytic degradation of glucose creates the building blocks for the biosynthesis of nucleotides and amino acids. As a result, the transition from oxidative to glycolytic metabolism effectively gives cancer cells the ability to endure difficult conditions with low oxygen levels. It causes cancer cells to proliferate, move to distant regions, and attack other tissues. It has been established that CSCs have a different metabolism from non-CSCs, whose phenotype, at least in part, resembles that of regular stem cells, which mainly consume glucose. The development of pluripotent markers coincides with metabolic reprogramming toward glycolysis and indications of mitochondrial involution in induced pluripotent stem cells [51]. However, many studies have suggested that secondary pathways such as fatty acid oxidation, PPP pathway, and glutaminolysis, as well as mitochondria and OXPHOS, may be essential for CSC metabolism [52] (Fig. 1). The uncontrolled expansion of tumor cells requires to be supported by increased uptake of nutrients [53, 54]. Metabolism adaptation has been introduced as one of the ways through which cancer cells get to supply their energy demands. The difference between normal cell metabolism and cancer cells metabolism such as increased glucose uptake and lactate production in the presence of oxygen was first noticed by Otto Warburg [55, 56]. The metabolism shifting can be applied to CSCs, although in recent experiments, the metabolism of CSCs has been the topic of debate, as controversial data on whether CSCs mostly rely on glycolysis or mitochondria-related metabolism have been reported [57].

Glucose is a source of energy for CSCs

The significance of glucose for CSC preservation and proliferation in various cancer cells, including the brain, lung, breast, liver, osteosarcoma, nasopharyngeal cancer, and glioblastoma, has been thoroughly demonstrated by numerous studies. Liu et al. recently showed that a subpopulation of cells with stem-like characteristics primarily relies on glucose as a fuel source by employing a panel of cancer cell lines. In addition, glucose was able to raise the proportion of cancer stem-like cells, which had increased levels of various glycolytic enzymes and lactate generation. The number of CSCs was also decreased, and their capacity to develop tumors in vivo was interfered with by inhibiting glycolysis [58–62]. When the activity of the mitochondrial complex I was blocked for the loss of FBP1, an acceleration of glycolysis and the acquisition of stem characteristics were seen. Additionally, it has been demonstrated that overexpressing FBP1 reduces the number of cancer cells with stem-like features in basal-like breast cancer cells and prevents the formation of tumor spheroids in vivo. FBP1 promotes the gluconeogenic pathway while suppressing glycolysis [61, 63]. Further supporting these findings, Shen et al. recently showed that compared to CD133-cells, a subgroup of hepatic cancer cells selectively activate aerobic glycolysis and inhibit the gluconeogenic pathway. The glycolysis rate and capacity of the CSC-like subgroup were increased, and the glycolytic enzymes HK2, GLUT1, pyruvate dehydrogenase kinase (PDK), and PGAM1 were all upregulated. In contrast, the gluconeogenic enzymes PEPCK and G6PC were down-regulated [60]. These findings imply that the primary catabolic pathway of CSCs from various tumor types is glycolysis, which inhibits anabolic de novo synthesis. This has also been mentioned in colorectal cancer (CRC), where CSCs have recently been found to have an odd metabolic signature. They combined high-resolution unbiased metabolomics with transcriptome analysis of five microarray datasets of $CD133^+$ and CD133 cell subpopulations derived from CRC cell lines and patients. This made it possible to depict the metabolic activity of CSCs, which was characterized by up-regulated fatty acid production and down-regulated expression of genes and metabolites from the glycolytic pathway and TCA cycle [64]. Recently, the metabolic profile of breast cancer cells grown as spheroids or in adherent conditions was examined using high-throughput data from proteome and targeted metabolomics analyses. The enhanced activity of the pyruvate kinase M2 isoform, lactate dehydrogenase, and glucose 6-phosphate dehydrogenase in cancer stem-like cells suggests a switch from mitochondrial oxidative phosphorylation toward fermentative glycolysis. In Goidts et al., RNA interference (RNAi) was used to screen the entire human kinome and phosphatome to identify genes and pathways essential for glioblastoma CSC survival. They discovered numerous genes involved in metabolism, particularly the glycolytic enzymes including 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 (PFKFB4), pyruvate kinase M2 hypotype (PKM2), and PDK-1, which were crucial for maintaining brain CSCs [65, 66]. Together, these findings support the unique function of glucose as the primary fuel for CSCs, and oxidative pathways may be adversely affected by the low oxygen availability in the hypoxic CSC niche. In this context, it has been demonstrated that TICs isolated from human glioblastoma xenografts use glycolysis to produce ATP and prefer low-oxygen environments to maintain their stemness characteristics and tumor-forming potential [67]. Hypoxia's role in CSC proliferation has been thoroughly studied, and it has been linked to glucose dependence, especially in the quiescent phenotype of CSCs. Mahase and colleagues have explored the potential

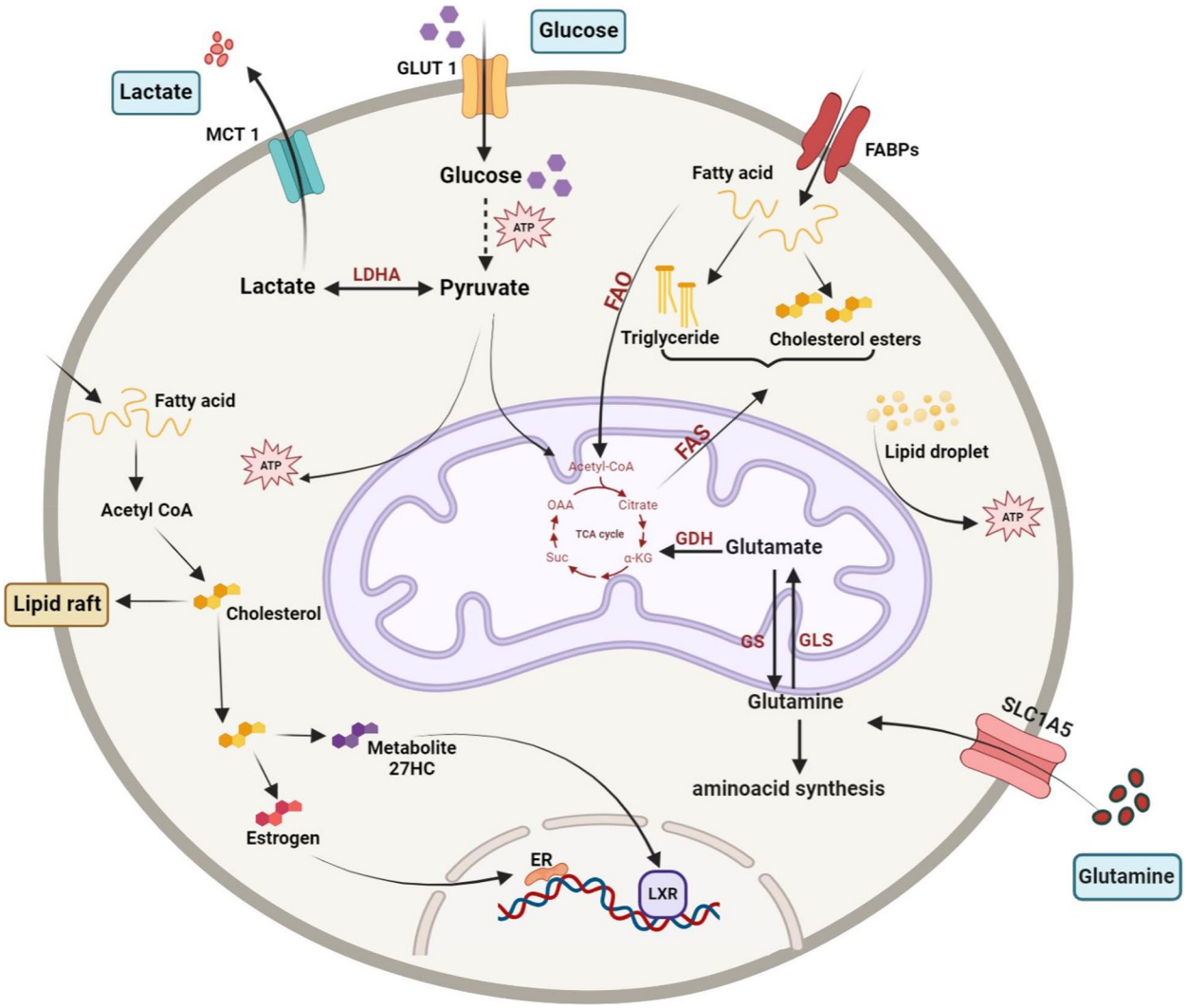

Fig. 1 Metabolic adaptation in CSCs and cancer cells. Even when there is a sufficient supply of oxygen, cancer cells frequently adopt the Warburg effect or aerobic glycolysis, relying on glycolysis rather than OXPHOS for ATP production. As a result, the pyruvate is turned into lactate and transferred outside of the cell, where it acidifies the tumor microenvironment and creates an immune-suppressive environment. Additionally, glutamine becomes more important to cancer cells for anabolic processes (such as the production of nucleotides and other amino acids) that promote cell growth and replenish the TCA cycle. In addition, glutamine plays a crucial role in glutathione production, which is essential for chemo-resistance. In cancer, fatty acid oxidation (FAO) and fatty acid synthesis (FAS) are increased to supplement glycolysis for energy and provide the necessary membrane components for accelerated cell development. Furthermore, the composition of their membranes and the signaling that promotes proliferation and invasion in cancer cells rely on the production of cholesterol

for various processes, such as CSC proliferation and metabolic changes, to explain the resistance to antiangiogenic medications in the therapeutic management of glioblastoma patients. It has been demonstrated that the formation of intra-tumor hypoxia following the injection of antiangiogenic drugs increases the subpopulation of cells with stem characteristics in glioblastoma, breast cancer, and lung cancer [68–70]. Hypoxia-inducible factor-1 (HIF-1) enables the transcription of genes involved in glucose regulation and ATP synthesis and has been related to an increase in the $ALDH^+$ population. Hexokinase-2, the first enzyme in the Embden-Meyerhoff/glycolytic pathway, is abnormally expressed by glioma cells in perinecrotic regions. Its overexpression is related to glioblastoma cell proliferation and aerobic glycolysis. Additionally, an increase in PDK-1 caused by HIF-1α-mediated action prevents pyruvate dehydrogenase activity and TCA cycle entry [69–71]. Glycolysis, which involves the production of nicotinamide adenine dinucleotide (NADH), pyruvate, and two ATP molecules,

seems to be the preferred metabolism pathway by cancer cells. Cancer cells change their metabolism pathways to glycolysis to maintain abnormal growth, while normal cells are more dependent on OXPHOS, ATP, lactate, and pyruvate production [72]. The reprogrammed metabolism to glycolysis has been shown to take over in different types of CSCs like breast cancer, osteosarcoma [73], ovarian CSCs [74], lung and colorectal CSCs [58], hepatocellular carcinoma [75], brain cancer [76]. Similar evidence for metabolism switching to glycolysis has been observed in induced pluripotent stem cells (iPS) [77]. Glycolysis could guarantee fast proliferation through glucose-6-phosphate (G6P) production that can be used in the formation of ribose groups and, consequently, the synthesis of nucleotides that is necessary for the rapid replication of cancer cells [78–80]. Increased expression of genes imprinted in glucose-related metabolism genes like glucose transporter 1 (GLUT-1), PDK-1, hexokinase 1 (HK-1), and c-Myc makes up the expansion of the population of CSCs, extends the lifespan of cells and their immortalization [77, 81]. Furthermore, the interference of oncogene transcription factors, including NANOG, OCT4, Wnt, Myc, K-Ras, and HIF-1α in the shift of CSCs to glycolysis, could provide beneficial support [82–85], which is consistent with the fact that reduction of mitochondrial-related metabolism and downregulation mitochondrial genes is associated with enhanced expression of epithelial-mesenchymal transition (EMT) genes linked to stemness [86]. Furthermore, maintaining stemness in some cancer types seems to be closely related to reduced mitochondrial-dependent metabolism [73, 87, 88]. On the other hand, considering the enhanced mitochondrial DNA and mature cell gene expression and decreased expression of stemness-related genes during differentiation, indicate that CSCs would likely tend to shift glycolysis [89]. Above all, low reactive oxygen species (ROS) production, enhanced detoxification system, creation of an acidic environment, and escaping the immune system cells, which consequently help the invasion and metastasis, are other beneficial effects for CSCs through metabolic reprogramming [90–92].

The OXPHOS phenotype in CSCs

Contrary to the conventional belief that CSCs primarily exhibit a glycolytic phenotype, several studies indicate that CSCs preferentially utilize mitochondrial respiration and oxidative metabolism. Numerous independent researchers have presented evidence of decreased glycolytic flow and enhanced mitochondrial-driven ATP generation. For example, it has been discovered that mitochondrial OXPHOS and fatty acid oxidation enzymes are up-regulated in CSCs isolated from individuals with ovarian cancer [93]. Consequently, current analysis and comparisons of the metabolic characteristics of spheroids developed from both ovarian and cervical carcinoma cells were completed. Intriguingly, the researchers noted that spheroid CSCs had a TCA cycle metabolism that is different from non-CSCs. Gao et al. recently FACS sorted CSCs from small cell lung cancer cells using a similar experimental strategy to examine their metabolic condition. Compared to their non-stem counterpart, CSCs were discovered to have a stronger dependence on OXPHOS and mitochondrial activity [94, 95]. It has been shown that CSCs isolated from gliomas use less glucose, generates less lactate, and keep their levels of ATP from oxidative phosphorylation high. In $CD133^+$ human glioblastoma cells, there has been a similar tendency toward using mitochondrial respiration over glycolysis, with a mechanism relying on the insulin-like growth factor 2 mRNA-binding protein. The researchers specifically showed that IMP2, which is involved in controlling oxygen consumption rate (OCR), mitochondrial mass, and the expression of various stemness markers, including CD133, SOX2, OCT4, and NANOG, is more highly expressed in $CD133^+$ glioblastoma cells. Given that IMP2 directly interacts with numerous genes for mitochondrial complexes to drive the assembly of complexes I and IV, it is reasonable to suppose that the increased IMP2 expression found in glioblastoma CSCs may result from the cells' high need for OXPHOS [96, 97]. In a mouse model of pancreatic cancer, Viale et al. also examined the population of dormant cells that survived the deletion of the oncogene RAS. It has been established that these inactive cells have stem-like characteristics and depend on mitochondrial activity and oxidative phosphorylation rather than glycolysis and glutaminolysis [98]. Notably, the transcription co-activator peroxisome proliferator-activated receptor gamma, co-activator 1 alpha (PPARGC1A, referred to as PGC-1), has been linked to the ability of cancer cells to metastasize. As demonstrated by employing human invasive breast tumor samples, PGC-1 has been clinically shown to relate oxygen consumption, OXPHOS, and mitochondrial biogenesis with the increased migratory and invasive potential of cancer cells [99]. The upregulation of PGC1 has been seen in circulating tumor cells and breast CSCs, where its suppression decreases stemness qualities, supporting the involvement of PGC1 in CSC maintenance and proliferation via mitochondrial activity. These findings suggest that the biology of CSCs depends on intact mitochondrial activity and function. Since CSCs produce more mitochondrial mass and membrane potential, more mitochondria-derived ROS are produced, and they consume more oxygen than differentiated cells in the tumor bulk; mitochondrial biogenesis is recognized as a crucial characteristic of CSCs in this setting

[93, 100–106]. According to a recent study, brain tumor-initiating cells, which show increased mitochondrial fission mediated by dynamin-related protein 1, play an essential role in mitochondrial dynamics (DRP1). It's remarkable to note that DRP1, which inhibits mitochondrial fission by severing the membrane stalk between two developing daughter mitochondria, was associated with a poor prognosis in glioblastoma, indicating that inhibiting mitochondria in BTICs may be a valuable strategy to decrease the progression of the disease [107]. Notably, the proliferation of stem-like cells in breast epithelium has been linked to the appropriate fragmentation and segregation of the mitochondrial population and the efficient preservation of the mitochondrial network. It should be noted that stem cells asymmetrically divide into one daughter cell that keeps stemness characteristics and another cell that is subjected to a differentiation program to contrast tissue aging and promote regeneration. Katajisto et al. showed that stem cells sort mitochondria using age by examining the destiny of old and young organelles during stem cells' asymmetrical division in the human breast epithelium. In addition, aged mitochondria are distributed asymmetrically among daughter cells by stem cells, with cells getting younger mitochondria being destined to keep stem features. To do this, stem-like cells use a highly effective method that includes mitochondrial spatial segregation. The loss of stem characteristics in the progeny cells may result from disrupting such carefully controlled processes during mitochondrial fission [108]. Following these findings, it has been shown that activating many oncogenic pathways, such as MAPK, contributes to mitochondrial fragmentation, which can be seen as an initial stage in reprogramming cells to become pluripotent [109]. Similarly, it has been demonstrated that c-Myc stimulates mitochondrial fusion in breast cancer cells to enhance clonogenic development, a characteristic of cells with stem characteristics. Notably, a mitochondrial retrograde signaling pathway has been demonstrated to initiate an EMT-like reprogramming, leading to altered morphology and increased migratory and invasive potential in human mammary epithelial cells. Maintaining a healthy mitochondrial population is required for maintaining and propagating the stem traits, so targeting these organelles in a therapeutic setting may represent a valuable strategy to eradicate CSCs. Based on these observations, mitochondrial functions and energetic dynamics may be involved in CSC propagation [110, 111]. On the other hand, mitochondria-dependent metabolism and OXPHOS could remain active and a source of energy supply in CSCs. Evidence indicated the usage of mitochondrial-dependent metabolism, increased mitochondrial ROS, and mass oxygen consumption in CSCs in Lung cancer [112], glioblastoma [97], Papillary Thyroid Carcinoma [113], Leukemia [114], ovarian cancer [115], and breast cancer [116]. It seems that the required ATP from OXPHOS plays an essential role in the metastatic and invasive properties of CSCs, which implies the possible role of mitochondria in CSCs [117, 118]. Additionally, ROS generation, which is mediated by mitochondrial metabolism, could take part in the progression of tumor and malignancy transformation [119]. Moreover, the increased mitochondrial mass has been located in invasive CSCs linked to chemotherapy resistance [120]. The activation of peroxisome proliferator-activated receptor-gamma co-activator one alpha (PGC1α), whose overexpression has been found in turmeric cells and the reduced stemness of breast CSCs is associated with the inhibition of this factor, seems to take a role in high mitochondrial metabolism in cancer cells [99, 121, 122]. The vulnerability of CSCs to treatment with inhibitors of OXPHOS has been illustrated in different studies, so far the repression of self-renewal and stemness properties and substantial temporary tumor growth/formation was observed during treatment with metformin as an inhibitor of the OXPHOS complex I [103, 123–125]. Therefore, mitochondrial metabolism can be a target to eliminate CSCs. There is raising evidence that not only CSCs take a balance between glycolysis and OXPHOS to make use of both of them, but also glutamine and lipid metabolism are intertwined in the metabolism of these cells. Glutamine takes part in the preparation of elements like amino-nitrogen and carbon, which are subsequently used in nucleotide, amino acid, and lipid production during the shortage of glucose to provide the energy needed for CSCs [126–128]. Furthermore, the role of lipids in the construction of cell membranes, energy consumption, and signaling transduction modifiers should be considered as a part of CSCs metabolism [129, 130]. Accumulation of unsaturated lipids like monounsaturated FAs (MUFAs) in CSCs has been confirmed by several studies. Stimulation of pathways involved in stemness was mediated by the enzyme stearoyl-CoA desaturase implicated in lipid desaturation. De novo through FA synthase also helps the survival and preservation of the properties of CSCs and is counted as a curial factor for recurrence and metastasis of the tumor [131–133]. In a recent study, it has been demonstrated that tyrosine kinase inhibitor (TKI) resistance in non-small cell lung cancer (NSCLC) could be caused by mutated epidermal growth factor receptor (EGFR) which uses the regulation of the fatty acid synthase (FASN) to induce TKI [134]. Taken together, it seems this capacity of switching between different metabolism statuses depending on the needs has made CSCs a challenging target to study, in light of the hypothesis of the plasticity of these cells.

Other metabolic sources for CSCs

The metabolic examination of $CD133^+/CD49f^+$ cells selected from hepatocellular carcinoma (HCC) revealed that liver-derived CSCs utilize fatty acid oxidation. In $CD133^+$ cells isolated from CRC patients, there was an increase in lipid content and Wnt/B-catenin activity. In CSCs isolated from ovarian cancer patients, fatty acid oxidation-related genes were up-regulated. Etomoxir, a carnitine palmitoyltransferase-1 inhibitor, has also been demonstrated to limit spheroid formation in breast cancer in vitro and reduce tumor growth in vivo by blocking fatty acid oxidation [93, 135–137]. On the other hand, the expression of CSC markers and the efficiency of sphere formation have been demonstrated to decrease when fatty acid synthesis is inhibited by Soraphen A, cerulenin, and resveratrol [138–140]. However, more research is necessary to fully understand the function of lipid metabolism in CSC biology, especially in response to unique alterations in the tumor microenvironment. In contrast to glycolysis and OXPHOS, CSCs have been demonstrated to increase the PPP, especially during hypoxia and reoxygenation. Furthermore, rapid oxygenation increases the production of essential PPP enzymes, while hypoxia decreases it and causes the expression of glycolytic genes. This relationship between the activation of glycolysis and the PPP pathway in a microenvironment with various oxygen saturations may be due to cell migration being driven by glycolysis in hypoxia and cell proliferation being mediated by PPP in acute oxygenation. The function glutamine metabolism plays in CSCs from various malignancies, such as ovarian, pancreatic, and lung cancer, is notable [94, 141, 142]. In c-Myc-overexpressing cells, glutamine metabolism appears crucial, indicating that a pluripotency gene profile favors glutamine dependency. It has been demonstrated that inhibiting glutamine availability decreases the stemness gene signature and makes pancreatic CSCs more susceptible to radiation therapy in vitro and in vivo. In line with these findings, a related study using a mouse model of systemic metastasis revealed that blocking glucose metabolism with the glutamine analog L-DON can prevent the spread of metastatic disease to the liver, lung, and kidney [142–144]. The tumor microenvironment plays an important role in the progression of all types of cancer through the stages of sub-invasion and metastatic spread. Several studies have investigated the relationship between hyaluronic acid (HA) receptors and cancer cells. HA is a key extracellular component that helps control and regulates cell adhesion, migration, and invasive proliferation. CD44 is a major cell surface receptor for hyaluronic acid, a major component of extracellular matrices. Interactions of HA with its binding proteins CD44 are important in promoting tumor progression [145]. Many cancer cells are known to overexpress HA receptors such as CD44. After uptake by cancer cells, HA is broken down into low molecular weight components by hyaluronidase through CD44 receptor-mediated endocytosis. CD44 receptor overexpression was shown in various cancer cells, including colon, ovarian, breast and squamous cell carcinoma [146]. High levels of CD44 mRNA and protein expression levels in breast cancer are associated with significantly worse overall survival [147]. Many studies in recent years have identified the role of CD44 in a subpopulation of tumor cells with self-renewal capacity, the so-called CSCs [146]. A number of clinical studies have shown an association between CD44v6 expression and tumor progression in various tumor types. Günthert et al. [148] showed a significant correlation between CD44v6 expression and lymph node metastasis, lymphatic invasion when they transfected CD44 or CD44v6 expressing plasmids into non-metastatic rat pancreatic cancer cells. In addition, Wang et al. indicated a significant correlation between CD44 expression and stage, tumor size, and lymph node metastasis of gastric cancer. CD44v6 was related with *lymph node* metastasis, lymphatic invasion, and venous invasion [149]. Furthermore, various studies showed that increased expression of CD44 or CD44v6 was found in gastrointestinal tumors and was associated with tumor invasion, lymph node metastasis, and patient survival [149]. Wu et al. investigated the biological role and regulation of HA and its receptors in human gastrointestinal cancers. In their study a correlation between HA accumulation and tumor progression has been demonstrated in various gastrointestinal cancers. HA and HA fragment-tumor cell interactions can activate downstream signaling pathways, increase cell proliferation, adhesion, migration and invasion [150]. In another study, Li et al. carried out a study on the expression of hyaluronan receptors CD44 in stomach cancers. The results of their study shown that among CD44 isoforms, v6 is more related to malignant transformation of gastric epithelium. Expression of receptor for hyaluronan-mediated motility (RHAMM), especially the cell surface variants, is closely correlated with tumor progression (P-value < 0.01) [145]. The CD44 expression may be mutually beneficial for gastric cancer cell invasion and metastasis. The roles of hyaluronic acid, hyaluronidases and HA receptors in cancer biology is complex and mediated by HA receptors expressed in cancer cells. Hence, HA was proposed as a drug carrier or for designing nanoparticles or liposomes for biocompatibility, biodegradability and based on the ability of CD44 to internalize HA [151]. Degradation of HA across a wide range of molecular sizes is stimulated by tissue ROS and Hyals that are found abundantly in tumor microenvironments. In particular, overexpression of Hyal-1 and Hyal-2 during cancer metastasis has been

reported in many in vitro and in vivo studies, and it has recently been suggested that HA fragments promote cancer progression through *Hippo-Yap* signaling. However, the role of Hayl-3 in cancer progression is controversial as some studies have shown inhibition of tumor growth, while others have reported increased levels of the molecule in some solid tumors [151]. Clinicopathological analyzes show a strong correlation between increased expression of HA and Hyaluronan Synthase 2 and decreased expression of Hyal1 in tumor cells and poor survival in pancreatic ductal adenocarcinoma patients. Serum HA is known as a biomarker for liver fibrosis and cirrhosis, and its concentration is easy to determine clinically. However, little is known about the prognostic value of serum HA levels in patients with hepatocellular carcinoma [150]. Mima et al. reported that high preoperative serum HA levels (100 ng/ml or higher) in hepatocellular carcinoma patients independently predicted poor prognosis after hepatectomy [152]. The results obtained from these studies confirmed the results of the present study.

The effects of mechanical forces on CSCs

Carcinogenesis is related to interactions between tumor cells and mechanical stress in the TME. High mechanical stress in tumors can change a cancer cell's metabolism, behavior, and capacity to create cancer stem-like properties, accelerate the growth of the primary tumor, and encourage metastasis [153]. Mechanotransduction transforms mechanical signals into biochemical signals that activate the signaling pathways associated with tumorigenesis [153]. Moreover, Biomechanical signaling in TME has an important effect on stemness fate of cancer cells and CSC differentiation. Matrix stiffness and fluid shear stress are two examples of the most important mechanical forces that cause differentiation, migration, invasion, proliferation, EMT and so on by inducing different signaling pathways. According to studies, the extracellular matrix (ECM) in TME has more stiffness than normal tissues. This is due to the fact that cancer cells have a great growth power and more cells are accommodated in the limited environment, and also extracellular components such as collagen and proteoglycans are overexpressed in this space [154, 155]. Many studies have investigated the effects of stiffness of ECM on the stemness of cancer cells. For example You et al. [156] found that stiff ECM in HCC causes the transmission of mechanical signaling through integrin β1 molecule into the cell. The family of integrins are converters of environmental mechanical forces into chemical signaling [156]. Sensing the stiffness of the environment by integrin β1 activates the AKT/ mammalian target of rapamycin (mTOR)/SOX2 signaling pathway [156]. SOX2 is a factor that maintains cell stemness and causes the expression of stem cell characteristics factors such as CD133 and EpCAM [156]. FAK is another membrane signaling factor that is activated by integrin β1. FAK usually activates many signaling pathways including phosphoinositide 3-kinases (PI3K), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and cyclin D (Fig. 2). It has also been proven that the stemness of the CSCs and the initiation of cancer cells through the maintenance of CSCs can be strengthened by this factor [157, 158]. To that end, ECM stiffness has a very special role in tumorigenesis and stemness of cancer cells, therefore, agents have been used to disrupt tumor ECM in several studies [159]. Hsp47 is a chaperone in the ECM space that helps collagen folding, secretion, and assembly and can be a good target for disrupting tumor ECM [159]. Substances such as transforming growth factor beta (TGF-β) inhibitor (TGF-β induces expression of Hsp47), AK778, Col003, and methyl 6-chloro-2-oxo-2,3-dihydro-1,2lambda ~ 4 ~ , 3-benzothiazole-4-carboxylate are among these agents that inhibit Hsp47 activity [159]. TME is a hypoxic space and many tumorigenic factors are secreted by tumor cells in this environment, and as a result, a wide capillary network is formed in TME. However, this capillary network does not have appreciable efficiency and high permeability and there is a high interstitial fluid pressure in TME. In addition, another result of these events is a relatively extensive lymphatic system in the TME. The presence of IFP and the lymphatic system creates a weak mechanical force called fluid shear stress (FSS) [154]. Although the flow of this liquid and the strength of this force is weak, it has an important effect on the biological fate of CSCs. For example, FSS causes the differentiation of CSCs in lung cancer following the activation of the Wnt/β-catenin signaling pathway [160]. In addition, according to U. Triantafilluet al's research, FSS increases CSC in breast cancer [161] (Fig. 2).

Epithelial-mesenchymal transition

Initial steps of metastasis of turmeric cells begin with EMT and involve epithelial cells losing their identity, changing morphologically and acquiring mesenchymal cell properties [162, 163]. This hijacked process by cancer cells is initially used for homeostasis, development of organs and tissue healing and consists of a series of transcriptional changes. Some of the involved factors in this process are HIF-1α, Twist-related protein 1/2, distal-less homeobox 2 (Dlx-2), Snail, zinc finger E-box-binding homeobox (ZEB) 1/2, and Slug [163–166]. The EMT, as the center of tumor malignancy, is closely correlated to CSCs [29, 167, 168], because it seems that at the base of CSCs generation, the EMT mechanism is involved and is linked with decreased mitochondrial activity and enhanced glycolysis [164, 169]. Moreover,

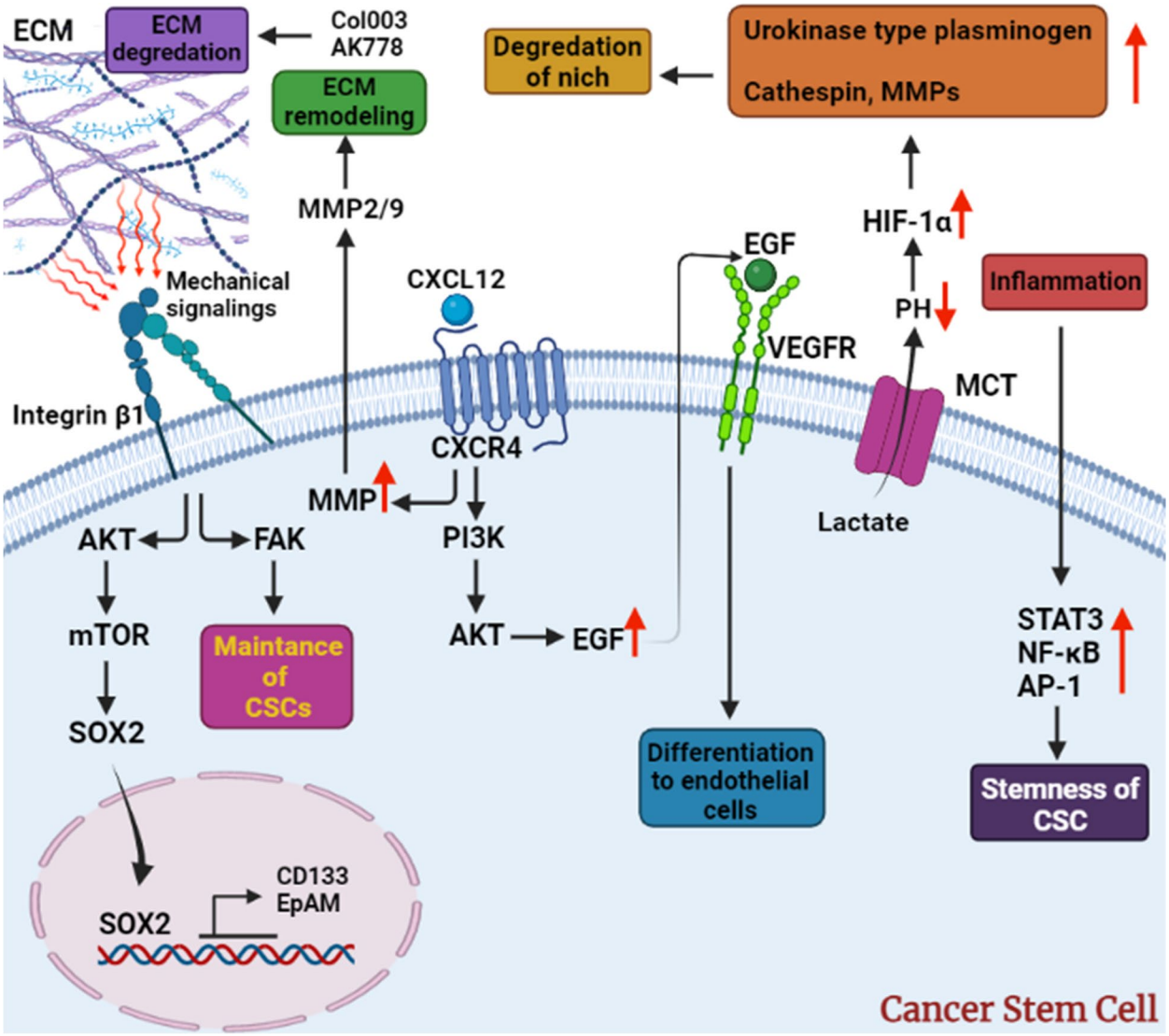

Fig. 2 The illustration indicates interactions between CSCs and their environment: mechanical and chemical forces have their roles in this environment. For instance, inflammatory factors cause evaluation of STAT3, NF-κB, and AP-1 that result in stemness of CSCs. Sometimes, some changes in CSCs cause alterations in ECM that have indirect effects on CSCs like lactate emission from CSCs to ECM decreases environmental PH and then increases HIF-1α that results in elevation of urokinase-type plasminogen, cathepsins, and MMPs. Elevation of these substances causes degradation of the niche (that is considered a mechanical change itself). On the other hand, CXCR4/CXCL12 axis triggers the PI3K/ AKT signaling pathway that evaluates EGF level in CSCs that binds to VEGFR and causes differentiation of CSCs to endothelial cells. Moreover, CXCR4/CXCL12 axis increases the MMPs level, which is an ECM remodeling factor in its own way. Mechanical forces (or signalings) from ECM are felt by integrin-β1 that starts FAK (maintenance of CSCs) and AKT/mTOR/SOX2 (expression of stemness markers such as CD133 and EpAM) signaling pathways

signaling pathways imprinted in EMT like Wnt/β-catenin are also involved in the stimulation of stem-ness features and acquisition of CSCs [170]. More interestingly, regulation of metabolic adaptation can occur with the help of molecules involved in EMT like Wnt and AKT, STAT3, Snail, HIF-1α, TGF-β, and Dlx-2 (Fig. 3) [63, 171–176]. Snail has been reported to be involved in the repression of mitochondria and supporting glycolytic metabolism [171, 174]. In EMT-derived cancer cells, STAT3 could promote glycolysis through positive regulation of transporters linked to anaerobic glycolysis [177]. Dlx-2, whose expression relies on the metabolic stress induced by ROS through the expression of SNAIL, contributes to the glycolytic switch and inhibition of mitochondrial activity mediated by TGF-β/Wnt signaling pathway [171]. By promoting EMT in breast cancer, overexpression of SNAIL could cause the resistance of breast cancer cells to the lysis induced by $CD8^+$ T cells [178]. Additionally,

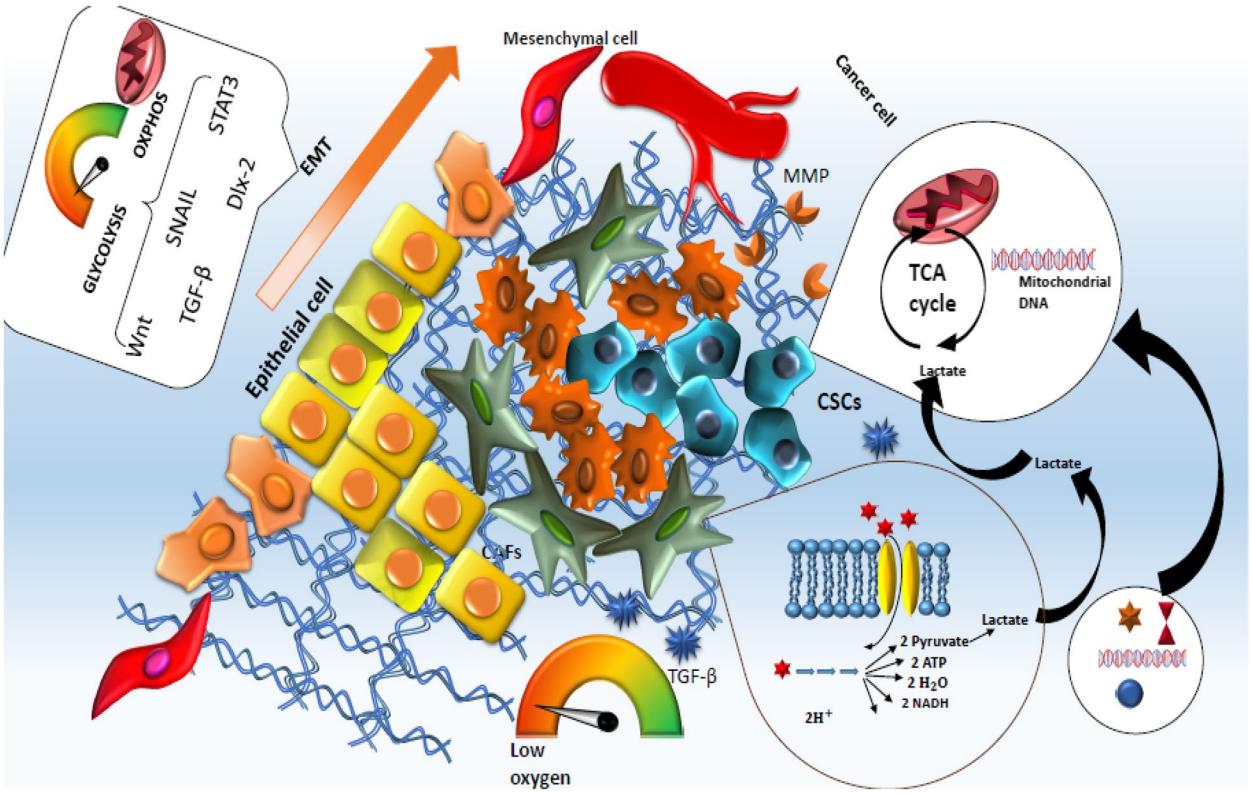

Fig. 3 At the base of CSCs production, the EMT mechanism is involved and is associated with a decrease in mitochondrial activity and an increase in glycolysis. Signaling pathways implicated in EMT, such as Wnt/β-catenin, are also involved in the stimulation of stemness characteristics and the acquisition of CSCs. Regulation of metabolic adaptation can occur with the help of molecules involved in EMT such as Wnt and AKT, STAT3, Snail, HIF-1α, TGF-β, and Dlx-2. Cancer-associated fibroblasts (CAFs) induce tumor remodeling through the release of factors such as matrix metalloproteinases (MMPs) and enzymes, and angiogenesis that summons other inhibitory cells, growth, and metastasis. Lactate released by CAFs following glycolytic metabolism in these cells is taken up and used by CSCs such as epithelial cells to supply the TCA cycle, which in turn promotes processes such as metastasis, self-renewal, and invasion of MSCs provide

negative regulation of mitochondrial function induced by HIF-1α by promoting the activity of PDK has made this factor one of the central regulators of the glycolytic switch [173, 179].

Cellular plasticity

As one of the complications ahead of tumor therapy, turmeric cells' plasticity is defined as their ability to swing between asymmetric division and symmetric division, CSCs and non-CSCs, quiescence, and proliferation [180, 181]. The dynamic conversion property of CSCs has been attributed to the emergence of drug resistance [182, 183]. Plasticity can make the heterogeneity of tumor worse and eradication of tumors more complicated as CSCs can convert from quiescence to proliferative or vice versa, making it possible for the recurrence of cancer years after chemotherapy [184]. The network between CSCs, surrounding cells, the niche of CSCs, and four intrinsic factors play a vital role in the regulation of plasticity by providing the agents and necessary signals in a wide range of forms [185, 186]. 1) The acidic microenvironment of a tumor contributes to the reprogramming of non-CSCs and their dedifferentiation of them [187]. 2) The inflammatory microenvironment could promote the recruitment of inflammatory cells and the release of factors that favor CSCs resulting in the activation of signaling pathways like Wnt, imprinted in de-differentiation [188–190]. 3) Metabolic adjusting, which was discussed in the previous section, is one of the central regulators of plasticity as a regulator of conversion from glycolysis to OXPHOS or vice versa [103]. 4) Hypoxic conditions of TME can also promote the induction of treatment resistance in CSCs and stemness [191].

CSCs and tumor angiogenesis

Angiogenesis has been recognized to be vital for tumor growth, metastasis, and migration. Vascularization can happen in different ways in the tumor, such as sprouting angiogenesis, recruitment of endothelial progenitor cells, intussuscepted angiogenesis, vascular mimicry, and

trans-differentiation of CSCs [192]. CSCs, besides their capability to differentiate to ECs, by secretion of factors such as VEGF, HIF-1α, and CXCL12, can promote the recruitment and migration of ECs and mesenchymal stem cells (MSC) to the niche of tumor and differentiation of them into ECs [193–195]. In this regard, high expression of MMP-2 and MMP-9 by CSCs contributes to the initiation of Extracellular matrix (ECM) remodeling. Moreover, the over-expression of VEGF receptors in these cells compared to their partners in angiogenesis is notable (Fig. 3) [196, 197]. On the other hand, the autocrine secretion of VEGF can be stimulated by high expression of CXCR4 and its ligand and activation of the downstream pathway through the PI3K/AKT signaling pathway, which eventually influences the expansion of CSCs via stimulation of stimulating neuropilin-1 [197, 198]. Finally, the transformation of ECs to endothelial progenitor cells seems to be promoted by the expression of Notch and vascular–endothelial cadherin (VE-Cadherin) involved in this process [196, 199–201].

CSCs and tumor invasion

Invasion is considered the first step of metastasis and migration to nearby or faraway organs. This process involves a cascade of steps that enables cells to pass through the tissue structures and vessel walls. Different models of migration are used in different malignancies such as amoeboid migration, mesenchymal migration, and collective cell migration [202]. The invasion begins with the loss of cell–cell adhesion mediated by the loss of specific proteins involved in adhesion, which also influences cell–matrix adhesion. Moreover, the ability to change and deregulate the surrounding extracellular matrix via matrix metalloproteinase is the next vital step to migration. In the next levels, named intravasation and extravasation, cancer cells pave the way to enter the blood vessels or lymphatic system, and after exiting the circulatory system, inhabit organ parenchyma and start colonization [203]. The release of TGF-β to support the cellular invasion and metastasis by CSCs is another way through which CSCs promote invasion [204–206]. Furthermore, the premetastatic niche (PMN) is the other part where CSCs could function as metastasis players. TGF-β and VEGF, which can be released by CSCs, enhance vasculature permeability, CCL-9, and inflammatory agent secretion and enhance the utilization of bone marrow-derived cells (BMDCs) [207–210]. CXCL-12, which plays an essential role in metastasis, angiogenesis, and MMP expression and protects its activity in TME, is also expressed in CSCs [211, 212]. Aerobic metabolism of glucose by cancer cells in TME results in the formation of lactate, which is lethal to normal cells, while cancer cells, through the expression of MCTs transporters, transfer this substance to their niche, leading to decreased pH of TME [79]. The acidity of the environment provided by lactate, which itself can stimulate HIF-1α, is the favorite factor of MMP, cathepsins B, L, D, and urokinase-type plasminogen activators to function better and facilitate the degradation of the surrounding niche [213–216]. More interestingly, phosphoglucose isomerase (PGI), as one of the enzymes involved in glycolysis, has been noted to act as an autocrine motility factor (AMF) with an anti-apoptotic effect. PGI is used for enhancing metastasis, invasion, and cellular migration through different mechanisms like upregulation IL-8 secretion, which is imprinted in migration, induction of EMT by promoting the expression of mesenchymal markers expression in epithelial cells and halting expression of epithelial markers [217–220]. PGI has been observed to be capable of inducing self-renewal properties and promoting tumorigenesis in glioma CSCs [221]. PKM2 as one of the other vital enzymes in glycolysis, has been correlated with the decrease of E-cadherin and promoting the signaling pathway of EGFR and, as a result, cellular migration [222]. Additionally, this enzyme has been observed to be able to promote the induction of cancer stem-like cells [223]. Lactate dehydrogenase A (LDHA), as the key element of converting pyruvate to lactate, overexpressed in tumor cells could also contribute to the regulation of TGF-β and the rise of MMP-2 in glioma cells [224]. In addition, in another study, breast cancer stem-like properties were generated via an LDHA-dependent way [225]. Taken together, it is reckoned that CSCs and cancer cells' metabolism at the time of hypoxia, which mostly turns to aerobic glycolysis, and acidification facilitate the initiation of invasion and migration to other niches.

CSCs and tumor microenvironment

The behavior of turmeric cells, including CSCs, is highly defined by the presence of heterogenic cell types, blood vessels, lymph vessels, ECM, and signals received from the microenvironment surrounding them. The tumor niche can be responsible for the creation of a web that defines the response of the immune system, induction of CAFs, MSCs, ECs, ECM, and soluble factors [226]. ECM with a unique composition contributes to impacting the signaling, cellular movements, invasion, and angiogenesis [227, 228]. Not only ECM acts as a blocking wall-facing agent used in chemotherapy and radiotherapy, but it also participates in the creation of hypoxia [229, 230]. Growth factors and other soluble agents existing in TGF-ß, interleukin-6, fibroblast growth factor (FGF), and hepatocyte growth factor (HGF). In addition, the protection of tumor growth and induction of resistance to therapies [231]. Some of the critical cell types present in the tumor microenvironment are Immune cells like TAM,

natural killer (NK) and dendritic cells (DCs), T lymphocytes and B lymphocytes, and Myeloid-derived suppressor cells (MDSC), fibroblast cells, which could form a network to benefit the tumor cells or fight against them [232]. More importantly, the dominant condition of TME could also define invasion and progression. Inflammation and hypoxia are two vital situations needed for the growth of the tumor [233]. The mutation rate needed for the initiation of a tumor and the proliferation rate can be accelerated in an inflammatory environment [234, 235]. The production of ROS, produced by the inflammatory immune cells recruited to the location of inflammation, contributes to DNA damage, which could also lead to the arrest of the mismatch repair system [236]. The cytokines, chemokines, and growth factors released in the process of inflammation contribute to the activation of transcription factors like STAT3, nuclear factor-kappa B (NF-κB), and AP-1 imprinted in cellular proliferation and the induction of reprogramming needed to gain stemness and self-renewal properties [237] suggesting that there must be a link between the CSCs and chronic inflammation. IL-6, as one of the factors mostly found during the incidence of inflammation, is vital for the survival of CSCs, as the exposed cells to this factor gained an increased capacity for invasion and resistance [238]. More interestingly, it seems that CSCs tend to firm their own niche in different ways [239]. This crosstalk between CSCs and TME through the metabolites, exosomes, cytokines, growth factors, and chemokines, including vascular endothelial growth factor (VEGF), HIF-1, matrix metalloproteinases (MMPs), CCL5, CCL2, TGF-β, IL-1β, IL-8, and IL-6 [240–245] can be the defining factor in the regulation of the processes such as metastasis, angiogenesis, immune escape and drug resistance [246].

TME contributes to CSCs metabolism

The surrounding niche of CSCs is one of the defining factors that could explain the plasticity of these cells' metabolism. Factors like CAF, endothelial cells, inflammatory agents, the presence of immunomodulatory cells, and conditions like inflammation and hypoxia could be considered as determining factors in the metabolic switch in CSCs [57, 247]. For example, activation of NF-κB causes to release inflammatory cytokines like IL-1β, IL-6, and IL-8 can promote the recruit of AKT and PI3K and subsequently contributes to the self-renewal property of CSCs [248–251]. A high rate of ketone bodies and lactate, which represent the usage of glycolysis and ketogenesis in TME, in the companionship of factors like TGF-β and HIF-1α, could contribute to the induction or preservation of stemness in CSCs [252–255]. In the following parts, the role of each of the mentioned factors will be discussed. Simultaneous high-speed proliferation and lack of enough blood vessels put most solid tumors in a hypoxia condition [256], resulting in the induction of HIF. The hypoxic condition of the tumor can be responsible for the alteration in TME like EMT, suppression of apoptosis, metabolic changes, invasion of the tumor, infiltration of modulatory cells, and production of modulatory agents, and neovascularization [257–259]. In addition, to the fact that hypoxia can support stemness and undifferentiated properties. The potential to enhance glucose transporters on the surface, and shift to glycolysis, facing the lack of nutrients and hypoxia, represents the high adaptability of these groups of cells [260, 261]. Moreover, in a study, an ensconced number of breast CSCs as a consequence of the production of HIF-1α and activation of AKT/β-catenin was observed after the generation of intratumoral hypoxia with the help of anti-angiogenic agents [262, 263]. Not surprising that in xenograft models of breast cancer, inhibition of HIF-1α was accompanied by a decreased population of breast CSCs [264–266]. In NSCLC, hypoxia also resulted in gefitinib-Resistant Lung CSCs enrichment, and the expansion of this population was mediated by insulin-like growth Factor 1 Receptor (IGF1) [267]. In glioma stem cells, enhanced activity of this population was observed under hypoxic conditions; additionally, suppression of HIF-1α and HIF-2α by shRNA caused a decline in the activity of CSCs [268]. Moreover, enhancement of stemness property in glioma and leukemia CSCs because of HIF-1α activation has been reported [269, 270]. Finally, the formation of CSCs seems to be under the influence of HIF-2α, which can stimulate the activation of c-Myc by controlling the expression of OCT-4 [271].

CSCs and CAFs

as the first assistance of CSCs which can be trained and reprogrammed to obtain a protumorigenic character, in the companionship of other suppressor cells by secreting growth FGF, HGF, and CXCL12, accelerating the tumor As the predominant population in solid tumors, fibroblast cells, named CAF are recruited during the healing process after a sustained inflammation. These cells are considered growth and metastasis via induction of tumor remodeling via the release of factors like MMPs, enzymes, and angiogenesis summoning other inhibitory cells [226, 272, 273]. Moreover, the protection fence provided by these cells could facilitate the therapy resistance and recruitment of immune cells to secret inflammatory factors, which makes the environment ready for tumor progression besides suppressing activated lymphocytes [272, 274, 275]. Moreover, supporting the invasive phenotype of CSCs by $CD90^+$ CAFs has been observed following the habitation of $CD44^+$ $CD90^+$ CSCs

at periphery sites of breast tumors, where they were in direct contact with CAFs [276]. In addition, their role in the regulation of CSCs metabolism has been noticed. Reprogrammed and dependent CAFs on aerobic glycolysis can also gain energy from autophagy to fuel the processes such as migration, proliferation, and cytokine secretion [277–279]. In this line, the usage of autophagy in CAFs could provide the demands of pancreatic ductal adenocarcinoma [280]. In breast cancer cells, enhanced expression of cell membrane-bound GLUT-1 transporter increasing the uptake of glucose is promoted by the secretion of cytokines by CAFs [281]. The usage of glutamine in CAFs, which consequently supports the tumorigenicity and microenvironment of CSCs, is a perfect target to stop the development of ovarian tumors [282]. Moreover, metabolic reprogrammed CAFs in NSCLC was correlated with a rise in the glycolytic metabolism of tumor [283]. Alternatively, in some experiments, it has been revealed that the metabolites produced in CAFs during a phenomenon called "reverse Warburg Effect" can be consumed by the CAFs surrounding cells, leading to enhanced tumorigenicity [284]. Moreover, the transference of mitochondrial DNA via exosomes from CAFs to breast CSCs promotes OXPHOS and possible therapy resistance in an OXPHOS-dependent manner [285], which provides evidence that CSCs show plasticity in their metabolism. Lactate released by CAFs, following the glycolysis metabolism in these cells seems to be absorbed and used by epithelial CSC-like cells to fuel the TCA cycle, which in return fuels processes such as metastasis, self-renewal, and invasion in CSCs [286].

CSCs and ECs

ECs are one of the vital parts of TME that orchestrate with other cells to provide tumor progression, which can be recruited to the niche of the tumor upon the section of VEGF, HIF-1, and SDF-1/CXCL12 by CSCs to initiate the process of angiogenesis [24, 287, 288]. Co-culturing CSCs and ECs have revealed that ECs play an essential role in supplying the factors required for the maintenance of self-renewal and stem-ness in CSCs [289]. In glioma and colorectal cancer, robust self-renewal and stemness of CSCs through the Notch signaling pathway was attributed to the presence of ECs [290, 291]. In breast cancer, the activation of NF-κB in CSCs, which led to the secretion of S100A8/9 and establishment of resistance to doxorubicin and cyclophosphamide, was a result of the production of TNF-α by ECs [292]. Activation of STAT3 by the IL-6 secreted in head and neck squamous cancer cells in tumor-associated endothelial cells has nominated this factor to be a part of CSCs and ECs network, considering the role of IL-6 in the induction of glycolytic pathway, as a glycolytic phenotype in ECs cells [293, 294]. Studies have introduced glycolysis as the primary source of energy in ECs, and PFKFB3 knockdown in ECs, resulting in sabotaging the glycolytic pathway, has caused a reduction in angiogenesis [293]. Cancer-associated endothelial cells (CAEC), under the influence of the accumulated lactate in TME, which results in enhanced IL-8/CXCL-8 signals, can support angiogenesis [294]. Although aerobic glycolysis has been recognized as the favorite source of energy in ECs [295], stimulation of signaling pathways imprinted in preserving the prevascular niche has been correlated with mitochondrial activity in ECs. As one of the crucial factors in angiogenesis, VEGF has indicated the capacity to promote mitochondrial metabolism in ECs, which could respond to the expansion of CSCs [278, 296, 297].

CSCs and Immunomodulation

Low concentration of nutrients plus high speed expanding cancer cells starving for glucose and the mass of metabolites left from turmeric cells metabolism make TME like a barrier that stops immune cells from getting fully functional. In particular, low levels of oxygen or hypoxia could lead to enhanced pyruvate dehydrogenase kinase and lactate dehydrogenase A expression, which subsequently sabotage mitochondrial respiration and ROS production and shut down the conversion of pyruvate to lactate, respectively. Deprivation of glucose seems to cause a reduction in aerobic glycolysis and the regulation of NFAT signaling, which influences and halts the functions of T cells [298]. Lactate besides protons (H^+), which are transported to the niche of turmeric cells, are among the most abundant metabolites released by these cells [299–301]. The accumulated lactate leads to low pH in the TME or acidification, which limits the activity of immune cells by suppressing the activation of NK cells and confining the production of IFN-γ, and induction of apoptosis in T and NK cells [298, 302, 303]. On innate immunity cells, like DC cells, remaining in the tolerogenic state, decreased expression of CD1, the release of IL-12 and enhanced secretion of IL-10, and diminished migration ability [304, 305]. Moreover, reprogramming of DCs mediated by TME could result in the formation of regDCs, capable of sabotaging antitumor activity and facilitating lung tumor invasion [306]. Concerning macrophage responses, there is some debate on the activity and properties of these cells in a lactic environment and polarization towards the M2 phenotype by stabilizing HIF-1α [307]. By stimulation of STAT3, M2 macrophages, which in a tumor are named tumor-associated macrophages, support population, invasion, and drug resistance of CSCs. Stimulation of self-renewal in CSCs can be promoted by the release of TGF-β,

IL-10, and IL-6 by TAM [308]. Moreover, the cytokines released by macrophages have been linked to the EMT reprogramming by the downregulation of miR-138. The stemness in NSCLC could also be regulated by TAMs through the upregulated expression levels of ubiquitin-specific peptidase 17-like family member 9, which could result in the production of inflammatory factors, which consequently lead to increased stemness [309]. NK cells, which are known for their function in cytokine production and cytotoxicity, play a vital role in immunity against cancer [310]. From taking part in the activation of $CD8^+$ T cells and monocytes, helping maturation of DCs, defining polarization of T cells to production of tumor necrosis factor-alpha (TNF-α), IFN-γ, and granulocyte–macrophage colony-stimulating factor (GM-CSF) and eradication of infected and tumor cells by two mechanisms of antibody-dependent cellular cytotoxicity, in the absence of prior stimulation through natural cytotoxicity [310, 311]. More notably, in targeting CSCs, NK cells have an essential role as a study has shown the increased susceptibility of CSCs to NK killing [312], which must be because of the decreased expression of MHC-I to protect their growth in TME [313]. T cells, categorized as tumor-infiltrating lymphocytes (TIL) in tumors in charge of regulating immune responses, consist of subtypes like Th2, and T-reg that could favor tumors, and in some cases could be recruited by turmeric cells, and groups like Th1 and $CD8^+$ T cells act against cancer and mediates eradication of cancer cells [314, 315]. Studies on the effect of low pH of TME have reported that pH like 6.6 can put the function and expansion of T cells in jeopardy, plus decreased expression of TCR, IFN-γ, IL-2, TNF-α consistent with the mentioned changes [316, 317]. Taken together, it seems that the acidic microenvironment of the tumor, which is the result of the glycolytic metabolism of CSCs and cancer cells, could protect them from the attack of immune cells in different ways and help the invasion of CSCs.

Therapeutic perspectives

Given the crucial role of CSCs in the development, invasion, and relapse of tumors, and their plasticity in the face of different conditions, choosing the most effective approach to eradicate these cells is challenging. Concerning the close relation between the self-renewal, stemness, and metastasis properties of CSCs and their metabolism, one of the proposed solutions is targeting the metabolism of CSCs. In xenograft models, experiments with a focus on mitochondrial respiration have led to the depletion of these cells via sensitization to chemotherapy. For instance, in metastatic melanoma, enrichment of JARID1B slow-cycling subpopulation was formed following the treatment with cisplatin and vemurafenib, inhibition of OXPHOS was then resulted in the suspension of $JARID1B^+$ subpopulation formation and making melanoma cells more vulnerable to chemotherapy agents [318] (Table 1). In PDAC cells with mutations in KRAS, targeting OXPHOS with inhibitors like oligomycin, combined with therapies aiming at KRAS, showed better elimination rather than just using treatments specified for the oncogene [98]. The metabolic shift in CSCs of colorectal cancer is correlated with 5-fluorouracil (5-FU) resistance, and a combination of 5-FU and metformin to block mitochondrial activity has effectively reduced the population of CSCs [319]. In glioblastoma CSCs, combination therapy of 3-bromopyruvate that targets glycolysis and doxorubicin led to effective inhibition of tumor and elimination of CSCs [320]. In a similar experiment on pro-neural and mesenchymal CSCs, high radiation therapy resistance and invasion of mesenchymal CSCs were diminished with the use of an inhibitor of ALDH [321]. Moreover, since CSCs recruit a wide range of cells and factors in their niche to support their survival and growth, perhaps targeting these allies could facilitate the eradication of CSCs. For example, targeting VEGF via monoclonal antibody combined with CXCR4 antagonist in glioblastoma resulted in enhanced survival, and the use of POL5551

Table 1 Therapeutic perspectives of targeting CSCs in the tumor microenvironment

Drug	Cancer/Cell line	Description	Refs
Cisplatin and vemurafenib	Melanoma	Enrichment of JARID1B slow-cycling subpopulation was formed Suspension of $JARID1B^+$ subpopulation formation and making melanoma cells more vulnerable to chemotherapy agents	[302]
Oligomycin,	PDAC cells with mutations in KRAS	Better elimination of CSCs rather than just using treatments specified for the oncogene	[303]
5-fluorouracil and metformin	Colorectal cancer	Effectively reduced the population of CSCs by blocking the mitochondrial activity	[304]
3-bromopyruvate and doxorubicin	Glioblastoma	Effective inhibition of tumor and elimination of CSCs	[305]
VEGF monoclonal antibody and POL5551	Glioblastoma	Enhanced survival via affecting the existing of CSCs	[307]
anti-GPR77 antibody	Breast and lung cancer	Diminish tumor formation and sensitizing lung and breast cancer cells to chemotherapy	[310]

alone as the CXCR4 antagonist affected the existing CSCs [322]. Although the usage of anti-VEGF led to an increased breast CSCs, through induction of hypoxia [262], in the CSCs population of NSCLC, combination therapy of anti-hepatoma-derived growth factor (HDGF) antibody and VEGF tyrosine kinase inhibitor was successful in diminishing this population [323]. Blocking Hedgehog signaling in breast cancer led to the halter of the activity of CAFs, which subsequently made CSCs more susceptible to chemotherapy [324]. Treatment of $CD10^+$ $GPR77^+$ CAFs with anti-GPR77 antibodies was shown to diminish tumor formation and sensitize lung and breast cancer cells to chemotherapy [325]. Though developing new therapies based on CAFs is still going on, such as the therapies via CAR-T cell, SynCon DNA vaccine, and Oncolytic adenovirus focused on fibroblast activation protein (FAP) [326–329], targeting JAK/STAT3 pathway [330] or Blocking pan-TGF-β and GARP [331]. One of the CAFs is a type II transmembrane glycoprotein termed FAP. It was shown that when FAP-specific CAR-T cells were used alongside a tumor antigen-specific CAR, an enhanced anti-tumor activity in A549 lung cancer cells was observed [332]. A pioneering study has also shown oral administration of DNA-based FAP vaccine-induced $CD8^+$ T cell-dependent killing of CAFs, which substantially increase the intratumoral uptake of chemotherapeutic drugs in multidrug-resistant murine colon and breast carcinoma. Of note, FAP-specific CAR-T cell treatment in an immunocompetent mouse model has been shown to boost host immunity. Similarly, the co-introduction of anti-FAP and anti-tumor CAR-T cells has also shown to enhance anti-tumor immunity in xenografted immune-deficient mouse models [333].

Conclusion

CSCs as the initiator of tumors, involved in processes of metastasis, invasion, and therapy resistance have been paid attention to be capable of being potential targets for tumor therapy. Mounting experiments are now focused on the metabolic side of these cells, which gets important in the occurrence of phenomena like EMT, hypoxia, metastasis, and tumor growth, as the contradictory data on glycolysis or OXPHOX reliance, represents the involvement of other factors. Therefore, a better understanding of the plasticity and the metabolic state of CSCs in different stages of malignancies, and how the counterparts or enemies of CSCs get to affect this machinery is required so that we could get one step closer to developing new therapies to eliminate CSCs via targeting the metabolism of CSCs or the partners of CSCs in the TME.

Abbreviations

CSCs	Cancer stem cells
EMT	Epithelial-mesenchymal transition
TME	Tumor microenvironment
TAM	Tumor-associated macrophages
CAF	Cancer-associated fibroblasts
EC	Endothelial cells
TICs	Tumor-initiating cells
AML	Myeloid leukemia
SCID	Severe combined immune-deficient
SOX2	Sex-determining region Y HMG-box 2
ALDH1A1	Aldehyde dehydrogenases 1A1
ABCG2	ATP-binding cassette sub-family G member 2
JAK/STAT	Janus kinase /signal transducer and activator of transcription
TCA	Tricarboxylic acid cycle
OXPHOS	Oxidative phosphorylation
PDK	Pyruvate dehydrogenase kinase
CRC	Colorectal cancer
RNAi	RNA interference
PFKFB4	6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 4
PKM2	Pyruvate kinase M2 hypotype
HIF-1	Hypoxia-inducible factor-1
NADH	Nicotinamide adenine dinucleotide
iPS	Pluripotent stem cells
G6P	Glucose-6-phosphate
GLUT-1	Glucose transporter 1
HK-1	Hexokinase 1
ROS	Reactive oxygen species
OCR	Oxygen consumption rate
DRP1	Mitochondrial dynamics
PGC1α	Peroxisome proliferator-activated receptor-gamma co-activator one alpha
MUFAs	Unsaturated lipids like monounsaturated FAs
TKI	Tyrosine kinase inhibitor
FASN	Fatty acid synthase
HCC	Hepatocellular carcinoma
RHAMM	Hyaluronic acid (HA), hyaluronan-mediated motility
ECM	Extracellular matrix
mTOR	Mammalian target of rapamycin
PI3K	Phosphoinositide 3-kinases
MAPK	Mitogen-activated protein kinase
ERK	Extracellular signal-regulated kinase
TGF-β	Transforming growth factor beta
FSS	Fluid shear stress
Dlx-2	Distal-less homeobox 2
ZEB	Zinc finger E-box-binding homeobox
MSC	Mesenchymal stem cells
BMDCs	Bone marrow-derived cells
PGI	Phosphoglucose isomerase
AMF	Autocrine motility factor
PKM2	Pyruvate kinase isomerase M2
LDHA	Lactate dehydrogenase A
FGF	Fibroblast growth factor
HGF	Hepatocyte growth factor
NK	Natural killer
DCs	Dendritic cells
MDSC	Myeloid-derived suppressor cells
VEGF	Vascular endothelial growth factor
HIF-1	Hypoxia-inducible factor-1
MMPs	Matrix metalloproteinases
NF-κB	Nuclear factor-kappa B
IGF1	Insulin-like growth Factor 1 Receptor
CAEC	Cancer-associated endothelial cells
TNF-α	Tumor necrosis factor-alpha
TIL	Tumor-infiltrating lymphocytes
5-FU	5-fluorouracil
HDGF	Anti-hepatoma-derived growth factor
FAP	Fibroblast activation protein

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Authors' contributions
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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

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Not applicable.

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The authors declare that they have no competing interests.

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