



Cysteine as a Carbon Source, a Hot Spot in Cancer Cells Survival

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Cancer cells undergo a metabolic rewiring in order to fulfill the energy and biomass requirements. Cysteine is a pivotal organic compound that contributes for cancer metabolic remodeling at three different levels: (1) in redox control, free or as a component of glutathione; (2) in ATP production, via hydrogen sulfide (H₂S) production, serving as a donor to electron transport chain (ETC), and (3) as a carbon source for biomass and energy production. In the present review, emphasis will be given to the role of cysteine as a carbon source, focusing on the metabolic reliance on cysteine, benefiting the metabolic fitness and survival of cancer cells. Therefore, the interplay between cysteine metabolism and other metabolic pathways, as well as the regulation of cysteine metabolism related enzymes and transporters, will be also addressed. Finally, the usefulness of cysteine metabolic route as a target in cancer treatment will be highlighted.

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INTRODUCTION

Posited as a glutathione precursor or as a source of sulfur and carbon, cysteine contributes for cancer cell strongness and prosperity, allowing their survival upon stressful microenvironmental conditions and upon drugs exposure (1, 2).

In the recent years, the role of cysteine and glutathione in the scavenging of reactive oxygen species (ROS), contributing for chemoresistance (3–9) have been under scrutiny. Cysteine and glutathione are crucial in the maintenance of the metabolic course (10–13), since the cancer metabolic rewiring implies the generation of oxidative stress (14–16). Nevertheless, cysteine has been underestimated as a carbon source, due to the core position of glycolysis in the cellular biosynthesis and bioenergetics, being major emphasis given to glucose as a preferential fuel and to glutamine as its main substitute [as reviewed in (17, 18)].

Despite few recent studies addressing cysteine as a key organic compound in cancer, the actual meaning of cancer cells' cysteine dependency is far from being completely known. Therefore, in the next sections, the metabolic dynamics of cysteine in cancer and the interconnections between cysteine metabolism and other metabolic pathways will be addressed.

CYSTEINE AS A CARBON SOURCE IN CANCER

The usefulness of cysteine as a carbon source is visible along the cysteine catabolic pathway, since cysteine catabolism originates organic compounds used in carbon and energy metabolism (19–23).

Cysteine Metabolism and Other Metabolic Pathways Intercrosses

The metabolic reliance of cancer cells on cysteine promotes a better adaptation to metabolically damaging conditions and the development of chemoresistance (1, 2), accounting for cancer success.

Cysteine catabolism occurs upon the action of four enzymes: cystathionine β -synthase (CBS); cystathionine γ -lyase (CSE), and 3-mercapto-pyruvate sulfurtransferase (MST), which works together with cysteine aminotransferase (CAT) (24, 25). Cysteine-derived organic compounds, such as pyruvate, α -ketobutyrate and glutamate (26), supply other metabolic pathways (Figure 1A), such as the tricarboxylic acid (TCA) cycle and glucose-related pathways. Besides organic compounds, cysteine catabolism generates hydrogen sulfide (H_2S) (27–32). Thus, the role of the enzymes has been directly associated with ATP production, as H_2S can donate electrons to electron transport chain (ETC) (27, 28, 33, 34), and indirectly with the role of H_2S as a paracrine and an autocrine signaling molecule in cancer, regulating cell proliferation, bioenergetics and angiogenesis (35, 36). The link between the enzymes involved in cysteine degradation and malignancy (27–29, 37–42) is thereby not easy to distinguish as being specifically related to the release of H_2S or to the generation of organic compounds.

Cysteine catabolism cannot be addressed without mentioning that *de novo* cysteine synthesis occurs through the transsulfuration pathway (TSP), deriving from methionine and serine (Figure 1B), which makes the synthesis of cysteine dependent on the availability of methionine cycle intermediates (43). Serine and glycine can be glutamine-originated, making an interconnection of glutamine and cysteine metabolism (3). In methionine cycle, homocysteine is synthesized, being further condensed with serine to generate cystathionine, by CBS. Afterwards cystathionine is hydrolyzed by CSE, giving rise to cysteine, and other compounds (e.g., ammonia, α -ketobutyrate or propionate) [as reviewed (44)].

Pyruvate kinase (PK) is considered a main regulator of energy homeostasis by the generation of glucose-derived pyruvate (45), but recently, cysteine catabolism and serine synthesis pathway (SSP) were considered the main supplier of pyruvate in cancer cells, as a way of overcoming the lack of PK expression (46).

One-Carbon Metabolism Concurrently Depends on and Controls Cysteine Bioavailability

The one-carbon metabolism is constituted by the methionine cycle and the folate cycle, which are dependent on serine and glycine bioavailability and from which certain intermediates are deviated to form cysteine (Figure 1B). Serine is synthesized from glucose and glutamine, and in turn serine gives rise to glycine [as reviewed (47)], which enters the folate cycle (48). Interestingly, cancer cells produce glycine from serine rather than import glycine (49), pointing out the upregulation of SSP as a cancer specialization. Moreover, phosphoglycerate dehydrogenase, a SSP key enzyme, was recently proposed as a poor prognosis marker in lung (50), gastric (51), and pancreatic (52) carcinomas.

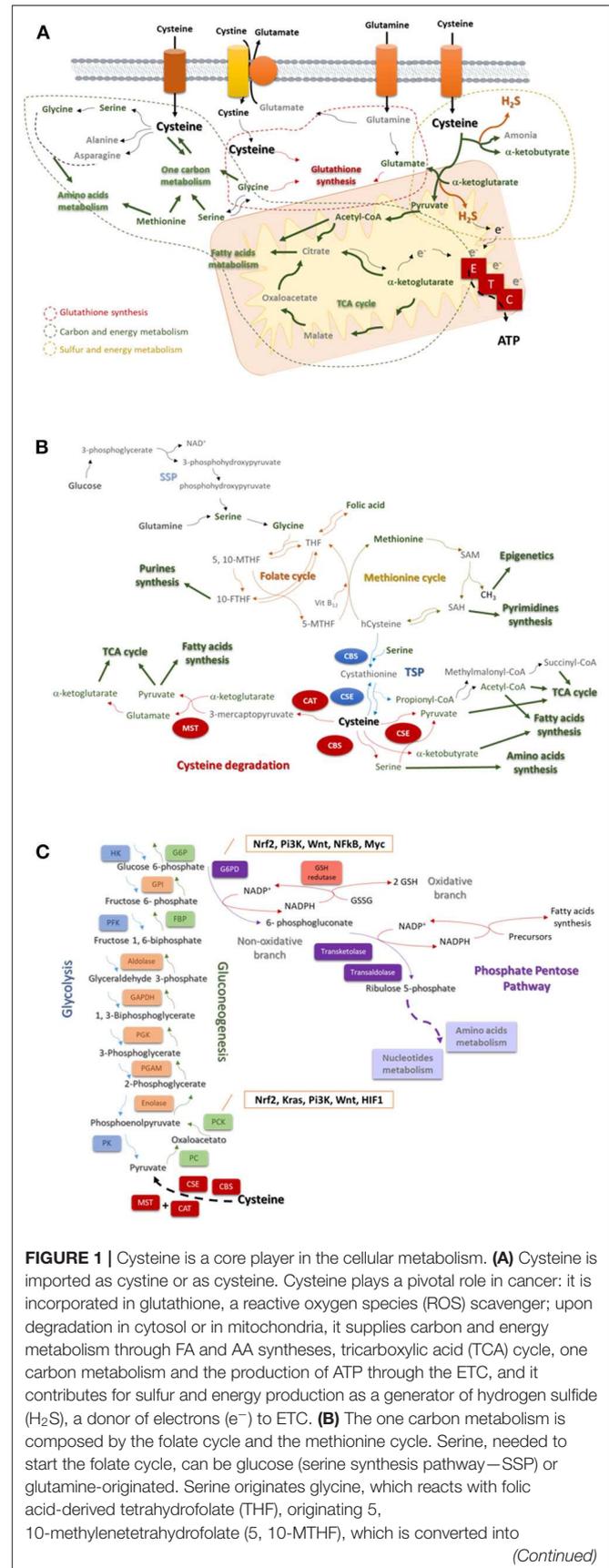


FIGURE 1 | Cysteine is a core player in the cellular metabolism. **(A)** Cysteine is imported as cystine or as cysteine. Cysteine plays a pivotal role in cancer: it is incorporated in glutathione, a reactive oxygen species (ROS) scavenger; upon degradation in cytosol or in mitochondria, it supplies carbon and energy metabolism through FA and AA syntheses, tricarboxylic acid (TCA) cycle, one carbon metabolism and the production of ATP through the ETC, and it contributes for sulfur and energy production as a generator of hydrogen sulfide (H_2S), a donor of electrons (e^-) to ETC. **(B)** The one carbon metabolism is composed by the folate cycle and the methionine cycle. Serine, needed to start the folate cycle, can be glucose (serine synthesis pathway—SSP) or glutamine-originated. Serine originates glycine, which reacts with folic acid-derived tetrahydrofolate (THF), originating 5, 10-methylenetetrahydrofolate (5, 10-MTHF), which is converted into

(Continued)

FIGURE 1 | 5-methyltetrahydrofolate (5-MTHF) or 10-methyltetrahydrofolate (10-MTHF). 5-FTHF reacts with vitamin B₁₂ (Vit B₁₂) and homocysteine (hCysteine), forming THF and methionine. 10-FTHF is incorporated in the synthesis of purines, essential for nucleotides synthesis. In the methionine cycle, methionine is converted sequentially into S-adenosylmethionine (SAM), and to S-adenosylhomocysteine (SAH). The consequent release of a methyl group (CH₃) will supply the methylation of DNA, RNA and histones. SAH is converted into hCysteine keeping on the methionine cycle, or it is deviated to the pyrimidines synthesis and consequently to nucleotides synthesis. Cysteine is *de novo* synthesized in the transsulfuration pathway (TSP), linking cysteine to the methionine cycle. The hCysteine, is converted into cystathionine through the condensation with serine. Cystathionine is hydrolyzed to cysteine and other organic compounds (e.g., α -ketoglutarate or propionate). Cysteine can be degraded and originate (directly or not) pyruvate, α -glutarate, α -ketobutyrate, serine, propionyl-CoA, succinate, and acetyl-CoA to supply the tricarboxylic acid (TCA) cycle, amino acids synthesis or the fatty acids synthesis. **(C)** Glycolysis is the degradation of a glucose molecule into 2 pyruvate molecules, through a sequence of reactions, having three irreversible steps catalyzed by hexokinase (HK), phosphofructokinase (PFK), and pyruvate kinase (PK). Gluconeogenesis is almost a reversion of glycolysis and cysteine-derived pyruvate is converted in glucose. The reversible steps are common to glycolysis and gluconeogenesis and are catalyzed by enolase, phosphoglycerate mutase (PGAM), phosphoglycerate kinase (PGK), Glyceraldehyde 3-phosphate dehydrogenase (GAPDH), aldolase, and Glucose-6-phosphate isomerase (GPI). The three irreversible steps of glycolysis impose gluconeogenesis to use four other enzymes: PC, pyruvate carboxylase; PKC, phosphoenolpyruvate carboxykinase; FBP, fructose 1,6-bisphosphatase; and G6PC, glucose 6-phosphatase. Gluconeogenesis is regulated by Nrf2, Kras, PI3K, Wnt, and HIF1. Besides being an intermediate of glycolysis and gluconeogenesis glucose 6-phosphate is the substrate of phosphate pentose pathway (PPP), which has two biochemical branches (an oxidative and a non-oxidative branch) of reversible reactions. The non-oxidative branch of PPP uses glucose-6-phosphate to generate ribulose5-phosphate for AA and nucleotides synthesis. While the oxidative branch of PPP generates NADPH, involving the action of glutathione (GSH) reductase and the interplay with reductive biosynthesis, namely FA synthesis. PPP is regulated by Nrf2, PI3K, Wnt, NFkB, and Myc.

The folate cycle depends on the dietary folate and controls the systemic levels of methionine and homocysteine (53), which directly regulates cysteine bioavailability. This cycle uses glycine and tetrahydrofolate (THF; converted from folic acid) and produces intermediates [5,10-methylene-tetrahydrofolate (5,10-MTHF) and 5-methylene-tetrahydrofolate (5-MTHF)] to supply purine synthesis and afterwards by the entrance of cobalamin (vitamin B₁₂) and the interconnection with the methionine cycle, folic acid is again synthesized (**Figure 1B**).

The import of methionine is a vital step in one carbon metabolism, since methionine is an essential amino acid (AA), which is sequentially converted into S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH), releasing methyl groups (CH₃) that will be used in DNA, RNA, and histones methylation (**Figure 1B**). SAH can be deviated to originate pyrimidines or originate homocysteine, which will react with vitamin B₁₂ and 5-MTHF in order to resynthesize methionine. Homocysteine can be deviated from one carbon metabolism and, together with serine, enter in TSP to originate cysteine and propionyl-CoA under the action of CBS and CSE (21, 54). Propionyl-CoA can be further converted into AA, fatty acids (FA) and TCA cycle intermediates (22, 23).

Methionine scarcity impairs cancer cells' proliferation (55), and methionine dependency is controlled by PI3K/AKT/mTOR

pathway through the induction of the expression of cyst(e)ine/glutamate antiporter xc- (xCT; *SLC7A11* gene) (56), ensuring that the levels of cysteine won't limit the bioavailability of methionine, since cysteine uptake downregulates TSP.

As above mentioned, the methyl groups generated in the one-carbon metabolism, when released from methionine cycle, are crucial for DNA, RNA, and histones methylation for epigenetic modulation (57), whose functioning is regulated by PI3K/mTOR and HIF2 α pathways, the same that control SSP and one-carbon metabolism (58, 59). Hence, the expression of LAT1 (*SLC7A5*), the main transporter of methionine, is associated with the activity of methyltransferases in lung cancer cells (60). Moreover, the relevance of one carbon metabolism is also highlighted by the association between the levels of folate in peripheral blood, DNA methylation and colorectal tumor staging (61). Accordingly, the existence of polymorphisms and the increased expression or activity of enzymes participating in one-carbon metabolism are considered markers for highly proliferative and aggressive cancer phenotypes and chemoresistance (57, 62, 63).

Cysteine Contribution for Gluconeogenesis and Phosphate Pentose Pathway (PPP)

Gluconeogenesis or the synthesis of glucose from non-glucidic compounds, such as glycerol, lactate, pyruvate, acetyl-CoA, or glucogenic AA, only recently started to be explored in cancer. Gluconeogenesis (**Figure 1C**) is a reversion of glycolysis, with 3 alternative reactions counteracting the 3 irreversible steps of glycolysis (64–67). Cysteine is a glucogenic AA, as it originates pyruvate, however, as far as I know, cysteine was not yet explored as a source of glucose in cancer. Nevertheless, in other biological models cysteine has been pointed out as an important regulator of enzymes, such as peroxidases that can interact with PK and block the conversion of pyruvate into acetyl-CoA, avoiding pyruvate entrance in TCA cycle or in FA synthesis (68) and favoring its deviation into gluconeogenesis, ensuring the cell needs of glucose.

Gluconeogenic enzymes are regulated by signaling pathways pivotal in carcinogenesis KRAS-dependent, PIK3/mTOR and Wnt pathways and HIF1 [as reviewed in (69) and in (70)]. The pro-survival character of gluconeogenesis is supported by the upregulation or the *de novo* expression of its enzymes in different cancer types, such as breast, colon, stomach, uterine cervix, liver, and pancreas (67).

The inhibition of the final step of gluconeogenesis redirects glucose 6-phosphate to phosphate pentose pathway (PPP) (**Figure 1C**), making gluconeogenesis a supplier of PPP in glucose depleted environments. Again, cysteine as a source of pyruvate can be at the origin of glucose-6-phosphate canalized to PPP.

The PPP occurs in parallel to glycolysis through two irreversible oxidative reactions followed by two biochemical branches (an oxidative and a non-oxidative branch) of reversible reactions (71). The non-oxidative branch of PPP (**Figure 1C**) uses glucose-6-phosphate to generate pentose phosphates for AA and nucleotides synthesis. While the oxidative branch of PPP generates NADPH, essential for FA synthesis and

redox balance (72–75). Indeed, a cellular dependence on PPP was described in cancer cells that are heavy cystine importers, requiring NADPH for cystine to cysteine intracellular conversion (76).

PPP is associated with increased cancer cell survival and proliferation (74, 77), implying the inhibition of phosphofructokinase (mainly PFK1) from glycolysis (78, 79), a direct competitor of glucose-6-phosphate dehydrogenase (G6PD), the limiting enzyme in PPP (75). PI3K/AKT pathway controls the expression and the activity of G6PD, whose dimerization is activated by phosphorylation (80). Wnt/c-MYC and p53-NFκB pathways induce the expression of G6PD, activating PPP as part of a more metastatic and chemoresistant cancer phenotype (81, 82).

Besides cysteine is a source of pyruvate, another important link of gluconeogenesis and PPP to cysteine metabolism and antioxidant character (83), is the fact that the expression of PCK1 (phosphoenolpyruvate carboxykinase 1) and G6PD is directly regulated by Nrf2, a master regulator of redox control (84, 85).

Regulation of Cysteine Anabolism and Catabolism, in Cancer

The metabolic reliance on cysteine is a common feature to different cancer types. Therefore, the upregulation of catabolic pathways and the expression of cyst(e)ine transporters is often observed in cancer together with the upregulation of cysteine synthesis. The TSP is dependent on the action of CBS and CSE, which can also act in cysteine catabolism (Figure 1B). The expression of CBS and CSE seems to be cancer type-related often dependent on the organ and the genetic background.

In ovaries, it seems that CSE must be silenced upon malignant transformation, since it is expressed in normal epithelial ovarian cells but it is absent in malignant tumors (27, 86). On the contrary, the high CBS expression is a feature of ovarian cancer, being associated with advanced stage and chemoresistance (27, 86). In colon cancer, the increased expression and activity of CBS and CSE is associated with high rates of proliferation and migration of cancer cells, controlled, respectively, by PI3K/AKT and Wnt pathways (28, 86, 87). Controversially to the evidence that CBS is linked to carcinogenesis, a study presents CBS as a tumor suppressor gene, claiming that in gastric and colorectal cancer the expression of CBS is inhibited by DNA methylation in association with KRAS mutations (88). Notwithstanding a study reporting the importance of both CBS and CSE in gastric carcinogenesis (89), other study shows a compensatory mechanism involving the two enzymes. It was demonstrated that CSE expression overlaps the absence of CBS, being CSE correlated to increased proliferation and decreased apoptotic rate (41). In thyroid cancer, CBS is the major responsible for H₂S production, which activates cancer cells proliferation and migration, through ROS/PI3K/AKT/mTOR and MAPK pathways (90). In breast cancer, tumors, and cell lines, CSE favors cell proliferation and migration under the command of STAT3, a member of JAK/STAT pathway (38); while in a murine model, CSE is stated as controlling the metastatic behavior of breast cancer cells through VEGF-dependent PI3K

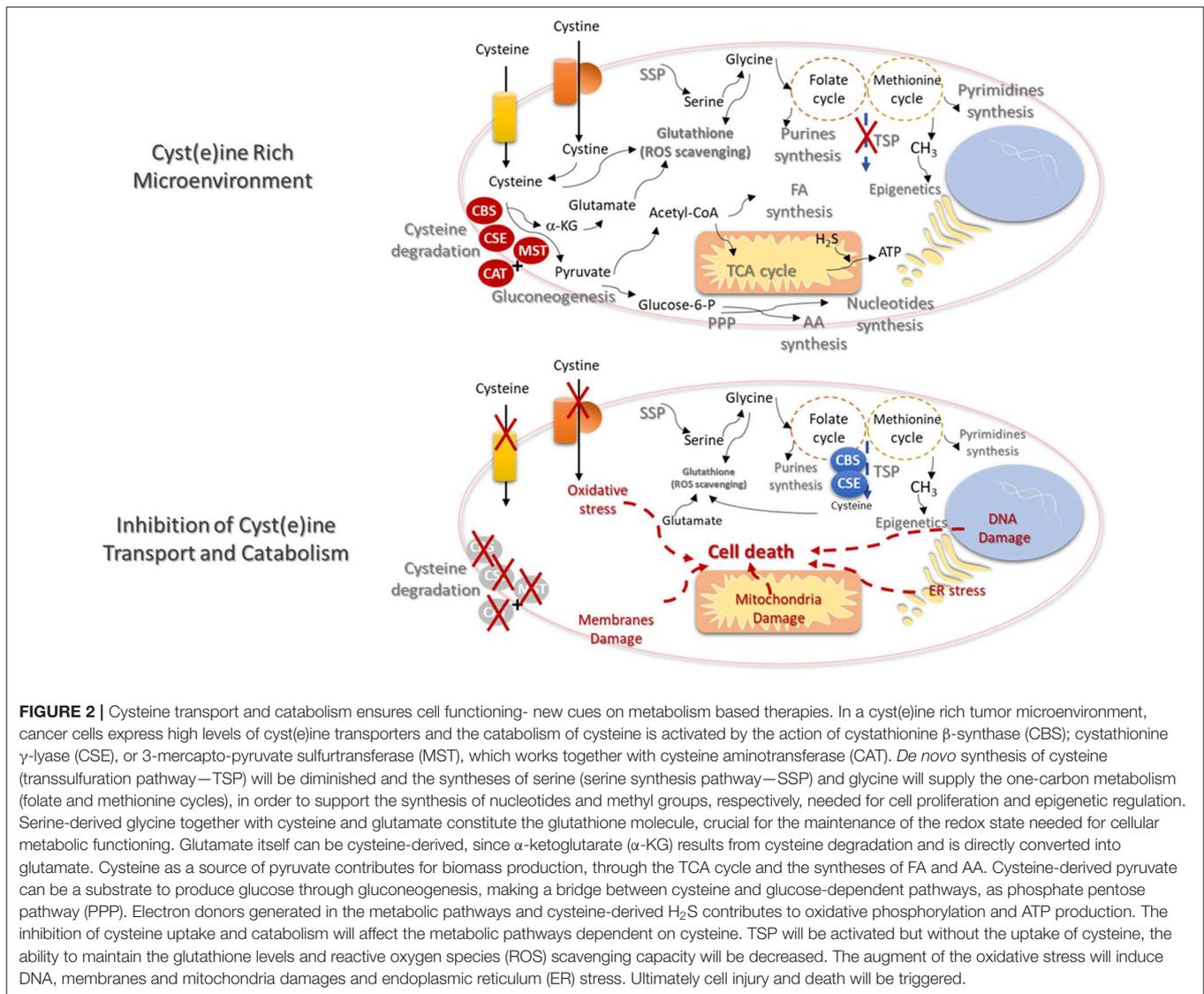
and MAPK pathways (91). In melanoma, CSE loss of expression accompanies the progression of the disease, being highly expressed in primary tumors and low expressed in metastatic lesions (30). The abovementioned data supports that the role of CBS and CSE enzymes, favoring or counteracting cancer, is highly adaptive and obviously dependent on the cysteine bioavailability itself, within certain cancer microenvironmental and metabolic contexts. Furthermore, if the role of CBS and CSE in cancer is related to cysteine anabolism or catabolism is not always clear.

Cysteine degradation catalyzed by CAT and MST (Figure 1B) is not deeply explored in cancer, since MST is more enzymatically efficient at a pH higher than the physiological, thus the role of CBS and CSE is considered more relevant in cancer biology (92). However, Zuhra et al. (93) demonstrated recently, in a colon cancer cell line, that MST can produce H₂S from N-acetylcysteine instead of cysteine-derived 3-mercaptopyruvate. Nonetheless, MST is constitutively expressed in normal differentiated cells and some studies have detected its expression or activity in various cancer cell lines and primary tumors, including brain, colon, liver, kidney, lung and bladder cancer, and melanoma [reviewed in (35)]. In some of those studies the MST expression was higher than CSE expression (94, 95), and an association between MST expression and chemoresistance was found (96, 97). Few functional assays tried to correlate the expression and/or activity of MST with the cancer cells features, however, using inhibiting and silencing assays, some studies proved that MST activity is important for cancer cells proliferation (98, 99). Unfortunately, most studies addressing cysteine degradation are focused in H₂S production and not in resulting organic compounds.

REGULATORS AND MEDIATORS OF CYSTEINE TRANSPORT, IN CANCER

The transport of cysteine across the cell membrane is a critical step in cysteine metabolic course (Figure 1), and it is often transported in its oxidized dimer, cystine. Amongst cystine transporters, the cystine/glutamate antiporters are the most studied in cancer context, but mainly on their role in glutamate export (100, 101), showing a correlation between glutamate export and increased cancer cells aggressiveness (100, 102–106). However, for glutamate export to occur cystine import is mandatory, thus the increased intracellular levels of cysteine must be relevant for cancer poor prognosis. This evidence is reinforced by the activation of cysteine endogenous synthesis (56, 107) in cancer cells upon xCT downregulation (108–110).

xCT is an undeniable linker between cysteine and the whole metabolic network. Cancer cells overexpressing xCT present an overactivation of the glucose-dependent PPP, as a mean of replacing NADPH consumed in the imperative conversion of cystine into cysteine (76). Furthermore, xCT makes a bridge between cysteine uptake and glutamine metabolism, since glutamine is the main precursor of glutamate, whose export is essential for xCT-mediated import of cysteine (17). The role of xCT, as a facilitator of cyst(e)ine protective antioxidant role



in cancer cells, is evidenced by the regulation of its expression by Nrf2 (111) and by signaling pathways activated by oxidative stress, including PI3K/AKT/mTOR (56, 112, 113) and MAPK pathways (110). Since augmented glutathione contributes for chemoresistance, the expression of xCT is also associated with resistance to drugs, platinum-salts (9) and epigenetic modulators (114), and with cell death evasion (115, 116). Considering a new cell death process, called ferroptosis, xCT is an important inhibitor, since the accumulation of lipid peroxides activates ferroptosis and cysteine-derived glutathione is the substrate used by glutathione peroxidase 4 (GPX4) in the dissipation of lipid peroxides (117).

The cysteine direct import (118) is mediated by cysteine transporters, and the expression of some of them have been addressed in cancer. Albeit, the promiscuity of these transporters in transferring different AA (e.g., cysteine, glutamine, and glutamate) impedes the direct association between their

overexpression and cysteine uptake. Even though, their expression is relevant in cancer as it happens with AT-B^{0,+} (SLC6A14), which is the transporter with the broadest selectivity for AA, including cysteine (119–123).

In brief, EAAT3 (SLC1A1) overexpression was detected in brain and prostate cancer cells (124–126), being associated with increased chemoresistance in colorectal cancer models (127). As mentioned above, LAT1 can affect the bioavailability of cysteine since it is the main methionine transporter, being its expression related to chemoresistance (128). ASCT1 (SLC1A4) is overexpressed in prostate cancer (129), however, its expression and relevance in cancer was addressed considering glutamine or glutamate transport. Because glutamine/glutamate and cysteine metabolic pathways are deeply connected (130, 131) and cysteine is also considered a modulator of glutamine transport (132, 133), certainly these transporters are crucial in the cysteine metabolism reliance of cancer cells.

DISCUSSION

The increased intracellular bioavailability of cysteine is itself a stimulus for metabolic remodeling. Considering the role of cysteine as a carbon source in a scenario of high concentrations of cysteine, with no limitation in cyst(e)ine uptake, most part of cysteine will enter the degradation route, reducing the need for cysteine synthesis, dependent on the deviation of homocysteine from the one-carbon metabolism (**Figure 2**). This would imply the accumulation of serine that is very important for glycine synthesis and the activity of folate and methionine cycles, in order to supply the synthesis of nucleotides and methyl groups, respectively, needed for cell proliferation and epigenetic regulation. Serine-derived glycine together with cysteine and glutamate constitute the glutathione molecule, essential for the maintenance of the redox state allowing cellular metabolic functioning and chemoresistance. Glutamate can be a product of cysteine conversion into pyruvate, with α -ketoglutarate consume. Further, glutamate can be converted into glutamine, which is considered the main substitute of glucose (134).

Cysteine as a source of pyruvate can liberate the cell from the dependency of glucose, and contribute for biomass production, through the TCA cycle and the syntheses of FA and AA. As aforementioned, cysteine-derived pyruvate can be a substrate to produce glucose, making a bridge between cysteine and glucose-dependent pathways, as glycolysis and PPP. All the metabolic pathways that generate electron donors participating in the oxidative phosphorylation can be supplied by cysteine. In another hand, cysteine degradation releases H_2S , which is itself an electron donor for ETC.

In brief, cysteine metabolic route is full of cues to find biomarkers for prognosis, recurrence and response to therapy, as well as suitable therapeutic targets to trigger cancer cell death due to cysteine starvation (**Figure 2**), as pointed out in different papers (135, 136). In certain type of cancer, it

may be an unsuccessful strategy, since many cancer cells upon cysteine scarcity or the inhibition of cyst(e)ine transport can upregulate TSP for endogenous cysteine production (137, 138). However, the need of methyl groups for epigenetic regulation, in some tumors, prevents the activation of cysteine synthesis and activates one-carbon metabolism (138). Therefore, the systemic decrease of cysteine levels is proposed as a suitable strategy in cancer clinical management, being supported by pre-clinical studies with promising results in breast and prostate carcinomas and leukemia. These studies showed that systemic treatment with cyst(e)inase decreases the levels of cysteine together with tumor burden (139). Cyst(e)inase degrades extracellular cysteine and cystine, leading to reduced intracellular cysteine and glutathione levels, affecting cancer cells redox capacity (44, 140), inducing the accumulation of ROS (26) and consequent ferroptosis (135, 136).

This review has also the objective of highlighting that efforts must be made to clarify the actual role of cysteine catabolism in cancer biosynthesis and bioenergetics, beyond H_2S production. Cysteine catabolism may not be a core metabolic pathway but deviation of cysteine-derived compounds into other metabolic pathways is pivotal in cancer cells metabolic drift and survival.

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The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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