Cysteine Aminotransferase

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The hydrogen sulfide (H2S)-generating enzymatic system composed of cysteine aminotransferase (CAT, EC 2.6.1.3, also known as aspartate aminotransferase, AST, or glutamate transaminase, GOT), and 3-mercaptopyruvate sulfurtransferase (MST, EC 2.8.1.2), is known to be implicated in the catabolism of cysteine [1].

Keywords: cysteine aminotransferase (CAT) ; 3-mercaptopyruvate sulfurtransferase (MST), cancer ; metabolic remodeling

1. Introduction

Metabolic remodeling is a critical skill of malignant cells, allowing their survival and spread. The metabolic dynamics and adaptation capacity of cancer cells allow them to escape from damaging stimuli, including breakage or cross-links in DNA strands and increased reactive oxygen species (ROS) levels, promoting resistance to currently available therapies, such as alkylating or oxidative agents. Therefore, it is essential to understand how metabolic pathways and the corresponding enzymatic systems can impact on tumor behavior. Cysteine aminotransferase (CAT) per se, as well as a component of the CAT: 3-mercaptopyruvate sulfurtransferase (MST) axis, is pivotal for this metabolic rewiring, constituting a central mechanism in amino acid metabolism and fulfilling the metabolic needs of cancer cells, thereby supplying other different pathways.

2. Cysteine Aminotransferase Structure and Localization

Two isoforms of CAT, classified according to their cellular localization as cytoplasmic (cCAT) and mitochondrial CAT (mCAT), are encoded respectively by GOT1 (glutamic-oxaloacetic transaminase 1) and GOT2 (glutamic-oxaloacetic transaminase 2) [2], which are extremely well conserved across species [3][4]. CAT is a homodimeric pyridoxal phosphate (PLP)-dependent aminotransferase [5][6], being considered the best studied PLP-dependent enzyme, given its easy large-scale purification and its stability [7][8]. The mCAT was in fact the first PLP-dependent enzyme to have its X-ray structure determined [9], leading to key insights on its catalytic mechanism, holding to this day [7]. Each cCAT monomer consists of two domains: A small domain composed of four α-helices and three β-strands, and a large domain comprising a 7-stranded β-sheet and several short α-helices. Protein dimerization is ensured by the large domains, with two PLP-binding sites which are stabilized by the surrounding residues [8]. PLP has a dual physiological effect: While it is vital for normal cellular metabolism, excessive levels of free PLP can non-specifically and covalently bind to thiol and amino groups [10][11]. Indeed, spontaneous formation of hydrogen sulfide (H_2S) by free PLP and cysteine has been reported [12]. Mutations in cCAT impact on its structure and prevent effective PLP binding by a dimer interface misalignment, which can lead to its dissociation and PLP release [8].

Firstly isolated from rat liver [13][14][15], both mCAT and cCAT were primarily studied within the context of pathologies associated with defects in the cysteine degradation pathway [16][17]. Overall CAT activity is higher in heart and liver, but it is also detected in kidney, brain, and skeletal muscle [5][6][18]. Regarding cysteine metabolism, CAT is generally referred to in association with MST, the focus of most studies. Meister (1953) and Wood and Fiedler (1953) first described the cysteine-catabolizing enzyme MST in rat liver, and it was further found to be distributed and well conserved throughout prokaryotic and eukaryotic organisms [19][20][21][22][23]. MST is a Zn-dependent enzyme, member of the rhodanese-like sulfurtransferase family, containing two rhodanese-like domains and existing in a monomer-dimer equilibrium, the first being the active form [1][24][25]. MST presents a broad distribution in most mammalian tissues, although its expression is tissue-specifically regulated, being at high levels in kidney, liver, brain, testes, large intestine, and endocrine organs [22][24][26]. Interestingly, an alternative function has been proposed for MST which may be relevant in the context of cancer cell biology. Indeed, Frasdorf and co-workers described MST as a tRNA thiouridine modification protein (TUM-1), being implicated in the thiolation of cytosolic tRNA, and identified two isoforms of this protein in human cell lines, presenting different subcellular localizations: TUM1-Iso1 was identified exclusively in the cytosol; and TUM1-Iso2 was found to be expressed both in the cytosol and the mitochondria [25]. Interestingly, both isoforms are reported as exhibiting similar

kinetic parameters, including protein stability, pH dependence and catalytic constants in the presence of non-physiological acceptors, as cyanide and DTT [25][27]. As mentioned, studies have clarified the subcellular localization of both CAT and MST in cytosol (cCAT; cMST) and mitochondria (mCAT; mMST). However, the CAT:MST axis may be more relevant in the mitochondria, since this is the site where cysteine is preferentially found [26].

3. Prospects

Metabolism reprogramming is an established hallmark of cancer. Several pathways which cancer cells rely on for invasive and proliferative potential have been dissected over the years, aiming to understand the metabolic puzzle that is certainly an important cue in cancer and that can lead to improvements in current diagnosis and prognosis tools and therapeutic strategies.

Amino acids metabolism is a crucial core in the entire cellular metabolism and here we showed that CAT plays a relevant role in the metabolic network by catalyzing the interconversion of different amino acids. Glutamate and cysteine are two components of GSH, and CAT uses both these amino acids as substrate. Thus, their bioavailability, directly dependent on CAT, will condition the antioxidant capacity of cancer cells mediated by GSH. This is a tricky point in the oxidative stress control, since GSH is the main non-protein cellular scavenger and its depletion leads the cell to undergo ferroptosis and death. In the other hand, the degradation of cysteine by CAT:MST promotes H_2S production, which presents antioxidant properties and can somehow overcome the depletion of GSH in oxidative stress control. Moreover, cysteine is placed as a relevant carbon source, since pyruvate is a product from its degradation by CAT:MST. Glutamine, besides controlling GSH synthesis by originating glutamate and glycine, also acts on the control of cysteine metabolism, degradation, and de novo synthesis. By originating glutamate and sequentially α-ketoglutarate, glutamine controls the degradation of cysteine through CAT:MST axis; and by originating glycine to supply the one carbon metabolism, glutamine controls the cysteine synthesis through the transulfuration pathway.

The CAT:MST enzymatic axis is an important system with growing interest in cancer metabolism, since it is known to be altered in cancer with an established association to cancer progression and poor prognosis. Nevertheless, amongst the cysteine degradation/H_2S production pathways, the CAT:MST pathway is under explored. Its pro-cancer role is related to the production of essential molecules and energy to answer cancer cells demands. However, deeper insights are necessary to uncover the crosslinks established within the CAT:MST axis metabolism in cancer cells and to understand if the accumulation of antioxidant agents that induce chemoresistance can be affected by a balance between different pathways and molecules, in particular the amino acids whose fate is controlled by CAT. Perhaps the most relevant aspect of CAT in cancer metabolism is the fact that it sits precisely at the crossroads of amino acids metabolism, antioxidant response capacity and H_2S-based signaling, all crucial factors for cancer cell adaptation within the tumor microenvironment. Therefore, the CAT:MST axis encloses a high potential of therapeutic management, mainly by targeting CAT which should disrupt and disturb the pathophysiological homeostasis sustaining cancer cells survival. Thereby, it will help in the definition of new therapeutic strategies and drugs, accounting for the improvement of the oncological disease management.

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