Cytidine 5’-triphosphate Synthetase: A Pyrimidine Biosynthetic Enzyme Critical to Cellular Synthesis and Cancer Chemotherapy

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Abstract

The pyrimidine biosynthetic enzyme Cytidine 5’-triphosphate (CTP) synthetase has an important role in the biosynthesis of RNA, DNA and phospholipids. The synthetase has been found to be highly regulated at the level of enzyme activity and enzyme synthesis in both prokaryotes and eukaryotes including humans. The enzyme has been the target of inhibition by various drugs since cellular proliferation requires CTP synthesis. The design of new drugs targeting CTP synthetase activity in humans could prove important to cancer chemotherapies since it may allow new cancer treatment procedures to be developed.

Keywords: Cytidine 5’-triphosphate synthetase; Pyrimidine biosynthesis; Phospholipid synthesis; Nucleic acid synthesis; Cancer chemotherapy

Introduction

The enzyme Cytidine 5’-triphosphate (CTP) synthetase (EC 6.3.4.2) catalyzes a critical reaction in pyrimidine nucleotide biosynthesis as well as phospholipid formation [1-3]. The enzyme catalyzes the synthesis of CTP by the amination of Uridine 5’-triphosphate (UTP) involving an Adenosine 5’-triphosphate (ATP)-dependent phosphorylation of UTP where glutamine serves as the nitrogen donor [1,2]. The amino acid residues aspartate and leucine have been found promote the hydrolysis of glutamine [4]. The active enzyme is a homotetramer but requires the presence of UTP and ATP. The regulation of CTP synthetase in prokaryotes has been investigated. In the Gram negative bacterium Escherichia coli, CTP synthetase was purified and its activity was shown to be regulated by its product CTP as well as UTP, ATP, Guanosine 5’-triphosphate (GTP) or dTTP [1,2]. GTP has been reported as allosteric activator or inhibitor depending upon the E. coli cellular conditions [5,6]. The E. coli enzyme consists of an N-terminal synthetase domain and a C-terminal glutaminase domain. The latter domain cleaves ammonia from glutamine and the ammonia is transferred from the glutaminase to the synthetase domain by a tunnel mechanism [5,7]. The bacterial enzyme existed as an inactive dimer that aggregated to an active tetramer having a molecular weight of 210,000 daltons [2]. Positive cooperativity was noted towards the binding of the substrates ATP and UTP while negative cooperativity was observed for the binding of GTP and glutamine to the enzyme [8]. Recently, it has been determined that reduced Nicotinamide Adenine Nucleotide (NADH) or Nicotinamide Adenine Nucleotide Phosphate (NADPH) is a moderate inhibitor of the E. coli synthetase with the cofactors enhancing inhibition by CTP and regulation by GTP [9]. Regulation of the purified CTP synthetase from the Gram positive bacterium Lactobacillus lactis was found to be different from the E. coli enzyme since L. lactis synthetase was inhibited by ammonium ions in the absence of the nucleotides ATP and UTP [10]. It is interesting to note that the enzyme CTP synthetase forms filaments in E. coli as well as Caulobacter crescentus. In C. crescentus, the filaments not only have synthetase catalytic activity but control the curvature of the C. crescentus cell. The formation of filamentous structures by the enzyme has also been found in eukaryotes indicating the enzyme subunit polymerization is conserved [11]. The synthesis of the Gram negative bacterium Salmonella typhimurium CTP synthetase was repressed by a cytidine or a thymidine compound [12]. The pyrimidine ribonucleotide pool data indicated that likely a cytidine or thymidine nucleotide was involved in the repression of CTP synthetase synthesis in S. typhimurium [13]. It was also shown that CTP synthetase was regulated at the level of gene expression in the Gram positive bacterium Bacillus subtilis. Cytidine nucleotides repressed the B. subtilis CTP synthetase synthesis by interacting with an unidentified regulatory protein [14].

Regulation of CTP synthetase in eukaryotes has been explored. Two isozymes of CTP synthetase exist in humans with the isoforms having 74% similarity in amino acid sequence [15]. Moreover, the crystal structure of isozyme CTP synthetase 1 has been determined [16]. Further, CTP synthetase isozyme 1 has been shown to be regulated by covalent modification. The enzyme protein kinase A was found to phosphorylate serine residues in the synthetase which increased CTP synthesis [17]. This regulation by protein kinase A has also been observed for the yeast Saccharomyces cerevisiae CTP synthetase [18]. In humans, CTP synthetase can aggregate into an intracellular macrostructure called the cytosome which is thought to be related to the metabolic status of the cell. It has been shown that the presence of cytosome does exist in certain human cancer cells [19]. Human synthetase subunit polymerization increases catalytic activity and its filament structure in humans is important to explaining the allosteric mechanisms of the enzyme [20]. Similarly in S. cerevisiae, the destabilization of CTP synthetase tetramers to inactive dimers increased filament formation in the yeast [21]. It is known that CTP synthetase activity is increased in rat or human tumor cells [22]. In addition, an increase in CTP synthetase activity was observed with the malignant transformation of human lymphoblastic cells [15]. With CTP synthetase being a critical enzyme in nucleotide and phospholipid synthesis, it has been targeted in an attempt to arrest cancer cells by decreasing their available CTP concentration. The drugs that have
been developed targetting synthetase activity include 3-deazauridine, acicin and cyclopentenyl cytosine. The effectiveness of these drugs upon tumor cells has varied [23-25].

Conclusion

In conclusion, the enzyme CTP synthetase has been widely studied in prokaryotes and eukaryotes due to its vital role in nucleotide formation, nucleic acid synthesis and phospholipid synthesis. Particularly for this reason, CTP synthetase has become a focus of cancer researchers. The inhibition of this pyrimidine biosynthetic enzyme by selected drugs in human cancer chemotherapy has shown promise in slowing cancer cell proliferation. Considering its growing importance to cancer chemotherapy, additional research on CTP synthetase needs to be done. New drugs that specifically target CTP synthetase in cancer cells could provide major advancements in human cancer cell treatments.

References