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 targetting 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

T e 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]. T e 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]. T e amino acid residues aspartate and leucine have been found promote the hydrolysis of glutamine [4]. T e active enzyme is a homotetramer but requires the presence of UTP and ATP. T e regulation of CTP synthetase in prokaryotes has been investigated. In the Gram negative bacterium *Escherichia coli*, CTP synthetase was purifed 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]. T e *E. coli* enzyme consists of an N-terminal synthetase domain and a C-terminal glutaminase domain. T e latter domain cleaves ammonia from glutamine and the ammonia is transferred from the glutaminase to the synthetase domain by a tunnel mechanism [5,7]. T e 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 purifed CTP synthetase from the Gram positive bacterium *Lactobacillus lactis* was found to be diferent from the *E. coli* enzyme since L. lactis synthetase was i... by ammonium ions in the absence of the nucleotides ATP ... It is interesting ilƒnuʿ 0 ώṅe®ᵐoe²0 ώὰnzym0 ώ0TP nthetase forms flaments in *E. coli* as well as *Caulobacter crescentus.* = nℝs M ϵπOl7

been developed targetting synthetase activity include 3-deazauridine, acivicin and cyclopentenyl cytosine. T e e fectiveness