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Editorial Open Access

Cytosine Deaminase: A Pyrimidine Base Salvage Enzyme Vital to the Effectiveness of a Substrate Mediated Enzyme Prodrug Chemotherapy

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Abstract

The pyrimidine salvage enzyme cytosine deaminase occupies an important function in the effectiveness of substrate mediated enzyme prodrug chemotherapy. The basis of this chemotherapeutic approach is that cytosine deaminase can catalyze the deamination of 5-fluorocytosine to 5-fluorouracil.The resultant 5-fluorouracil formed is a radiosensitizer agent that enhances the radiological targetting of a variety of cancer cells in humans for elimination.

Keywords: Cytosine deaminase; Pyrimidine salvage; 5-Fluorocytosine; Prodrug; Cancer chemotherapy

Editorial

The pyrimidine salvage pathway enzyme cytosine deaminase (EC 3.5.4.1) catalyzes the deamination of cytosine to uracil [1,2]. The resultant uracil is converted to the ribonucleotide uridine 5'-monophosphate by the enzyme uracil phosphoribosyltransferase. Cytosine deaminase has been detected in a variety of prokaryotic and eukaryotic organisms [1-7]. The importance of cytosine deaminase to chemotherapy is related to its ability to catalyze the deamination of the pyrimidine base analogue 5-fluorocytosine to 5-fluorouracil. The use of cytosine deaminase is one of the substrate mediated enzyme prodrug therapies that is used to treat various forms of cancer [8,9]. The pyrimidine analogue 5-fluorocytosine is considered a prodrug because it is non-toxic [8,9]. The 5-fluorouracil produced by cytosine deaminase has been shown to be a strong radiosensitizer that improves the efficacy of radiation treatment [10]. The bacterial gene for cytosine deaminase has been placed in an adenoviral vector under the control of a viral promoter. In the presence of this viral vector, low dose irradiation of human colon cancer results in cytosine deaminase actively catalyzing the deamination of 5-fluorocytosine promoting cytotoxic cell effects [10]. With cancer cells rapidly proliferating, the cancer cells require high levels of ribonucleotide triphosphates to sustain RNA synthesis. The 5-fluorouracil is eventually converted to 5-fluorouridine 5'-triphosphate which blocks RNA synthesis in organisms. The metabolism of 5-fluorouracil also results in the inhibition of the enzyme thymidylate synthetase causing a scarcity of thymidine nucleotides that blocks DNA synthesis. Essentially, this analogue specifically targets cancer cell growth by causing cessation of their nucleic acid synthesis leading to their cell death. Unfortunately, cytosine deaminase in organisms prefers cytosine as a substrate. The deamination of 5-fluorocytosine to 5-fluorouracil occurs at a slower rate making it less effectiveness in eventually producing 5-fluoronucleotides. One approach to overcome this problem is to alter the structure of cytosine deaminase by site-directed mutagenesis [11]. By altering the active site of cytosine deaminase, its ability to catalyze the deamination of 5-fluorocytosine can be increased. Molecular chemotherapy involving the use of bacterial or yeast cytosine deaminase has been utilized to treat pancreatic cancer, prostate cancer, colon cancer, breast cancer and lung cancer [12-15]. This substrate mediated enzyme prodrug therapy clearly can target a wide range of cancer cells.

In conclusion, the enzyme cytosine deaminase and its ability to catalyze the deamination of the pyrimidine analogue 5-fluorocytosine has become a focus of cancer researchers. This pyrimidine salvage enzyme is being used in chemotherapeutic treatments to target certain types of cancer cells. Considering its potential importance to chemotherapy for cancer, additional research on cytosine deaminase needs to be undertaken to better understand how this enzyme functions and how its activity towards 5-fluorocytosine can be further enhanced using molecular methodologies as well as advanced delivery systems that will result in site-specific cancer cell treatments.

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