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REVIEW

# Cytidine deaminase as a molecular target in cancer: an insight<sup>†</sup>

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<sup>†</sup>A heartfelt tribute to the memory of Professor Asima Chatterjee, the legendary scientist-teacher-humanitarian, on the occasion of her birth centenary (1917-2017).

**Cancer is one of the leading causes of death globally. Although more than 400 varieties of cancer have been reported, based on cell lines, still the actual reason of all types of cancer is not very clear. Several internal and external factors have been identified and the study is ongoing. Up to now about 73 proteins have been identified that are capable to influence directly various phases of cancer including mutation, cell proliferation, invasion, angiogenesis, and metastasis. Cytidine deaminase is one of the important proteins that is responsible for various types of cancer that includes gastric, liver, biliary tract, bladder, breast, pancreatic ductal adenocarcinoma (PDAC) and so on. Two excellent inhibitors of cytidine deaminase are commercially available. A brief overview is presented in this advanced review. Any omission is completely unintentional.**

**Keywords:** Cytidine deaminase; Cancer; Inhibitor; APOBEC; AID

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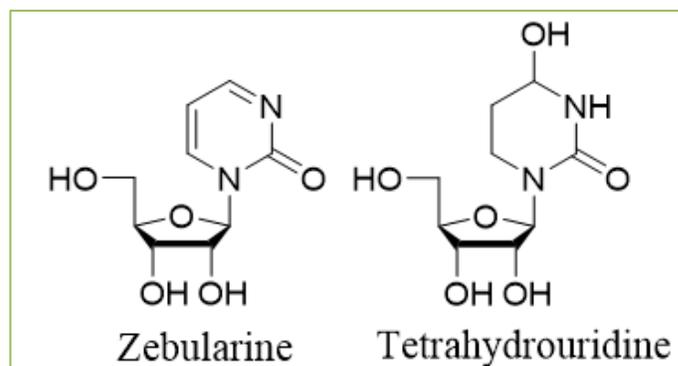
## Introduction

Cancer is the second leading cause of death worldwide and about 8.8 million people died in cancer only in 2015. Late-stage determination and limited accessibility in diagnosis/pathological evaluations, and subsequent treatment, particularly in the low- and middle-income countries, are very frequent. It is imperative to mention that about 1 in 6 deaths around the world is due to cancer<sup>[1]</sup>. On the other hand, appropriate knowledge and understanding of molecular targets are an important part in the battle against cancer. In fact a huge number of proteins play crucial role in different stages of cancer starting from DNA mutation, invasion, angiogenesis, metastasis and so on<sup>[2]</sup>. Deaminases are enzymes that catalyze deamination of a molecule, a

process that removes an amine group from the molecule by means of hydrolysis. This occurs in the liver or kidneys and usually the enzyme will remove only one amine group from any extra proteins. Cytidine deaminases (CDA) are the members of multisubunit enzymes (allosteric enzymes) family that are found in every mammal. It is encased in human tissues, organs, and it is encoded in the CDA gene. The CDA gene encodes this enzyme that is involved in pyrimidine salvaging. The protein that is then encoded, forms a homotetramer that causes a catalyzation that in itself is an irreversible hydrolytic deamination of cytidine and deoxycytidine to uridine and lastly deoxyuridine. There are several deaminases that are responsible to maintain of the cellular pyrimidine pool, this particular one is one of them<sup>[3]</sup>.

## Discussion

It is well-known that cancer starts primarily by developing certain mutations in DNA. DNA contains certain genes that activate and signal the corresponding cell what to do and how to do it. The only issue here is when those instructions inadvertently create errors that hinder the natural cellular processes. Cell mutations may happen in multiple ways; it can be by birth and develop sometimes thereafter or it be caused due to external factors. There are over 400 types of cancers that exist and with that multiple types of pathways attempt to defeat them before they metastasize, with the most common CDA-dependent types include, but are not limited to, bladder, breast, colon, lung, melanoma, prostate, thyroid kidney, endometrial, pancreatic and non-Hodgkin's lymphoma. Studies have linked cytidine deaminase to activation of mutation that creates certain cancers. APOBEC (catalytic polypeptide-like), a family of evolutionarily conserved CDAs, are involved in several significant biochemical processes in human body such as antibody diversification/maturation, restriction of viral infection, and generation of somatic mutations. APOBEC is wide spread in various human cancers which mentions the correlation to 14 different types of cancer found through a genome and exome data set criteria. APOBEC3 protein families, a DNA cytidine deaminase, are up-regulated in several types of cancer. The application to these criteria was applied to 954,247 mutations in 2,680 exomes. The APOBEC pattern of mutation was present in bladder, cervical, breast, lung, and head and neck cancer. It was found to reach 68% of the mutation patterns in some samples. Multiple studies have concluded the similar findings with correlation between CDA and cancer. CDA in this instance was concluded to be a necessary expression for the development of cancer in animal models as well as those found in human skin cancers such as melanoma, and head and neck cancer. It has been reported that mutation demonstrated by an oncogene or tumor suppressor gene expression that when heavily accumulated the mutation this would result in cancer. The cytidine deaminase family, is an essential enzyme for somatic hyper mutation and additionally for class-switch recombination of antibody genes. It was also reported that there is involvement of cytidine deaminases the development of cancers in the gastrointestinal tract, mammary gland, and prostate<sup>[4-10]</sup>. Interestingly, downregulation of cytidine deaminase was reported for the patients with Bloom syndrome, a genetic disease related to a strong predisposition to a wide range of cancers. Recently it has been reported that CDA-deficient tumor cells can be specifically targeted with small molecule antitumor drugs,



**Figure 1. Commercially available CDA inhibitors Zebularine and Tetrahyrouridine (THU).**

opening up new possibilities to treat cancer<sup>[11]</sup>. APOBEC3 and AID boost immune response by mutating immune or viral genes. Because of their genome-mutating activities these proteins are capable to promote tumorigenesis. AID is a 198 amino acid DNA-editing enzyme that deaminates dC to dU in ssDNA. AID promotes hypermutation in immunoglobulin (Ig) loci that induces genome-wide mutations, subsequent breaking of double-strand leads tumor formation<sup>[12-18]</sup>.

Human CDA plays major role to catalyze metabolic processing of nucleoside-type anticancer and antiviral agents. Accordingly, it is a promising target for the development of small molecule anticancer adjuvants. Two well-known commercially available cytidine deaminase inhibitors are shown in Figure 1. Zebularine binds to the active site as covalent hydrates and inhibits *in vitro* DNA-methylation and subsequently tumor growth is inhibited *in vivo*. On the other hand, the orally active drug THU modulates antiproliferative effects.

## Conclusion

Cytidine deaminases are prevalent in many organisms and in human CDA plays major role to develop certain types of cancer. Although several studies have had been conducted around the globe still more precise investigation is obligatory to reveal a better picture. Development of more effective inhibitors with higher potency (to the malignant cells) and lower toxicity (to the normal cells) are timely and challenging to encounter cancer.

## Conflicting interests

The authors have declared that no conflict of interests exists.

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## Author contributions

The idea was generated by DB. CAA outlined the manuscript. Both the authors wrote the manuscript.

## Abbreviations

AID: Activation-induced cytidine deaminase; APOBEC: apolipoprotein B mRNA editing enzyme; CDA: Cytidine deaminase; dC: deoxycytidine; DNA: Deoxyribonucleic acid; dU: deoxyuridine; ssDNA: single-stranded DNA.

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