BIOTRANS
LA ROCHELLE 2023

N°1317 / PC
TOPIC(s) : Enzyme discovery and engineering

Substrate promiscuity of cytidine deaminases

AUTHORS

Nina URBELIENĖ / INSTITUTE OF BIOCHEMISTRY, LIFE SCIENCES CENTER, V, SAULETEKIO 7, VILNIUS
Justas VAITEKŪNAS / INSTITUTE OF BIOCHEMISTRY, LIFE SCIENCES CENTER, VILNIUS UNIVERSITY, SAULETEKIO 7, VILNIUS
Jonita STANKEVIČIŪTĖ / INSTITUTE OF BIOCHEMISTRY, LIFE SCIENCES CENTER, VILNIUS UNIVERSITY, SAULETEKIO 7, VILNIUS
Rolandas MEŠKYS / INSTITUTE OF BIOCHEMISTRY, LIFE SCIENCES CENTER, VILNIUS UNIVERSITY, SAULETEKIO 7, VILNIUS

PURPOSE OF THE ABSTRACT

Cytidine deaminase (CDA) (EC 3.5.4.5) is an enzyme that catalyses the deamination of cytidine to uridine, which is an important step in nucleotide metabolism. In addition, CDA is known to exhibit substrate promiscuity, meaning that it can catalyse the deamination of other cytidine analogues for example 5-azacytidine, zebularine, gemcitabine, which are used in cancer treatment. Moreover, CDAs could be used for synthesis of N4-hydroxycytidine derivatives with antiviral activity.

Our studies have shown that some prokaryotic homo-tetrameric CDAs catalyse the nucleophilic substitution at the 4th position of N4-acyl-, N4-alkyl, N4-alkyloxycarbonyl-cytidines and S4-alkylthio-, O4-alkyl-uridines, converting them to uridine and corresponding amide, amine, carbamate, thiol or alcohol as leaving group.

CDA enzymes, which are active with a broad spectrum of substrates, may play a role in salvaging and/or breaking down modified pyrimidine nucleosides. This could include the removal of alkyl groups from mutagen-damaged uridines or the demethylation of S4-methylthiouridine, a molecule that is formed under stress in living organisms. The discovery of this substrate promiscuity of CDAs has expanded our understanding of the cellular turnover of cytidine derivatives, including how pyrimidine-based pro-drugs are activated and/or metabolized in the body.

FIGURES

FIGURE 1

FIGURE 2

KEYWORDS

cytidine deaminase | Substrate promiscuity of CDAs | N(S,O)4-substituted pyrimidine nucleosides | pro-drug metabolism

BIBLIOGRAPHY