CDA (Cytidine Deaminase)

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Identity

Other names: CDD
HGNC (Hugo): CDA
Location: 1p36.12

Note: CDA catalyzes hydrolytic deamination of cytidine and deoxycytidine into uridine and deoxyuridine, respectively.

DNA/RNA

Description
The human CDA spans approximately 30 kb and consists of 4 exons. No splice variant was reported.

Transcription
The full length CDA mRNA is 985 bp with an open reading frame of 441 bp.

Pseudogene
No pseudogene was reported.

Protein

Note
X-ray crystal structures of CDA from Yeast (1R5T) and Bacillus Subtilis (1JTK, 1UX0, 1UX1 and 1UWZ) are publicized in the PDB.

Description
The human CDA protein consists of 146 amino acids and has a molecular weight of 16,184. This is a soluble cytoplasmic protein and it is involved in pyrimidine salvaging.

Expression
Although the protein expression profile in tissues has not been revealed, its mRNA expression determined by Northern blotting was observed in high levels in liver and placenta, low in lung and kidney, but not in heart, brain and muscle (Laliberte and Momparler, 1994). High CDA activity was reported in liver and spleen, and moderate in lung, kidney, large intestine mucosa and colon mucosa (Ho, 1973).
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Localisation
This protein is localized in cytoplasm.

Function
CDA catalyzes hydrolytic deamination of cytidine and deoxyctydine into uridine and deoxyuridine, respectively. This protein also inactivate chemotherapeutic nucleoside analogs 2,2-difluorodeoxycytidine (gemcitabine) and cytosine arabinoside (cytarabine, Ara-C).

Mutations

Germlinal
Two nonsynonymous genetic varitions, 79A>C (Lys27Gln) and 208G>A (Ala70Thr), have been found in the human CDA gene (Yue et al., 2003). Ethnic differences in the minor allele frequencies of these variations have been reported. The 79A>C (Lys27Gln) was found at 0.30-0.36 frequencies in Africans, at 0.20-0.21 in Japanese and at 0.04-0.10 in Africans (Ueno et al., 2007). In contrast, the 208G>A (Ala70Thr) was found at 0.13 in Africans and 0.04 in Japanese, but not in Caucasians. Interestingly, the 208G>A (Ala70Thr) has not been detected in African-Americans. The mutant protein with 70Thr was reported to have remarkably reduced activities in vitro (Yue et al., 2003) and in vivo (Sugiyama et al., 2007). On the other hand, controversial results on the effects of activities have been obtained for 79A>C (Lys27Gln). The recombinant enzyme with Gln27 retained its catalytic activities for cytidine and ara-C as substrates (Yue et al., 2003), while showing reduced activity with increased Km value in the case of gemcitabine (Gilbert et al., 2006). However, the minor allele of this SNP was reported to be associated with higher enzymatic activities for gemcitabine based on tests using lysates of red blood cells taken from Caucasian cancer patients (Giovannetti et al., 2008; Tibaldi et al., 2008). In line with this, the minor allele was associated with decreased response, shorter time to progression and overall survival, and lower frequencies of grade 3 and 4 neutropenia in Caucasian non-small cell lung cancer patients treated with gemcitabine and cisplatin (Tibaldi et al., 2008).

Adverse reactions by anti-cancer drugs

Note
CDA is involved in the metabolic inactivation of anti-cancer drug gemcitabine and cytosine arabinoside (ara-C). CDA polymorphisms 208G>A (Ala70Thr) has been associated with adverse reactions including neutopenia by gemcitabine. Reduced clearance of gemcitabine and plasma CDA activities significantly depended on the number of minor allele 208A (70Thr) in 256 Japanese patients with cancer (Sugiyama et al., 2007). This polymorphism was also associated with increased incidences of grade 3/4 neutropenia in the patients coadministered with other anti-cancer drugs (Sugiyama et al., 2007). Notably, one patient with homozygous 208A (70Thr) showed severe hematologic and nonhematologic toxicities during chemotherapy with gemcitabine and cisplatin, and had 1/5 value of gemcitabine clearance and 12% of plasma CDA activity compared to those of the patients without CDA nonsynonymous polymorphisms (Yonemori et al., 2008, Sugiyama et al., 2007). Among the other panels of Japanese pancreatic cancer patients, three patients encountered life-threatening toxicities after chemotherapies including gemcitabine (Ueno et al., 2009). Two of them had homozygous CDA 208A (70Thr), and showed extremely low plasma CDA activity and gemcitabine clearance. Together with the previous one patient, homozygous 208A (70Thr) was suggested to be a key factor causing gemcitabine-induced severe adverse reactions in the Japanese (Ueno et al., 2009). With regard to another nonsynonymous polymorphism, the minor allele of CDA 79A>C (Lys27Gln) was associated with decreased response, shorter time to progression and overall survival, and lower frequencies of grade 3 and 4 neutropenia in Caucasian non-small cell lung cancer patients treated with gemcitabine and cisplatin (Tibaldi et al., 2008). Homozygous 79C (27Gln) was also associated with increased postinduction treatment-related mortality with ara-C in patients with acute myeloid leukemia (Bhatla et al., 2008).

References

Implicated in

Acute myeloid leukemia
Disease
CDA genetic polymorphisms (79A>C, Lys27Gln; 208G>A, Ala70Thr; 435T>C, silent) were not associated with susceptibility to acute myeloid leukemia in Chinese children (Yue et al., 2007).

Colorectal cancer
Note
Combination of the five gene expression levels (CDA, MGC20553, BANK1, BCNP1 and MS4A1) in peripheral white blood cells could be used as a biomarker for diagnosis of colorectal cancer (Han et al., 2008).


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