Dihydropyrimidine dehydrogenase

- Dihydropyrimidine enzyme activity and its effect on chemotherapy toxicity: importance of genetic testing
- Proteomic profiling of gliomas unveils immune and metabolism-driven subtypes with implications for anti-nucleotide metabolism therapy
- Antitumor efficacy of oncolytic HSV-1 expressing cytosine deaminase is synergistically enhanced by DPD down-regulation and EMT inhibition in uveal melanoma xenograft
- Drug delivery of oral anti-cancer fluoropyrimidine agents
- Dihydropyrimidine Dehydrogenase Is a Prognostic Marker for Mesenchymal Stem Cell-Mediated Cytosine Deaminase Gene and 5-Fluorocytosine Prodrug Therapy for the Treatment of Recurrent Gliomas

Dihydropyrimidine dehydrogenase (DPD) is an enzyme that plays a crucial role in the metabolism of pyrimidines (uracil and thymine) and certain chemotherapeutic drugs, such as 5-fluorouracil (5-FU) and its prodrugs. Below is an overview:

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Biological Function - **Pyrimidine Catabolism:** DPD catalyzes the initial and rate-limiting step in the degradation of pyrimidines by converting uracil and thymine to their respective dihydropyrimidine derivatives. - **Drug Metabolism:** DPD is critical for the breakdown of 5-fluorouracil (5-FU) and other fluoropyrimidines, which are commonly used in cancer treatment. Insufficient DPD activity can lead to severe drug toxicity.

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Clinical Relevance 1. **DPD Deficiency:**

1. A genetic deficiency in DPD can result in the accumulation of toxic levels of pyrimidines and can lead to various clinical manifestations, including intellectual disability, developmental delay, and seizures.
2. Patients with partial or complete DPD deficiency are at significant risk for severe toxicity when treated with 5-FU or capecitabine.

2. **Pharmacogenomics:**

1. Genetic variants in the *DPYD* gene, which encodes DPD, affect enzyme activity. Some common variants associated with decreased activity include *DPYD* polymorphisms like c.1905+1G>A and c.1679T>G.
2. Testing for *DPYD* variants or DPD activity before initiating 5-FU therapy is recommended in many clinical guidelines to avoid toxicity.

3. **Therapeutic Implications:**

1. In cases of partial DPD activity, dose adjustments or alternative chemotherapeutics may be necessary.
2. For patients with complete DPD deficiency, 5-FU and related drugs are contraindicated.

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Enzyme Mechanism - **Reaction:** DPD uses NADPH as a cofactor to catalyze the reduction of uracil and thymine to 5,6-dihydrouracil and 5,6-dihydrothymine, respectively. - **Localization:** It is primarily expressed in the liver, where it facilitates the catabolism of pyrimidines and detoxification of fluoropyrimidine drugs.

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Research Applications - Understanding DPD's role in drug metabolism is critical for personalized medicine approaches in oncology. - It is a target for therapeutic intervention to optimize cancer treatments and reduce adverse effects.

Case reports

A 43-year-old man with moderately differentiated rectal adenocarcinoma on capecitabine presented to the emergency department with complaints of nausea, vomiting, diarrhea, weakness, and lower abdominal pain for several days. Laboratory findings include grade 4 neutropenia (ANC 10) and thrombocytopenia (platelets 36,000). Capecitabine is used as a component of first-line adjuvant therapy by approximately 2 million patients worldwide each year. Capecitabine is metabolized to fluorouracil via the enzyme dihydropyrimidine dehydrogenase (DPD). With worsening pancytopenia and diarrhea, genetic testing for DPD deficiency was sent. Prompt treatment with uridine triacetate was initiated for presumed DPD deficiency. Unfortunately, he passed away from an infectious complication and was later confirmed to have a heterozygous DPYD*2A mutation.

The case demonstrates uneven testing guidelines for DPD prior to initiating 5-FU chemotherapy, appropriateness of treating with uridine triacetate, and analysis of next-generation sequencing (NGS) on tumor samples and co-incidentally obtaining germline DPD deficiency status. Our case also highlights the severe clinical impact of having DPD deficiency even with early uridine triacetate therapy.

Conclusion: It is our recommendation to perform DPD deficiency in curative intent cancer treatment and this information can increasingly be obtained in standard tumor NGS profiling, a growing norm in medical oncology [1)].

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Shamaei Zadeh A, Roberts D, Williams A, Pandey D, Villano JL. Dihydropyrimidine enzyme activity and its effect on chemotherapy toxicity: importance of genetic testing. Cancer Chemother Pharmacol. 2025 Jan 18;95(1):26. doi: 10.1007/s00280-024-04740-x. PMID: 39825952.