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The Biochemistry of Pyrimidine Base Catabolism: Why Understanding the Cellular Recycling of Pyrimidine Bases is Important

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Pyrimidine base catabolism usually involves either a reductive pathway or an oxidative pathway with the former more prevalent in humans as well as in plants, unicellular eukaryotes and bacteria [1-4]. The reductive pathway involves three enzymes which include dihydropyrimidine dehydrogenase (EC 1.3.1.2), dihydropyrimidinase (EC 2.5.2.2) and β-ureidopropionase (EC 3.5.1.6) [2-4]. The importance of the catabolism of pyrimidine bases in humans is directly related to the use of 5-fluorouracil as a chemotherapeutic agent during the treatment of cancer [5,6]. Genetic deficiencies for any of the reductive pathway enzyme activities also appear to result in problems for those individuals affected [7,8]. The pyrimidine catabolic pathway is thought to be also involved in the degradation of pyrimidine-based antimicrobials. The initial enzyme dihydropyrimidine dehydrogenase is important to the effectiveness of 5-fluorouracil as a chemotherapeutic agent [9]. If the activity of the dehydrogenase is reduced, the toxicity of 5-fluorouracil can increase [5,9]. If 5-fluorouracil is rapidly degraded by the dehydrogenase, less of the analogue will be available to halt cancerous cell growth. Genetic deficiencies of the dehydrogenase have been reported and result in the urinary excretion of uracil, dihydrouracil, thymine and dihydrothymine. Individuals with dihydropyrimidine dehydrogenase deficiency exhibit symptoms that include mental retardation and seizures [7,8]. Genetic deficiency of the second reductive pathway enzyme dihydropyrimidinase in humans results in the accumulation of dihydropyrimidine bases in the blood, cerebrospinal fluid and urine plus can lead to 5-fluorouracil toxicity [10,11]. This autosomal recessive disease results in mental retardation, gastrointestinal problems and seizures [10]. Beyond the importance of pyrimidine catabolism to cancer treatment, the second pathway enzyme dihydropyrimidinase has been shown to degrade antiepileptic agents [12]. This enzyme usually also has the ability to hydrolyze hydantoins and this could prove vital in the development of large-scale bioreactor systems for the inexpensive production of β-amino acids and D-amino acids [4]. Genetic deficiency for the third reductive pathway enzyme β-ureidopropionase has been reported in humans [13]. High levels of N-carbamyl-β-alanine and N-carbamyl-β-aminoisobutyric acid have been detected in urine and plasma of those affected individuals [13]. The individuals afflicted with this enzyme deficiency exhibit a number of neurological problems including intellectual disabilities, seizures and microcephaly [13]. The severity of the neurological symptoms appears to be greater in human β-ureidopropionase deficiency than in human dihydropyrimidine dehydrogenase or dihydropyrimidinase deficiency [13]. Patients with β-ureidopropionase deficiency did not exhibit the gastrointestinal problems observed in the dihydropyrimidinase deficient patients [10,13].

Although the literature exploring pyrimidine base catabolism has made significant strides relative to better understanding the rate of pyrimidine base catabolism as it relates to cancer treatment using 5-fluorouracil, further research is needed to better characterize the reductive pathway and its regulation in other organisms. The opportunity exists to compare how the reductive pathway of pyrimidine catabolism is regulated in diverse organisms. This should provide new insights into how the pathway is regulated at the level of transcription and the level of enzyme activity. By taking advantage of this opportunity to understand pyrimidine base catabolism better, new approaches in using 5-fluorouracil as a chemotherapeutic agent more effectively may be developed and new industrial applications to produce β-amino acids and D-amino acids may result.

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