Exploring the Role of ?-Amidase as a Repair Enzyme for Hydroxyglutaramate and Hydroxysuccinamate

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Most enzymes in metabolic pathways were thought to be highly specific for a given substrate. However, it is now apparent that many metabolic enzymes are not as specific as previously thought and occasionally make “mistakes”, generating potentially harmful byproducts. As a result, nature has evolved repair enzymes to convert these byproducts back to useful metabolites. For example, L-2-hydroxyglutarate is a byproduct of malate dehydrogenase (a key enzyme of the energy-generating tricarboxylic acid (TCA) cycle). A repair enzyme converts L-2-hydroxyglutarate to a-ketoglutarate, a useful intermediate of the TCA cycle. In certain disorders, this repair enzyme is defective, resulting in a large buildup of L-2-hydroxyglutarate in tissues and body fluids. In addition to neurological problems, these patients exhibit greatly increased cancer rates. The current research seeks to determine whether ?-amidase, an enzyme important in the metabolism of glutamine, acts as a repair enzyme for mistakes made by lactate dehydrogenase (LDH), thereby preventing the buildup of potential oncometabolites. It has been shown that LDH may catalyze the production of potentially toxic byproducts – hydroxyglutaramate (HGM) and hydroxysuccinamate (HSM). I hypothesize that ?-amidase will convert these potentially toxic compounds into biologically-useful substances. In order to investigate ?-amidase as a potential repair enzyme, enzyme assays were performed to determine whether HGM and HSM are substrates of ?-amidase. Using a spectrophotometer to measure product formation, it was concluded that HGM and HSM are substrates of ?-amidase. This work has uncovered two previously unreported metabolic reactions of ?-amidase that may possibly prevent accumulation of potential oncometabolites.

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