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Substrate Specificity of A Thymidine Phosphorylase in Human Liver Tumor*

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We have found that thymidine phosphorylase activity is greatly enhanced in human tumors as compared with normal tissues and is responsible for the conversion of 5′-deoxy-5-fluorouridine (5′-DFUR) and 1-(tetrahydro-2-furanyl)-5-fluorouracil (Tegafur) to 5-fluorouracil (5-FU), an activated form. The activation of 5′-DFUR is catalyzed by uridine phosphorylases in experimental tumors of animals.

Thymidine phosphorylase (TP) catalyzes the reversible conversion of thymidine (dThd) and phosphate to thymine and 2-deoxyribose 1-phosphate. Uridine phosphorylase (UP) catalyzes the reversible conversion of uridine (Urd) and phosphate to uracil and ribose 1-phosphate. UP acts primarily on Urd and also cleaves dThd and 2′-deoxyuridine. Thus, its substrate specificity seems to be broad. On the other hand, TP is reported to be highly specific for 5-substituted 2′-deoxyuridines.

The findings that 5′-DFUR and Tegafur are phosphorolyzed by TP in human tumors suggest that the specificity of the human enzyme is somewhat different from those of the enzymes from other sources.

A thymidine phosphorylase preparation was partially purified from human liver tumor tissues (poorly differentiated adenocarcinoma). The substrate specificity of the enzyme was investigated with eleven pyrimidine nucleosides. dThd and 2′-deoxyuridine were good substrates, while Urd, 3′-deoxyuridine, 5′-deoxyuridine, and 2′,3′-dioxy-3′-hydroxymethyluridine were not. Uridines substituted at the 5-position by a cyano, bromo, or chloro group were also phosphorolyzed by the enzyme, but the activity for 5-fluorouridine was much lower. 5′-Deoxy-5-fluorouridine was also cleaved. Either a 5-substituent or a 2′-deoxy structure seems to be essential for a good substrate.

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