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Behavior of Activities of Thymidine Metabolizing Enzymes in Human Leukemia-Lymphoma Cells This paper discusses the modulation of activities of four important enzymes involved in the metabolism of thymidine in malignant human leukemia-lymphoma cells as compared to the activities of the enzymes in normal human lymphocytes. The enzymes studied were the catabolic enzymes dihydrothymine dehydrogenase (DHT DH) and thymidine phosphorylase (TP) which play crucial roles in nucleic acid metabolism by regulating the availability of thymidine, and thymidine kinase (TK) and thymidylate synthase (TS) which are cellular “ salvage” enzymes involved in DNA synthesis. The studies were conducted with cell cultures obtained from 13 human leukemia-lymphoma cell lines consisting of T- and B-cell lines as well as Non-T- and Non-B- cell lines. The various enzymes were assayed in extracts obtained from cells subjected to rapid freezing and thawing in liquid nitrogen. Activities of the catabolic enzymes were higher by several orders of magnitude compared to the synthetic enzymes in normal cells. However, in all leukemia-lymphoma cells examined, the thymidine degrading enzyme activities were decreased for example, by 5-42% in the case of dihydrothymine dehydrogenase (with complete absence of DHT DH activity noted in chronic myelogenous leukemia K-562 cells) and up to 38% in the case of TP relative to normal cells. In contrast, the activities of the synthetic enzymes namely, thymidylate synthase and TK were increased significantly by up to 407 times and up to 79 times, respectively of the normal human lymphocytes.

Thymidine is utilized by cells both for DNA synthesis and energy production through oxidation to CO2 and water. Therefore, the reduction in the activity

of the thymidine degrading enzymes is also important since it would lead to enhanced availability of the compound for DNA synthesis. Furthermore, the enhanced activities of the thymidine synthesizing enzymes would also contribute to DNA synthesis which is very essential for rapid cell growh and proliferation. A comparison of kinetic properties of the catabolic enzymes, DHT DH and TP in the normal lymphocytes showed that the specific activity of DHT DH was considerably less than that of phosphorylase thereby indicating that DHT DH is the rate-limiting enzyme and, therefore, a better enzyme to evaluate the capacity of human leukemia-lymphoma cells to degrade thymidine.

Thymidine kinase (TK) converts thymidine, or deoxythymidine (dT) to the respective monophosphate. Increases in TK activity have been observed to correlate with the presence of many types of human neoplasia in particular, hematologic malignancies. Serum TK is known to have a strong prognostic value for patients with non-Hodgkin’s lymphoma (Rehn et al., 1995). TK estimations in human lymphoproliferative diseases have suggested that this enzyme could be useful as an early marker of cellular maldifferentiation. Rehn et al. showed that serum TK levels depend on tumor burden as well as the cellular content of TK i. e., cell proliferation rate (1995). On the other hand, Platelet-derived endothelial cell growth factor (PD-ECGF) which is an angiogenic factor has been shown to be actually thymidine phosphorylase (TP). TP is an intracellular enzyme that catalyzes the conversion of thymidine to thymine. TP has been shown to be active in angiogenesis and invasion, and up-regulated in several malignant diseases.

The main findings of this study were: (1) existence of reciprocal regulation of

catabolic and anabolic enzyme activities involved in thymidine metabolism in human leukemia-lymphoma cells, (2) DHT DH is the rate-limiting enzyme and a better indicator of the potential for enzyme degradation of thymidine, and (3) decrease in DHT DH activity shown, for the first time, to be related to the amount of the enzyme in leukemic cells. Drugs used in chemotherapy work in different ways to stop the growth of cancer cells. The significant differences noted in the activities of the various enzymes in different leukemia-lymphoma cell types could provide important cues for deciding the best enzyme targets for chemotherapy.

References

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