Purine Pathway Enzyme Abnormalities in Acute Lymphoblastic Leukemia

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Abstract

The status of three purine pathway enzymes, adenosine deaminase, 5'-nucleotidase, and purine nucleoside phosphorylase, was evaluated in the leukemic cells of patients with acute lymphoblastic leukemia and correlated with routine immunological cell surface markers. A distinct pattern of enzyme activity was noted in T-lymphoblasts which have significantly higher adenosine deaminase activity (p < 0.02) and lower 5'-nucleotidase (p < 0.001) and purine nucleoside phosphorylase (p < 0.01) activities than do non-T, non-B lymphoblasts. This enzyme pattern is similar to that observed in normal human thymocytes but is not shared by the mature, normal T-lymphocytes of peripheral blood, suggesting that it may reflect the differentiation status of malignant T-lymphoblasts. These findings, which confirm the biochemical heterogeneity of acute lymphoblastic leukemia, may provide an avenue for selective chemotherapy of this disease.

Introduction

Recently, there has been considerable interest in the relationship of the enzymes of the purine metabolic pathway to lymphocyte function. This interest has been stimulated by the demonstration of absence of these enzymes in specific immunodeficiency diseases. Abnormal activities of 3 purine pathway enzymes, ADA, 5'-N, and PNP, have been associated with clinically defective lymphoid function (5-7, 9). These observations have suggested the possibility that abnormal enzyme activity might exist in malignant lymphoid cells. In the present report, we present our findings on the status of these enzymes in acute leukemic lymphoblasts and discuss the relationship of enzyme activity to specific immunological subclasses of ALL.

Adenosine Deaminase

ADA is responsible for the conversion of adenosine to inosine (Chart 1). ADA is ubiquitous in human tissue and is present in its highest concentration in lymphoid cells (3). Giblett et al. (7) first reported the association between ADA deficiency and severe combined immunodeficiency disease. Some 20 to 30% of patients with severe combined immunodeficiency disease have absent ADA activity (11). These children demonstrate profound impairment of T-cell function and varying degrees of B-cell dysfunction, although there is some evidence that the primary defect involves the T-cell axis. Smyth and Harrap (17) first demonstrated the presence of abnormal ADA activity in ALL. They compared the ADA activity of acute leukemic lymphoblasts to that of normal lymphocytes and found a wide range of ADA activity in the lymphoblasts ranging from near normal to markedly increased. Measurement of the lymphoblast ADA activity in immunological subsets of ALL (Chart 2) revealed a 3-fold increase in enzyme activity in T-lymphoblasts in comparison to non-T, non-B lymphoblasts and normal lymphocytes (18). These findings are compatible with the observation that elevated ADA activity is also present in immature normal human thymocytes (3).

5'-Nucleotidase

5'-N converts nucleotides such as AMP to their corresponding nucleosides (Chart 3). The majority of 5'-N exists as an ectoenzyme located on the plasma cell membrane (10). Although the exact function of 5'-N is unknown, in cells such as lymphocytes which generally do not synthesize purines de novo, it is believed to facilitate the generation of nucleosides which are subsequently actively transported into the cell. Decreased 5'-N has been reported in the peripheral blood lymphocytes of immunodeficient patients with congenital X-linked agammaglobulinemia and adult-onset agammaglobulinemia (5, 9). Transient decreases in enzyme activity have also been observed in the lymphocytes of patients with infectious mononucleosis (13) Abnormalities in 5'-N activity have also been reported in murine leukemia and lymphoma cells as well as in normal murine lymphocytes after mitogenic stimulation with concanavalin A (14). More recently, the activity of this enzyme has been found to be decreased in the malignant cells of patients with chronic lymphocytic leukemia, irrespective of cell surface marker classification (13).

We examined the activity of 5'-N in acute leukemia lymphoblasts and investigated the possibility of a correlation between this biochemical marker and conventional immunological subsets of this disease (15). As shown in Chart 3, 5'-N activity manifests considerable heterogeneity within lymphoblasts, exhibiting a pattern which corresponds to cell surface marker classification. 5'-N activity is significantly decreased in lymphoblasts to that of normal lymphocytes.
blasts with T-cell characteristics. In contrast, non-T, non-B lymphoblasts possess 5'N activity which is comparable to that of normal peripheral lymphocytes. It is unclear whether the decreased enzyme activity in T-lymphoblasts represents an actual decrease in functional enzyme or the presence of a structurally abnormal enzyme molecule. However, as in the case of ADA, the pattern of 5'N activity in T-lymphoblasts is similar to that observed in normal human thymocytes (4).

Purine Nucleoside Phosphorylase

PNP reversibly converts inosine to hypoxanthine (Chart 1). Both complete and partial inherited deficiencies of this enzyme have been associated with clinical immunodeficiency (6). Notably, PNP deficiency has been specifically linked to defects in T-cell function. This observation, together with the fact that both ADA and 5'N manifest distinctive abnormalities in enzyme activity in T-lymphoblasts, prompted investigation of PNP activity in ALL. As shown in Chart 4, the median PNP activity of T lymphoblasts is less than one-half that of either non-T, non-B lymphoblasts or normal peripheral blood lymphocytes (1). This observed reduction in PNP activity in T-lymphoblasts extends the scope of the purine metabolic abnormalities in T-cell ALL.

Discussion

The application of improved immunological techniques to the study of lymphoid cancer has provided a biological approach to the classification of ALL. The ability to characterize acute
leukemic lymphoblasts on the basis of cell surface markers has proven to be of prognostic and potential therapeutic import. In addition, it has also provided a biological basis for the varied clinical presentations of patients with this disease (8, 15). Thus, characterization of acute leukemic lymphoblasts on an immunological basis emphasizes the biological heterogeneity of ALL.

In our studies, we have demonstrated quantitative abnormalities of 3 purine pathway enzymes in acute leukemic lymphoblasts. These findings indicate that there is also a biochemical heterogeneity in ALL. A specific enzyme pattern exists which distinguishes T-lymphoblasts from non-T, non-B leukemic cells. T-lymphoblasts exhibit markedly increased ADA, low PNP, and greatly diminished 5'N.

Immature normal human thymocytes have a pattern of enzyme activity similar to that observed in T-lymphoblasts. This enzyme pattern is not shared by presumably more mature, normal T-lymphocytes of peripheral blood (2, 4), suggesting that the specific enzyme patterns observed in T-lymphoblasts may reflect the state of differentiation of these malignant cells. However, the precise biological significance of the abnormal purine pathway enzyme activity in ALL remains unclear.

The techniques used in these studies are functional assays of enzyme activity. They do not permit one to assess whether the enzyme abnormalities are simply quantitative or reflect actual structural changes in the enzymes themselves. It is also unclear whether these enzyme abnormalities represent a metabolic consequence of the neoplastic process or are in some causative way linked to the development of cancer.

The observation of increased ADA activity in T-lymphoblasts is currently being exploited in Phase I trials of the compound 2'-deoxycoformycin, a potent inhibitor of ADA (12). Thus, perhaps the most intriguing aspect of the biochemical heterogeneity of ALL is that it may provide an avenue for selective chemotherapy of this disease.

References

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