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Poly(A)-polymerase Levels in Leukemia

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A. Introduction

Formation of individual functional mRNA sequences in eukaryotic cells requires many steps in addition to transcription. These include RNA splicing, base modification, polyadenylation-de-adenylation, transport from nucleus to cytoplasm, and assembly into the polyribosomes. A number of recent reports indicate that various control mechanisms may operate in these several steps of mRNA maturation before its translation [1]. Elucidation of such control mechanisms concerning eukaryotic gene expression in addition to its biological interest may be clinically useful in lymphoid malignancies.

Polyadenylation of the 3′-hydroxyl end of HnRNA and mRNA could theoretically be regulated by poly(A)-polymerase [2, 3]. To clarify the possible involvement of this enzyme in mRNA maturation and stabilization we have carried out measurements of poly(A)-polymerase in various human leukemias. We found that acute leukemias have higher enzyme levels than those observed in chronic lymphocytic leukemias.

B. Results

As can be seen in Table 1 peripheral blood lymphocyte soluble cell extracts from patients with acute leukemia have higher poly(A)-polymerase activity than that observed in lymphocytes from chronic lymphocytic leukemia patients. The mean polymerase unit per milligram soluble protein in 30 cases of chronic lymphocytic leukemia was 7.03 whereas in acute leukemic cases it was 49.25. This difference of enzyme levels is statistically significant. Among the acute leukemias acute myeloblastic leukemia seems to have the highest enzyme levels. However, more cases must be studied to substantiate this conclusion. Peripheral blood lymphocytes from normal donors have very low enzyme activity. The polyadenylation reaction showed an absolute requirement for divalent cations (Mn^{2+} being better than Mg^{2+}) and exogenous initiator. There were no significant differences observed in the level of poly(A)-polymerase initiated with oligo (A) ($A_{\overline{10}}$) or poly(A)($A_{\overline{200}}$) with soluble extracts from acute and chronic leukemic patients. The oligo(A)-initiated polymerase activity from all soluble cell extracts shows linear incorporation of AMP for 1 h. In contrast the poly(A)-initiated polymerase activity

Table 1. Poly (A)-polymerase levels in various leukemias

Diagnosis	Enzyme units (nmol/h)/mg
Chronic lymphocytic leukemia [30][a]	7.03± 8.17[b]
Acute leukemias [14][c]	49.25±39.03[b]
Normal peripheral blood lymphocytes [7]	2.73± 2.67[b]

[a] Numbers in parentheses indicate the number of cases studied
[b] Level of significance 99% (mean±SEM)
[c] Acute leukemias include nine acute lymphoblastic leukemias (ALL), two acute myeloblastic leukemias (AML), and three chronic granulocytic leukemias (CGL) in blast crisis

from both acute and chronic leukemic soluble cell extracts shows linear incorporation of AMP for more than 1 h with an apparent initial lag phase. All enzyme assays may be carried out at protein concentrations of crude cell extract between 1 and 3 mg/ml. Preliminary data in our laboratory indicate differences in the mol.wt. of the enzyme between the acute and chronic cases. Also in acute leukemias the poly(A)-polymerase consists of two enzyme species whereas in the chronic leukemic cases only one of these can be detected (as reported elsewhere).

C. Conclusions

The results of this study indicate that peripheral blood lymphocytes of patients suffering from acute leukemia have higher poly(A)-polymerase activity than lymphocytes from CLL patients. Of the acute leukemias, the highest levels of the enzyme were observed in AML cases. However, more cases must be tested to prove this.

There is evidence that polyadenylation of HnRNA and mRNA is an early post-transcriptional process presumably mediated by poly(A)polymerase. It has also been suggested that poly(A) confers stability and consequently enhances translational efficiency of some mRNAs [4, 5, 6]. It could be assumed that high poly(A)polymerase levels result in increased poly(A) content of mRNA and HnRNA. Therefore, the observed high levels of poly(A)polymerase in rapidly proliferating acute leukemic cells, which have increased translational needs, possibly correlate with a longer lifetime of mRNA. The opposite occurs in CLL.

Elucidation of mRNA adenylation by poly(A)-polymerase and the subsequent functional lifetime of mRNA in various types of leukemia may shed light in understanding better the cellular basis of cell proliferation and have some clinical significance in lymphoid malignancies.

References

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