Aminoacyl-tRNA Synthetases in Liver, Spleen and Small Intestine of Aged Leukemic and Aged Normal Mice

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The specific activities of 17 aminoacyl-tRNA synthetases in liver, lung, heart, spleen, kidney and small intestine of old female normal and leukemic (reticulum-cell sarcoma, type A) mice have been monitored. No difference appears for lung, heart and kidney; small increases with varying particular changes for liver and marked increases in spleen and small intestine of the tumor bearing mice have been found, following a similar pattern. This finding suggests a coordinated adaptation to modulation of the requirements of protein synthesis imposed by histiocytic sarcoma.

The theory that changes in the extent and pattern of biosynthesis of macromolecules play a critical role in ageing and transformation has provided a conceptual framework for experiments [1]. Because the aminoacylation of tRNA by the aminoacyl-tRNA synthetases is a central step in protein biosynthesis [2], the activities of the aminoacyl-tRNA synthetases may have a rate-controlling function in protein synthesis. Since we have shown that in general the activities of the aminoacyl-tRNA synthetases decrease in different organs upon ageing, following an organ specific pattern [3], this study clarifies the extent to which disease factors may modify the effect of ageing on the pattern of aminoacyl-tRNA synthetases and suggests a coordinated adaptation to the specific requirements of protein biosynthesis.

Organs from three 39 months old non-tumor-bearing and leukemic (reticulum cell sarcoma, type A according to Dunn [4]) Han:NMRI mice (mean life span of Han:NMRI mice: 24 months) were treated individually according to the standard methods [3], and the specific activities of 17 aminoacyl-tRNA synthetases (enzyme units per mg of protein) were determined. The average standard deviation for the six repetitive measurements was 5–11% for the different activities. This spontaneous neoplastic process was detected at autopsy and the exact histological diagnosis was only possible after histological examination. The enzyme pattern of the lung, heart, and kidney shows no differences for tumor bearing and non-leukemic mice with 50%, 43%, and 60% relative activity compared to young mice; the normal age-related pattern remains unaffected [3]. Significant differences appear for liver, spleen and small intestine (incl. Peyer's patches). These are reflected by histological differences. Histologically the liver revealed packed proliferations of tumorous cells with typical elongated or indented nuclei. The normal architecture of the spleen was completely obliterated by ill-defined, pleomorphic, neoplastic histiocytic cells which also dominated in the Peyer's patches, replacing the normal follicular structure. Furthermore, numerous degenerating cells are present both in spleen and Peyer's patches, indicative of a rapid cell proliferation. Typical multi-nucleated giant cells of foreign-body type were found in the mesenteric lymph-nodes. Lung, heart and kidney were not affected. Only a small increase in the overall specific activity of aminoacyl-tRNA synthetases with all possible modes of change is measurable in liver. A more general trend is revealed for the enzymes from spleen and small intestine. All specific activities of these enzymes increase significantly in the organs affected by the tumorous process. The possibility that there are synthetase inhibitors in the non-tumor bearing organs or activators in the tumor-affected organs were excluded. When portions of crude extracts from both types were mixed, the activity was found to be additive.

On monitoring the activity pattern of aminoacyl tRNA synthetases it appears remarkable that there is a similarity between these organs that clearly differs from the peculiar age-related pattern of decrease [3]. Detailed comparison on the level of all synthetases reveals a rather correlated increase for the activities of spleen and small intestine, the activity for alanine being the only clear exception. This similarity for spleen and small intestine raises evidence that with the increase of the neoplastic histiocytic cell number the level of many cytoplasmic aminoacyl-tRNA synthetases in these

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Table I. Specific activities of 17 aminoacyl-tRNA synthetases in organs of old non-tumor-bearing (A) and tumor-bearing (B) female Han:NMRI mice given as the percentage of the specific activity in organs of young mice (= 100%).

Amino acid	Liver (A)	Liver (B)	Spleen (A)	Spleen (B)	Small intestine (A)	Small intestine (B)
Alanine	5	2.5	20	190	95	178
Arginine	40	30	20	70	48	104
Cysteine	14	14	40	135	nd[a]	nd
Glutamic acid	25	32	40	75	87	260
Glycine	25	34	50	320	nd	nd
Histidine	86	62	60	525	112	710
Isoleucine	13	41	66	300	72	220
Leucine	42	58	50	215	135	330
Lysine	33	40	70	350	75	240
Methionine	82	25	76	360	70	350
Phenylalanine	11	17	90	250	80	300
Proline	10	50	68	330	150	710
Serine	30	66	61	215	40	185
Threonine	20	24	34	93	44	180
Tryptophane	46	72	20	125	nd	nd
Tyrosine	26	52	52	350	42	220
Valine	12	33	35	200	nd	nd
average	31	38	49	243	80	306

[a] nd = not determined.

organs changes in a more or less coordinate fashion. This is consistent with the finding that different synthetases are organized into aggregates in eukaryotes [5, 6]. A coordinated response of aminoacyl-tRNA synthetases to modulation of growth rate changes has been reported for eukaryotes only in the case of yeast [7]. Marked differences in aminoacyl-tRNA synthetase activity may have significance for cellular control, especially by modulation of readout of specific messengers. Therefore variations in aminoacyl-tRNA synthetase activities may affect growth regulation by modifying the translational capacities of the cell, as was suggested for hepatomas [8].

The data presented in this report are tentatively consistent with a coordinated adaptation of aminoacyl-tRNA synthetases to requirements imposed by reticulum cell sarcoma manifestation, *e.g.* increased immunoglobulin synthesis mediated by macrophages with correlation of individual activity increase to proportions of the amino acids in immunoglobulins from known sequences [9, 10].

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