Biosynthesis of Liver and Tumor RNA Ribose in the Tumor-Bearing Rat. (23227)

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Rapid glucolysis with the aerobic accumulation of lactic acid is a prominent metabolic aberration manifested by tumors(1). It is therefore of interest to ascertain whether other alterations in tumor carbohydrate metabolism may exist. Towards this end a study has been undertaken on the biosynthesis of the pentose, ribose. The recent development of isotopic tracer and degradative technics(2) has permitted *in vivo* studies of the various alternate pathways of pentose biosynthesis in the normal rat(3,4). These studies have now been extended to the tumor-bearing rat in an attempt to gain insight into the biosynthetic pathways of RNA in the tumor, as well as to determine the effect of the tumor on nucleic acid pentose synthesis in the liver of the host animal.

Methods. Adult male Wistar rats weighing between 75 and 100 g were inoculated intraperitoneally with approximately one million Yoshida ascites tumor cells. Five days after inoculation food was withdrawn from all animals and on the sixth day the animals were administered by stomach tube 1 ml of 25% glucose/100 g body weight. One hour later each animal received a subcutaneous injection of 20 μc of glucose-2-C^{14} (supplied by Dr. H. I. Isbell of the National Bureau of Standards). After a 6 hour isotope incorporation period the animals were sacrificed by a blow on the head and then exsanguinated. The ascitic tumor cells were removed with a hypodermic syringe and the peritoneal cavity washed with saline to collect remaining tumor cells. The livers were then removed and further washed with saline to remove adhering tumor cells. Employing technics previously described(4), the tumor and liver RNA were separately isolated, the RNA purine-bound ribose was liberated by acid hydrolysis, freed of ionic contaminants with ion exchange technics and then further purified employing paper chromatographic procedures. The isolated liver and tumor RNA ribose was degraded using *Lactobacillus pentosus*(5,6) followed by chemical degradation technics; each ribose carbon atom was thus individually isolated as $BaCO_3$(7). The specific activities of the $BaCO_3$ samples thus obtained were estimated with either a windowless flow counter or a liquid scintillation counter.

Results. The results of duplicate experiments are depicted in Table I as the per cent specific activity in a given carbon atom relative to ribose carbon atom 2. The liver RNA ribose of the tumor-bearing rat presents an isotope distribution pattern that is conspicuously different from that of the control rat bearing no tumor. Whereas the bulk of radioactivity in the liver ribose of control animals is in carbon atom 2, with considerable activity in carbon one and little or no activity in ribose carbon atoms 3, 4, and 5, the radioactivity in the liver ribose of the tumor-bearing rats is widely dispersed throughout the ribose molecule, with considerable radioactivity present in carbon atoms 3, 4, and 5. In the tumor, however, ribose carbon atom 2 exhibits the highest specific activity; the remaining activity is distributed essentially equally throughout the rest of the ribose molecule.

Discussion. The conspicuous finding in this study is the extensive randomization of the C^{14} throughout the carbon chain of ribose in both the tumor and the liver RNA of the tumor-bearing animal. This effect is more marked in liver RNA ribose than in the tumor RNA ribose. The distribution of the C^{14} labeling pattern in liver RNA ribose of the Yoshida tumor-bearing rat is thus in sharp contrast to the labeling pattern previously observed in the normal rat liver RNA ribose (4). This alteration in labeling pattern may be subject to 2 alternative interpretations: (1) The tumor exerts an influence on liver metabolism; or (2) rapid metabolism by the

TABLE I. Incorporation of Glucose-2-C^{14} into Liver and Tumor RNA Ribose of Yoshida Ascites Bearing Rats.

	Ribose carbon No.				
	1	2	3	4	5
Tumor	36.2*	100	40.6	45.4	30.8
	35.2	"	45.4		
Liver	100	"	94.4	93.5	84.4
	90.5	"	72.7	93.6	72.7
Control liver	34.4	"	5.3	0	0
(Tumor-free rat(4))	23.6	"	2.0	0	0

* Values expressed as % of specific activity in C_2.

tumor of the administered glucose-2-C^{14} results in a randomization of label throughout the hexose; the observed pattern of ribose labeling in the liver resulting from normal pentose synthesis by the liver, utilizing, however, a hexose precursor in which all carbon atoms are labeled. This latter alternative is supported by the recent finding that glucose-2-C^{14} administration to tumor-bearing mice resulted in liver glycogen containing C^{14} distributed throughout all carbons of the hexose (8). These findings have been interpreted as indicating that the tumor caused an extremely active reversible conversion of the administered C^{14} glucose through the Embden-Meyerhoff and tricarboxylic acid cycles resulting in migration of the C^{14} from its original position to other locations in the glucose molecule. Whether these alterations are due to the tumor *per se* or to the indirect influence of the presence of the tumor on the metabolism of other tissues remains obscure.

While uncertainty as to the labeling pattern of the hexose precursor of ribose in tissues of tumor-bearing rats precludes precise interpretations of the pathways of pentose biosynthesis, the preponderance of label in carbon 2 of ribose would seem to eliminate decarboxylation of hexose as the dominant reaction in pentose biosynthesis(4).

Summary. Pathways of pentose biosynthesis in the liver and tumor of control and tumor bearing rats have been studied employing glucose-2-C^{14} as the isotopic precursor. Presence of the tumor in the animal caused marked alteration in the labeling pattern, of liver RNA ribose, with the C^{14} being distributed almost equally throughout the carbon chains. However, tumor RNA ribose is characterized by greater isotopic asymmetry with carbon atom 2 being most radioactive. Possible metabolic mechanisms underlying these observations are discussed.

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Plasma Catechol Amines in Psychiatric Patients. (23228)

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Interest in the determination of plasma concentrations of catechol amines has increased since the development of sensitive fluorometric methods by Lund(1) and Weil-Malherbe and Bone(2). The ethylenediamine method of Weil-Malherbe and Bone is more sensitive but less specific to epinephrine and norepinephrine than the Lund method. It has been used to follow the changes in blood levels of catechol amines in psychiatric

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