Acetoacetate Coenzyme A Transferase Activity in Rat Hepatomas

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SUMMARY

The presence of succinyl-coenzyme A:acetoacetate CoA transferase (CoA transferase) (EC 2.8.3.5), an initiator of ketone body utilization in nonhepatic tissue, was examined in liver from normal, partly hepatectomized, neonatal, and tumor-bearing rats, as well as in a series of transplantable rat hepatomas ranging widely in growth rate. While levels of CoA transferase are extremely low in normal, host, and regenerating liver, considerable amounts of activity are detectable in neonatal liver and in the hepatomas. In fact, the content of CoA transferase in the series of Morris hepatomas increases progressively with increase in tumor-growth rate. The fastest-growing tumor studied (7288Ctc) contains about the same amount of CoA transferase activity as rat skeletal muscle (i.e., an activity of about 0.1 mmole of acetoacetate used per min per g tissue). These results clearly indicate that the faster-growing hepatomas have adequate capacity to utilize ketone bodies in bioenergetic or biosynthetic activities. Furthermore, the enzymes from normal and hepatoma 7288Ctc tissues are quite similar with respect to (a) size of about 10^6 daltons, (b) reaction mechanism requiring formation of an enzyme:CoA intermediate (from ping-pong kinetic data), and (c) various kinetic parameters (such as Michaelis constants, product competitive inhibition constants, and acetoacetate substrate inhibition). The enzymes from rat skeletal muscle and Morris hepatoma 7288Ctc have the same isoelectric point (7.6), which differs from that for the rat heart enzyme (6.8).

INTRODUCTION

The ability of a malignant tumor to utilize preferentially metabolic products from normal tissues in the host organism is of obvious importance for the normal proliferation of the cancer, as well as for controlling this growth by therapeutic manipulation of the metabolic difference. This metabolic advantage for the cancer cell is gained by enzymatic alterations, e.g., in amounts or properties of critical enzymes (2, 15, 17, 19), that occur during the neoplastic transformation. In earlier studies, we observed such an enzymatic difference in the metabolism of ketone bodies by the mouse hepatoma BW7756 (3). Complete utilization of ketone bodies as energy sources requires the presence of CoA transferase (EC 2.8.3.5), which is essentially absent in normal liver (thereby allowing this tissue to be ketogenic), but which is present in significant amounts in nonhepatic tissues (4, 20) and in the mouse hepatoma (3). An early study (18) on acetoacetate oxidation by normal and tumor tissue slices indicated a metabol... pattern for a few rat hepatomas that was more characteristic of nonhepatic tissues; however, a systematic study of hepatoma ketone body usage, particularly with respect to the enzymological aspects, has not appeared. Following is a report of the results of our investigations, correlating tumor levels of CoA transferase activity with growth rates in a spectrum of Morris rat hepatomas and detailing various molecular and kinetic properties of a tumor CoA transferase.

MATERIALS AND METHODS

Chemicals. CoA, as the free acid, was purchased from P-L Biochemicals (Milwaukee, Wis.). Acetoacetyl-CoA, succinyl-CoA, and acetyl-CoA were prepared from diene, succinic anhydride, and acetic anhydride, respectively, using procedures described previously (4). Hydrolysis of ethyl acetoacetate provided lithium acetoacetate (4). LKB Instruments (Rockville, Md.) provided the ampholine solutions for the isoelectric-focusing studies. All other chemicals were obtained from Sigma Chemical Co. (St. Louis, Mo.) and were of the highest purity available. Rabbit muscle glyceroldehyde phosphate dehydrogenase (EC 1.2.1.12), pig heart 3-hydroxyacyl-CoA dehydrogenase (EC 1.1.1.35), and ovalbumin (Grade V) were also purchased from Sigma Chemical Co. ICN Nutritional Biochemical Co. (Cleveland, Ohio) supplied bovine serum albumin (unesterified, fatty acid-poor Fraction V)

Animals and Tumors. The various Morris hepatomas were transplanted in Washington by s.c. or i.m. injection of minced tissue into male Buffalo or ACI rats. These rats were shipped to Baltimore and maintained on a Purina pellet diet and water ad libitum. Tumor-bearing rats were sacrificed by cervical fracture when tumors were of usable size (generally, >10 g/250-g rat), but necrosis was minimal. Heart and liver tissue from several neonatal Buffalo rats...
were determined by the Lowry method (11), with bovine serum albumin as a standard.

Preparation of Tissue Extracts. Tissues or tumors, freed of connective tissue and necrosis, were weighed quickly and minced with scissors in a chilled 0.02 M potassium phosphate solution (pH 7.0). Minced heart tissue was incubated with the bacterial protease Nagarse (4 mg/g net weight of heart) before further treatment (4). The tissue minces were homogenized at 4° in a glass:Teflon homogenizer by 4 to 6 passes with a motor-driven pestle. The final volume of medium was adjusted so as to give a 1:20 (w/v) dilution of the original weight of tissue. Portions (1 to 2 ml) of these 5% homogenates were treated sonically for a total of 2 min (15-sec sonic treatment periods followed by 15 sec of cooling) at 4° and 100 watts of power in a Bronwill sonic oscillator equipped with a needle tip (Bronwill Scientific Co., Inc., Rochester, N. Y.). The sonically treated solutions were centrifuged at 48,000 x g for 15 min, and the pellet was suspended in 0.02 M potassium phosphate buffer (pH 7.0), so that the ratio of the volume of the buffer used to the original g of tissue (wet weight) was 2 to 3 (instead of about 20). After similar sonic treatment, as described above, the suspension was centrifuged for 1 hr at 4° and 48,000 x g. On occasions, a second centrifugation of the supernatant was needed to clarify the solution. The supernatant (2 to 3 ml), along with glyceraldehyde phosphate dehydrogenase and ovalbumin (ca. 10 mg), was placed on a column (1.5 x 90 cm) of Biorad P-150 equilibrated with the same phosphate buffer at 4°. The CoA transferase activity was eluted with this buffer. Fractions (1 ml) containing CoA transferase activity were determined by assaying for the disappearance of acetoacetyl-CoA stimulated by the addition of succinate. The peak fraction of dehydrogenase activity was determined by measuring the oxidation of DL-glyceraldehyde 3-phosphate; ovalbumin was detected by its absorbance at 280 nm.

The chromatographed CoA transferase from the 7288CtC tumor was placed in a solution containing sucrose (0.67 M, 0.23 g/ml) and LKB carrier ampholytes (approximately 12 µl/ml) for developing a gradient of pH 7 to 9, which was later introduced at the midpoint in filling an LKB 110-ml capacity isoelectric-focusing apparatus. A voltage of 400 V was initially applied (0.6 watt, initially) and, after 16 hr, this was increased to 600 V; the temperature was always kept at 4°. Electrofocusing was terminated about 48 hr later, and l-ml fractions were collected. The pH gradient was determined (by using fractions deaerated with N2), and the presence of CoA transferase was detected as described for the chromatographic studies.

The Km value for acetoacetate was determined in 2 different ways, using the chromatographed particulate fractions from the 7288CtC tumor. One method for determining the Km values used conditions already described for directly measuring acetoacetyl-CoA formation. Replicate measurements were made at each of 5 different concentrations of acetoacetate (0.2, 0.3, 0.5, 1.0, and 2.0 mM). A second determination was made by determining acetoacetyl-CoA formation by means of the coupled enzyme reaction with β-hydroxyacyl-CoA dehydrogenase. The reaction mixture (final volume, 1.0 ml) contained (in addition to the transferase solution) 0.067 M Tris-HCl (pH 8.1), 0.15 mM NADH, 0.22 mM succinyl-CoA (which was added last), the dehydrogenase (1.2 IU), and acetoacetate concentrations of 0.02, 0.03, 0.05, 0.10, and 0.5 mM. Saturating concentrations of succinyl-CoA in the range of 0.25 to 0.32 mM were determined for the tumor transferase and were used in both assay procedures. The Km values for acetoacetate were then obtained from a Lineweaver-Burk plot of the data.

The maximal velocity for the reaction producing acetoacetyl-CoA (Vmax in the forward direction) was also obtained from these data on the particulate fractions. In addition, the maximal velocity for the reverse direction (involving acetoacetate production) was determined with 0.06 mM acetoacetyl-CoA (the saturating concentration) and succinate.
Concentrations of 5, 15, 30, 40, and 50 mm.

Product inhibition was examined using succinate at 1.0, 2.5, and 5.0 mm, and the aforementioned variable concentrations of acetoacetate and saturating concentrations of succinyl-CoA. Acetoacetate concentrations of 2.5, 5.0, and 10.0 mm were used in the corresponding product inhibition studies.

RESULTS

Levels of CoA transferase activity in various tissues from normal adult rats are highest in heart and lowest in liver (4, 20). These 2 tissues from host animals were consequently used as controls for the measurements of enzyme activity in tumor homogenates, since their levels were unaffected by the presence of a tumor (Table 1). This observation of the identity of CoA transferase levels in heart and in liver from normal and tumor-bearing animals pertains when the data are expressed in terms of units/g tissue (wet weight) or per g sonically treated protein, or when the activity is measured in the reverse direction (consumption of acetoacetyl-CoA) or in the forward direction (data not shown in Table 1). If a Tris-HCl buffer containing sucrose and mannitol (to which is added deoxycholate before sonic disruption) was used for homogenization instead of a phosphate buffer, no significant changes were seen in total liver CoA transferase activity; total heart activity decreased about 40%, as has been noted previously (4).

CoA transferase activity may be slightly elevated in regenerating liver (at 48 hr), but the rise is less than 20%. Only in newborn rats (less than 48 hr old) did the enzyme levels in heart and liver deviate significantly from the values found in adult rats. Heart levels decreased 70% and liver levels increased over 2-fold (Table 1).

In Table 2 are listed the results of the studies with the different hepatomas. The range of values for the total tumor transferase activity extends from a normal liver level or slightly higher (e.g., hepatoma 44) to 10 to 20 times this level (7288Ctc). Once again, this observation is valid regardless of assay direction or basis for expressing activity (g tissue or mg protein); in fact, the use of 2 different homogenizing media (phosphate buffer or Tris:sucrose:mannitol solution containing deoxycholate) did not produce any significant differences, as shown in Table 2.

Selected molecular and kinetic properties of CoA transferase from the 7288Ctc hepatoma were then examined, in order to provide a basis for comparison with the enzyme from normal rat tissues. A molecular size of approximately 10² daltons was determined by gel filtration chromatography. The peak of tumor transferase activity elutes between the peak fractions of rabbit muscle glyceraldehyde phosphate dehydrogenase (M.W., 144,000) and egg albumin (M.W., 45,000). This results suggests that the size of the tumor enzyme is quite similar to those found for the transferases from various rat tissues (at the same stage of purity) (4) as well as from pig heart (9).

Isoelectric focusing studies indicate that the tumor transferase migrates as a major active band with a pI value of 7.6 and a broad band centered at pH 7.2 that contained about concentrations of 5, 15, 30, 40, and 50 mm.

### Table 2

Total CoA transferease activity in various transplanted rat hepatomas

<table>
<thead>
<tr>
<th>Tumor and site</th>
<th>Generation</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>44 s.c. (2)⁵</td>
<td>13⁴</td>
<td>0.58 ± 0.05⁵</td>
</tr>
<tr>
<td>963 i.m. (2)</td>
<td>16</td>
<td>1.02 ± 0.09</td>
</tr>
<tr>
<td>7794A s.c. (2)</td>
<td>42</td>
<td>0.93 ± 0.16</td>
</tr>
<tr>
<td>7800 s.c. (2)</td>
<td>71</td>
<td>1.17 ± 0.20</td>
</tr>
<tr>
<td>5123c s.c. (3)</td>
<td>125⁶</td>
<td>1.21 ± 0.13</td>
</tr>
<tr>
<td>5123B s.c. (3)</td>
<td>143</td>
<td>1.64 ± 0.42</td>
</tr>
<tr>
<td>9618A i.m. (3)</td>
<td>56</td>
<td>1.77 ± 0.08</td>
</tr>
<tr>
<td>3924A i.m. (3)</td>
<td>312</td>
<td>2.87 ± 0.18</td>
</tr>
<tr>
<td>7777 i.m. (3)</td>
<td>100</td>
<td>2.93 ± 0.69</td>
</tr>
<tr>
<td>7288Ctc s.c. (3)</td>
<td>125</td>
<td>4.86 ± 0.41</td>
</tr>
</tbody>
</table>

¹ Numbers in parentheses, number of animals.
² Mean ± S.E.

### Table 1

Total CoA transferease activity in heart and liver of normal, neonatal, and tumor-bearing rats

<table>
<thead>
<tr>
<th>Type</th>
<th>Heart</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (3)⁶</td>
<td>81.5 ± 11.3 ⁶</td>
<td>760 ± 100</td>
</tr>
<tr>
<td>With regenerating 48-hr liver (4)</td>
<td>76.8 ± 9.6 ⁶</td>
<td>730 ± 100</td>
</tr>
<tr>
<td>Neonatal (3)</td>
<td>23.0 ± 3.8 ⁶</td>
<td>270 ± 20</td>
</tr>
<tr>
<td>Tumor-bearing (26)</td>
<td>81.2 ± 5.0 ⁶</td>
<td>780 ± 110</td>
</tr>
</tbody>
</table>

⁶ Numbers in parentheses, number of animals.
⁷ Mean ± S.E.

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15% of the total activity (Chart 1). It is presently uncertain whether this minor band of transferase activity corresponds to the presence of several isozymes or of proteolytic artifacts in the partially purified preparations. CoA transferase from rat brain and muscle migrate as single active bands (pl = 7.6); kidney transferase contains 2 distinct active components, a major one with pl = 7.6 and a minor one with pl = 7.2 (4). Heart transferase migrates as a single band with a pi value of 6.8. Thus, the tumor CoA transferase more strongly resembles rat muscle or kidney enzymes with respect to charge than the heart enzyme.

Similarities in several kinetic features were also noted for transferases from normal and malignant cells. The parallel line plots of the initial velocity data (shown in Chart 2 for only the half-reaction involving utilization of acetoacetate) are the kinetic patterns expected for the classic ping-pong mechanism, and these have been observed for the transferase from various animal tissues (4, 6, 7, 9). Confirmatory evidence for this predicted mechanism is provided by substrate inhibition studies, which also provide an additional parameter for comparison purposes (5). At high acetoacetate concentrations (>5 mM), transferase activity becomes inhibited, as is predicted for enzymes displaying ping-pong kinetics and is observed for CoA transferase from various rat tissues. From the Hill plot of these data (Chart 3), an inversion concentration of 7 mM can be determined. This value corresponds to the concentration at which substrate inhibition becomes significant and agrees with the values determined for other CoA transferases (in the range of 4 to 6 mM) (5).

Finally, in Table 3 are assembled various kinetic parameters determined for the enzyme (at comparable stages of purity) from several normal rat tissues (4). The K1 values for production inhibition by acetoacetate and succinate are also in the same range of values for the transferase from normal tissues. The expected competitive type of inhibition is also shown with the transferase from both malignant and nonmalignant tissues. The Vmax values for each half-reaction are lower than those for rat heart CoA transferase, but this undoubtedly reflects differences in the states of purity. The values for the ratio of Vmax (reverse direction) to Vmax (forward direction) are similar (in the range of 45 to 62) for the transferases from normal and tumorous tissues (4). As is the case with respect to the structural features examined for the tumor transferase, the kinetic parameters of the various rat tissue CoA transferases do not appear to differ significantly.

DISCUSSION

CoA transferase initiates ketone body utilization by converting acetoacetate to the activated CoA derivative that can then be cleaved thiolytically to yield 2 equivalents of the important metabolic intermediate, acetyl-CoA. Normal hepatocytes, by virtue of the presence of HMG-CoA synthase (EC 4.1.3.5) and the virtual absence of CoA transferase, can produce but not consume ketone bodies (21). The situation with respect to these 2 enzymes is reversed in normal peripheral tissues, which allows these tissues to utilize ketone bodies as fuels, especially when carbohydrate becomes less available, as in starvation. Our results (Table 2) indicate clearly that the malignant hepatocytes contain CoA transferase activity that can reach a specific activity comparable to that found in normal rat skeletal muscle (5.5 μmoles acetoacetate formed per min per g tissue) (4). Comparing levels of tumor transferase with tumor growth rates (Chart 4) leads to the conclusion that the faster-growing tumors have higher transferase content and, consequently, greater capability to utilize ketone...
2.0

ysis (or ketone body oxidation), which is determined by the opposing metabolic processes of ketogenesis and ketol.

undifferentiated 3924A tumor lacks the synthase. Thus, the hepatomas, that high levels of HMG-CoA synthase are

view on ketone body metabolism would appear to be consonant with the molecular correlation concept proposed

synthase and CoA transferase, respectively. This point of levels of the key enzyme for each process, HMG-CoA

unique to liver and well-differentiated hepatomas; the levels of the transferase enzyme (Table 3) reveal its ability to compete for

consistent with a ping-pong reaction mechanism, involving an enzyme: CoA intermediate, that is identical to all other

tional characteristics of normal and neoplastic tissue en

acetoacetate on equal terms with CoA transferases from

7.6 for the predominant species (Chart I) is identical to that found for rat skeletal muscle (4). The kinetic properties

properties are based on studies using CoA transferase preparations from normal and hepatoma tissues that are at

have not yet been delineated for the transferases from other tissues. Inhibition of acetoacetate consumption by the product succinate and by the substrate itself (acetoacetate) is also similar for CoA transferases from normal and malignant sources. Regulatory, possibly allosteric, properties have not yet been delineated for the transferases from normal tissues, but these might eventually indicate functional differences in enzymes from normal and malignant tissues that are more significant than those observed to date. All of the above comparisons of kinetic and molecular properties are based on studies using CoA transferase preparations from normal and hepatoma tissues that are at the same stage of purity. Since these preparations are still heterogeneous with regard to protein composition, some distinct differences may eventually surface. However, at this point, these transferases do show significant similarity in the particular properties examined. Nevertheless, as has been noted in the case of normal tissues (4), it seems that any tumor tissue differences in selective utilization of ketone bodies must be rationalized presently more in terms of tissue content of CoA transferase, tissue blood supply, etc., and less in terms of any functional properties of the enzyme.

Two other aspects of the problem regarding the significance of CoA transferase in tumor proliferation are the availability of substrates (particularly acetoacetate) to the tumor enzyme and tumor cell utilization of the enzyme reaction products (particularly acetocetyl-CoA). One facet of the availability problem, blood levels of ketone bodies, has not been systematically examined in hepatoma-bearing rats. Preliminary findings in our laboratory indicate that plasma levels of total ketone bodies are elevated (by 20% to 50-fold) in fed, tumor-bearing rats. However, these levels seem to correlate poorly with tumor growth rate. Granting that a greater availability of ketone bodies is realized for the cancer, another problem must be considered that relates to the complete conversion of \( \beta \)-hydroxybutyrate to acetoacetate. Tumor content of the enzyme required for this oxidation, \( \beta \)-hydroxybutyrate dehydrogenase (EC 1.1.1.30), has been found to decrease with increasing tumor-growth rate (14), which implies a possible limitation in tumor capacity for utilizing ketone bodies. However, the amount of dehydrogenase present in the fastest-growing tumor bodies. As a corollary to this conclusion, HMG-CoA synthase levels would be expected to decrease with increasing tumor growth rate. McGarry and Foster (12) have observed, on the basis of results from a limited number of hepatomas, that high levels of HMG-CoA synthase are unique to liver and well-differentiated hepatomas; the undifferentiated 3924A tumor lacks the synthase. Thus, the spectrum of hepatomas does show an ordered imbalance in the opposing metabolic processes of ketogenesis and ketolysis (or ketone body oxidation), which is determined by the levels of the key enzyme for each process, HMG-CoA synthase and CoA transferase, respectively. This point of view on ketone body metabolism would appear to be consonant with the molecular correlation concept proposed by Weber (15).

The role, if any, played by CoA transferase in determining hepatoma growth characteristics may be analyzed from several perspectives, such as enzyme properties, substrate availability to the tumor, and tumor cell usage of products from the CoA transferase catalyzed reaction. Clearly, our results (Table 2; Chart 4) show that the enzyme is present in the malignant hepatocyte and in amounts that correlate positively with growth rate. CoA transferase from hepatoma 7288Ctc with an approximate molecular weight of 100,000 is similar in size to the transferases from all normal rat tissues examined to date (4), and the isoelectric point of 7.6 for the predominant species (Chart 1) is identical to that found for rat skeletal muscle (4). The kinetic properties (Charts 2 and 3) indicate a significant similarity in functional characteristics of normal and neoplastic tissue enzymes. The parallel line plots of initial velocity data are consistent with a ping-pong reaction mechanism, involving an enzyme: CoA intermediate, that is identical to all other CoA transferases (7, 9). The kinetic parameters for the tumor enzyme (Table 3) reveal its ability to compete for acetoacetate on equal terms with CoA transferases from

<table>
<thead>
<tr>
<th>Kinetic parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( K_m ) (mm)</td>
<td></td>
</tr>
<tr>
<td>Acetoacetate</td>
<td>0.49 ± 0.07a</td>
</tr>
<tr>
<td>Succinate</td>
<td>0.16b</td>
</tr>
<tr>
<td>Acetoacetyl-CoA</td>
<td>0.028</td>
</tr>
<tr>
<td>Succinyl-CoA</td>
<td>0.079</td>
</tr>
<tr>
<td>( K_i ) (product inhibition) (mm)</td>
<td>0.89</td>
</tr>
<tr>
<td>Succinate</td>
<td>4.4</td>
</tr>
<tr>
<td>( V_{max} / V_{forward} ) max</td>
<td>54 ± 5</td>
</tr>
</tbody>
</table>

* This value was obtained using the direct spectrophotometric assay and is the average of measurements on material from 2 separate tumors.
* This value was obtained using the coupled assay (involving \( \beta \)-hydroxyacyl-CoA dehydrogenase).
* A pattern consistent with competitive inhibition was observed for both succinate and acetoacetate.
* Activity was determined in terms of \( \mu \)moles of acetoacetate used (forward reaction) or formed (reverse reaction) per min per mg of protein.

CoA Transf erase in Rat Hepatomas

<table>
<thead>
<tr>
<th>CoA Transferase Activity</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate acetoacetate formed (( \mu )mol/g tissue)</td>
<td>7288Ctc</td>
<td>7292A</td>
<td>76577</td>
<td>7792A</td>
<td>9418</td>
<td>9463</td>
</tr>
<tr>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
<td></td>
</tr>
</tbody>
</table>

Chart 4. Correlation of total tumor CoA transferase activity and growth rate of the various Morris hepatomas. The total transferase activity in the various tumors (Table 2) is plotted against the time between transplants for the tumors.
studied (3924A), over 3% relative to normal liver (14), is comparable to the amounts found in most nonhepatic rat tissues (2 to 12%) (10). This comparison suggests that β-hydroxybutyrate dehydrogenase content in these tumors is adequate for allowing ketone body utilization (but perhaps not ketone body production). Furthermore, interconversion of ketone bodies need not occur exclusively in the consuming tissue. In rats' blood, β-hydroxybutyrate can be continually converted by the liver into blood acetoacetate for extrahepatic utilization (1, 13). In this context, it is worth noting that the progressive increase in CoA transferase activity with increasing tumor growth rate, along with corresponding decreases in HMG-CoA synthase and β-hydroxybutyrate dehydrogenase activities, may indicate a dramatic shift in metabolic activities from a normal hepatocyte to a malignant hepatocyte as a ketone body producer to a malignant hepatocyte as a ketone body consumer.

Finally, the question regarding actual tumor usage of ketone bodies must be considered. Unfortunately, in vivo studies relevant to the subject of ketone body usage have not been performed in hepatoma-bearing rats, so we can only speculate on the possible metabolic significance of our findings. First, the functioning of CoA transferase assures a modest supply of acetyl-CoA for utilization intra- and extramitochondrially (via citrate). Second, the transferase can provide an alternative reductant that might tend to correct the altered redox state of pyridine nucleotides that exists in the cytoplasmic and mitochondrial compartments of the malignant hepatocytes (16). An obvious need exists for more detailed information in this area of ketone body metabolism.

In conclusion, the correlation of tumor content of CoA transferase with tumor-growth rate indicates that this phenomenon is more a consequence of neoplasia than one of its primary events. However, additional studies are needed to assess relative metabolic significance of this enzymic alteration.

REFERENCES

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