Turnover and Transport of Plasma Very-Low-Density Lipoprotein Triglycerides in Mice Bearing Ehrlich Ascites Carcinoma

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ABSTRACT

To study cancer-induced hypertriglyceridemia and the contribution of circulating very-low-density lipoprotein (VLDL)-triglyceride fatty acid (TGFA) to the tumor cells, we have measured the turnover rate of VLDL-triglyceride (TG) in the plasma and the transport of TGFA and TG-glycerol to 8- and 9-day-old Ehrlich ascites tumors in male Swiss-Webster mice maintained on a 58% glucose, fat-free diet. The inflow and outflow of plasma VLDL-TG, labeled endogenously in control and tumor-bearing mice with [2-3H]glycerol and [1-14C]palmitate, were followed for 30 min after i.v. injection of labeled serum into control and tumor-bearing recipients, respectively. The fatty acid and glycerol moieties of plasma VLDL-TG were removed at the same rates and followed simple first-order kinetics for at least 15 min \( t_{1/2} = 4.7 \pm 0.30 \) and \( 16 \pm 0.75 \) (S.E.) min in control and tumor-bearing mice, respectively \( (p < 0.001) \), with corresponding rates of TG secretion and removal \( = 0.20 \pm 0.01 \\text{mg TG per min per mouse} \). The plasma TG pool size was increased by 50% in the tumor-bearing mice compared to controls \( (p < 0.02) \). Thus, cancer-induced hypertriglyceridemia occurs despite a decrease in the rate of hepatic TG secretion in tumor-bearing mice as compared to control mice. Therefore, the rate of plasma VLDL-TG removal is apparently decreased even more than the hepatic VLDL-TG secretory rate. In tumor-bearing mice, when 70 to 75% of the VLDL-TG radioactivity had been removed from the plasma, tumor total lipid radioactivity rose to only about 1% of the dose. Approximately one-half of this represented VLDL-TGFA, and the rest of the radioactivity was present in the extracellular fluid-TG pool of the tumor. This corresponded to a rate of about 1.5 nEq TGFA per min per 7-ml tumor transported from the host to the tumor cell phospholipid fatty acid pool. Only a small fraction of the total lipid fatty acid of the tumor cell appeared to be derived from plasma VLDL-TGFA.

INTRODUCTION

We have been interested in 2 aspects of triacylglycerol metabolism in mice bearing Ehrlich ascites carcinoma: (a) elucidation of the process(es) by which hypertriglyceridemia develops in cancerous animals; and (b) determination of the relative quantitative importance of various forms of lipid FA3 in meeting the requirements of a growing cancer for its energy supply and synthesis of cell organelles and membranes. Earlier studies have shown that the cancer-induced hypertriglyceridemia appearing in mice bearing Ehrlich ascites carcinoma is transient in nature \( (10, 16, 17, 20) \) and that the degree of hypertriglyceridemia is dependent upon both the strain of mouse and its dietary state \( (17) \). We have shown that this hyperlipidemia is probably of endogenous origin, at least in part, since it occurs when animals eat a high-carbohydrate, fat-free diet \( (20) \). However, we have not been able to obtain any evidence with Triton WR-1339 to support the view that hypertriglyceridemia develops as a consequence of hypersecretion of VLDL-TG by the liver \( (20) \). In fact, most of our earlier data indicated that the rate of hepatic VLDL-TG secretion in cancer-bearing mice was slower than in controls. If so, this would imply that defective VLDL-TG removal was the cause of the hypertriglyceridemia. A similar conclusion was reached by Begg \( (8) \) and Posner \( (26) \), both of whom have concluded that decreased chylomicron-TG clearance and decreased heparin-releasable plasma LPL activity are found in cancer-bearing rats and that slow rate of exogenous fat removal from the circulation probably contributes to the cancer-induced hyperlipidemia that occurs in these animals. In the present study, we have attempted to measure both the rates of VLDL-TG secretion and removal in tumor-bearing mice during near steady-state conditions.

There are very few quantitative studies reported in the literature that deal with the utilization of VLDL-TGFA by cancer cells. Brenneman et al. \( (10) \) and Mathur and Spector \( (21) \), have reported that VLDL-TG, with properties that are very similar to those of blood plasma VLDL-TG, can be present in high concentrations \( (up to 500 \text{ mg/dl}) \) in Ehrlich ascites tumor ECF \( (10) \), and the VLDL-TG in the ECF may be readily taken up (with and without prior hydrolysis) by the tumor cells \( (11) \). From the close similarity of plasma and ECF VLDL-TG characteristics, the lack of any evidence that Ehrlich ascites cells were the source of ECF VLDL-TG, and the higher levels of VLDL-TG in plasma, it was concluded that blood plasma was the probable source of ECF VLDL-TG \( (10, 21) \) and that these complex particles might be an important source of FA for the tumor \( (11) \). However, it is noteworthy that the latter study was carried out in vivo with exogenously labeled VLDL-TG, which may not behave physiologically.

No one as far as we know, has measured the rate of VLDL-TG transport in vivo from the plasma of the host to the tumor.

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2 To whom requests for reprints should be addressed, at Veterans Administration Wadsworth Medical Center, Building 115, Room 316, Wilshire and Sawtelle Boulevards, Los Angeles, Calif. 90073.
3 The abbreviations used are: FA, fatty acid; VLDL, very-low-density lipoprotein; TG, triglyceride; LPL, lipoprotein lipase; TGFA, triglyceride fatty acid; ECF, extracellular fluid of the tumor; FFA, free fatty acid; TLC, thin-layer chromatography; TL, total lipid; PL, phospholipid; TLFA, total lipid fatty acid; PLFA, phospholipid fatty acid.
We have carried out studies of 2 other possible sources of tumor lipid FA, FFA transport from the circulation of the host to the Ehrlich ascites tumor (6, 22) and de novo lipogenesis by the tumor (18). In the present study, we have attempted to evaluate the maximum contribution of plasma VLDL-TGFA to the FA needs of the tumor and to determine the transport rates of the FA moieties of VLDL-TG into tumor fluid and cells. We have also assessed, using doubly labeled VLDL-TG, the extent to which plasma TG is transferred intact, without prior hydrolysis by capillary LPL (23), into the tumor fluid.

MATERIALS AND METHODS

Mice. Male Swiss-Webster mice (Hilltop Laboratory Animals, Inc., Los Angeles, Calif.) were used. Two days before tumor inoculation, the mice were divided into control and tumor groups, placed on Purina laboratory chow, and given water ad libitum. Initial body weights were: controls, 32.9 ± 0.4 (S.E.) g (n = 13); tumor, 31.8 ± 0.3 g (n = 16).

Tumor. The subline of Ehrlich-Lehré ascites tumor cells used in this study was obtained from Dr. T. A. Khwaja, Director, Animal Tumor Research Facility, University of Southern California. The inoculum, given i.p., contained 15 × 10⁶ cells/mouse. Immediately following inoculation, all mice were placed on a 58% glucose, fat-free diet (4). On Day 5 of tumor growth, pellets of food were placed inside the cages of tumor-bearing mice to make it easier for them to obtain food. Experiments were conducted on Days 8 and 9 of tumor growth, and the tumor volume was 6.1 ± 0.8 (S.E.) ml (n = 13). All the mice gained weight: controls, 3.9 ± 0.4 g; tumor, 10.2 ± 0.6 g.

Tracers. [2-3H]Glycerol (1.5 Ci/mmol) and [1-14C]palmitic acid (58 mCi/mmol) were obtained from Rosechem (formerly Dhom) Products, North Hollywood, Calif. Both tracers were found to be >99% pure by TLC. The FA-albumin complex of palmitic acid was prepared by a slight modification of the method of Friedman et al. (13), described in detail earlier (5). No FA carrier other than that in the tracer and in the mouse serum was used in preparation of the complex.

Control and tumorous doses were used to obtain control and tumorous recipient VLDL-TG doses, respectively. Each donor dose of 100 μl, delivered i.v. via the tail vein to anesthetized mice, contained 700 μCi of [2-3H]glycerol and 20 μCi of [1-14C]palmitate. The donors were killed 25 min later, blood was collected following decapitation, and aliquots of the pooled sera after appropriate dilution with 0.9% NaCl solution were used for recipient doses. The pooled, labeled serum was used to collect blood from the ophthalmic sinus (5) for all samples except the terminal ones. The latter samples were collected after 30 min after injection of the dose. Heparinized microcapillary tubes were used for recipient doses. The pooled, labeled serum was used in preparation of the complex.

RESULTS

Turnover of Plasma VLDL-TG. The rates of disappearance of [2-3H]glycerol- and 1-14C-fatty acyl-labeled VLDL-TG from the blood plasma of control and tumorous mice, over 30 min following i.v. injection of the doubly labeled tracer, are shown in Chart 1. The fractional rate of VLDL-TG clearance from the plasma of tumorous mice was less than one-third that of control mice. The curves describing the turnover of plasma VLDL-TG-glycerol (Chart 1B) in both groups of mice could be fitted by a single exponential function. This was also true for VLDL-TGFA (Chart 1A) in the tumor-bearing mice; however, in control mice, a single exponential function was observed for only 15 min. The 30-min value fell above the extrapolated function. The fractional irreversible disposal rate values in tumor-bearing mice were practically identical for TGFA and TG-glycerol. These findings suggest that, during removal of VLDL-TG from the plasma, at least in the tumorous mice, the glyceryl and FA moieties are removed at the same rate and without appreciable selective recycling of the FA moiety. The exception, 14C-labeled VLDL-TGFA in control mice, shows an upward bending of the curve between 15 and 30 min; however, in the first 15 min, when recycling of labeled plasma TGFA through the liver is negligible, VLDL-TGFA and glycerol also turned over at approximately equal rates in the control mice.

Computer-derived least-square best fits of the data to a single exponential function are shown in Chart 1. The 30-min 14C value for the controls was not included in the analysis. Note that the data are based upon an assumed volume of distribution of VLDL equal to the plasma albumin space, 5.0% of body weight, measured previously (5). However, the extrapolated zero-time intercepts of the fitted lines were significantly higher than the theoretical value of 100% in the control mice, and even in the tumor-bearing mice, the initial values at t = 60 sec
were consistently above 100%. This finding indicates that the volume of distribution of VLDL in mice is significantly smaller than that of albumin. The results of the analyses of the data from Chart 1 and the measured pool sizes are summarized in Table 1. The initial $t_{1/2}$ of plasma VLDL-TG removal of tumorous mice was more than 3 times that of control mice. The plasma TG pool size was about 50% larger in the tumorous than in the control mice, and the turnover rate of TG (mg/min) in the latter was more than twice as fast as in the tumorous mice.

**Plasma TG $^{3}$H:$^{14}$C Ratios.** The $^{3}$H:$^{14}$C ratios of plasma TG in control and tumor-bearing mice, on the basis of both total radioactivity and specific activity measurements of isolated TG fractions, clustered closely (±5%) around the theoretical value (1.0) that would be expected if the FA moieties did not recycle into plasma VLDL-TGFA. In the control group, the $^{3}$H:$^{14}$C ratio at 30 min fell to 0.36, due to the upward bend of the curve for plasma $^{14}$C-TGFA at that time. This is a greater drop than we would expect from recycling of TGFA alone or from the theoretical conversion of $^{14}$C-FFA (estimated to be present in the injected dose) to $^{14}$C-TGFA, and its significance is unclear to us. However, the data which were of primary relevance to our further analysis were those of the tumor-bearing mice in which...
we wished to ascertain whether the labeled TGFA appearing in the tumor fluid and cells would retain the same \(^3\text{H}:^{14}\text{C}\) ratio as that observed in plasma (see below).

**Appearance of Radioactivity in Lipids of Whole Tumor.**

The cumulative increase over 30 min of \(^{14}\text{C}-\text{FA}\)-labeled lipids in the whole tumor is shown in Table 2. At the end of the experiment, about 1% of the injected dose appeared in the TLFA of the tumor. After 15 min, approximately one-half of the \(^{14}\text{C}-\text{TLFA}\) in the tumor was present in the ECF as \(^{14}\text{C}-\text{TGFA}\), and most of the remaining half was found in cellular \(^{14}\text{C}-\text{PLFA}\) (Table 2). \(^{14}\text{C}-\text{TGFA}\) associated with or in tumor cells (not shown in Table 2) accounted for only up to 10% of the \(^{14}\text{C}-\text{TGFA}\) found in the whole tumor. Low but statistically significant levels of radioactivity were also found in the tumor ECF-FFA fraction.

The time course of both \(^{14}\text{C}-\text{TGFA}\) and \(^3\text{H}-\text{TG}\)-glyceryl appearance in the tumor extracellular fluid following the i.v. injection of doubly labeled VLDL-TG is shown in Chart 2 along with the curve of plasma VLDL-TG disappearance (mean of Chart 1A and Chart 1B). As can be seen from these data, the FA and glyceryl moieties appeared as a unit (i.e., the \(^3\text{H}:^{14}\text{C}\) ratios of the tumor ECF-TG were approximately 1.0 at all times) and accounted for only a minor fraction of the label that left the circulating VLDL-TG compartment. When 70 to 75% of the injected TG dose left the plasma at 30 min, about 0.5% of the injected TG dose was recovered in the tumor ECF as TG. Most of the tumor fluid \(^3\text{H}\) radioactivity was found in the form of TG, less than 10% of which was associated with the tumor cells; however, highly significant amounts of radioactivity (not shown) were found in cell \(^3\text{H}-\text{PL}\).

Although the \(^3\text{H}:^{14}\text{C}\) ratios of 1.0 in tumor extracellular fluid TG (Chart 2) are consistent with the view that the tumor ECF-TG is derived directly from circulating plasma VLDL, our attempt to demonstrate a simple precursor-product relationship (29) between the specific activities of TG in the 2 compartments was not conclusive because of the short duration of our observations. The specific activity data are shown in Chart 3. Since the \(t_{\text{max}}\) of the tumor ECF-TG specific activity was not reached, it is not possible to determine whether that curve would intersect the plasma TG specific activity curve at the \(t_{\text{max}}\) (7, 29). At 30 min, the tumor ECF-TG specific activity was only 6% that of plasma TG as shown in Chart 3. Extrapolation of these curves indicates that the \(t_{\text{max}}\) might be attained between \(t = 60\) to 90 min. Assuming a \(t_{\text{max}}\) of 75 min and using a simple 2-pool model (7), we estimate that the rate of intact VLDL-TG transport from plasma to tumor ECF was approximately 0.5 \(\mu\text{g}\) TG per min per 7-ml tumor. This represents less than 1% of the rate of plasma VLDL-TG removal from the circulation.

Another finding shown in Chart 3 is the relationship between tumor ECF-TG and whole-tumor TG specific activities. The latter were only about 30% of those of the ECF-TG throughout the study. This implies that a pool of TG twice the size of the extracellular pool was present in the cells and that the intracellular TG pool was poorly labeled in both the fatty acyl and glyceryl moieties. As shown in Table 3 and data presented above, these conclusions were borne out by direct measurements of the cellular and extracellular TG pools. Approximately 1.0 mg of relatively nonradioactive TG was located intracellularly, and only 0.5 mg of TG was in the extracellular compartment (per 7-ml tumor) in this particular study.

**Rate of Plasma VLDL-TGFA Transport and Conversion to Tumor Cell PLFA.** The incorporation of plasma \(^{14}\text{C}-\text{VLDL}\)-TGFA into tumor cell PLFA, the reference curve of labeled

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**Table 2**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Tumor(^{14}\text{C}-\text{TLFA}) (% of dose)</th>
<th>Extracellular TGFA</th>
<th>Cellular PLFA(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.063 ± 0.063(^c)</td>
<td>63 ± 11</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>0.14 ± 0.019</td>
<td>38 ± 3.8</td>
<td>53 ± 13</td>
</tr>
<tr>
<td>5</td>
<td>0.29 ± 0.17</td>
<td>36 ± 6.6</td>
<td>39 ± 11</td>
</tr>
<tr>
<td>10</td>
<td>0.29 ± 0.17</td>
<td>53 ± 13</td>
<td>49 ± 6.0</td>
</tr>
<tr>
<td>15</td>
<td>0.47 ± 0.14</td>
<td>51 ± 0.9</td>
<td>47 ± 14</td>
</tr>
<tr>
<td>30</td>
<td>1.1 ± 0.30</td>
<td>42 ± 1.6</td>
<td>38 ± 7.0</td>
</tr>
</tbody>
</table>

\(^a\) Whole tumor = cells plus fluid of a 7-ml tumor.  
\(^b\) Based upon combined analyses of \(^{14}\text{C}-\text{PLFA}\) in isolated, stored, frozen, and washed cells and in samples of whole tumor (shown by analysis to be present only in the cellular fraction).  
\(^c\) Mean ± S.E. (\(n = 13\)).
VLDL-TGFA disappearance from the circulation of the host, and a simple model that we have used to analyze the data are shown in Chart 4. We have calculated that the rate of plasma VLDL-TG turnover was 88 µg TG per min in our cancer-bearing mice. This corresponds to $103 \times 3 = 310$ nEq TGFA per min (assuming the molecular weight of TG is 850 and 3 equivalent FFA released per mol of TG turned over). Of the labeled TGFA that disappeared from plasma in 30 min, only about 0.5% appeared in the tumor cell PLFA (per 7-ml tumor). On the basis of a least-squares fit to the data, about 1.5 nEq of circulating VLDL-TGFA per min per 7-ml tumor was used to supply the tumor cells with their FA needs for membrane PLFA synthesis.

**DISCUSSION**

Our results provide strong evidence that cancer-induced hypertriglyceridemia in mice bearing Ehrlich ascites carcinoma is due to defective removal of VLDL-TG, the production rate of which was actually reduced by 44%. A similar inhibition was noted earlier by Kannan *et al.* (20) using Triton WR 1339. Hepatic lipogenesis is also depressed at this stage of tumor growth, probably due to inanition (18). Fasting lowers plasma TG levels in mice (16, 17), but chronically lowered insulin levels and other hormonal changes that followed reduced food intake might cause an inhibition of VLDL-TG removal from the circulation that was even greater than the inhibition of VLDL-TG secretion by the liver. Decreased food intake and lowered plasma insulin levels are associated with diminished LPL activity in the capillary endothelium of white adipose tissue in rats (23). However, further studies are required to establish whether LPL activities of other extrahepatic tissues (cf. Ref. 12) responsible for VLDL-TG clearance from the circulation are similarly affected by tumor growth and/or the associated decreased food intake.

Cancer-induced hypertriglyceridemia in mice bearing Ehrlich ascites carcinoma can occur in the absence of dietary fat (20), as we have confirmed here, and is therefore at least partially of endogenous origin. Nevertheless, dietary fat could contribute...
to this lipemia in animals on normal fat-containing diets. Studies with labeled chylomicron-TG need to be carried out to establish whether the clearance of exogenous fat is impaired in tumor-bearing mice. Earlier workers have concluded that the clearance of circulating chylomicron-TG is impaired in cancer-bearing rats (8, 26).

Fat metabolism of mice with Ehrlich ascites carcinoma is similar to that seen in states of relative insulin insufficiency: loss of body fat (17); decreased plasma VLDL-TG removal (presumably associated with a correspondingly decreased uptake of VLDL-TGFA by white adipose tissue); decreased rates of hepatic and extrahepatic FA synthesis from all 2C units (18); decreased hepatic TG secretion and probably increased mobilization of adipose tissue TGFA [based upon elevated mid-morning plasma FFA levels (6)]; and increased FFA oxidation

Although Kannan and Baker (17) reported little fat loss in Swiss-Webster (in contrast to CBA) mice bearing this tumor, subsequent studies have shown that, at late stages of tumor growth, marked loss of body fat occurs in Swiss-Webster mice as well. R. Kannan and N. Baker, unpublished observations.

With regard to the contribution of host plasma VLDL-TGFA to tumor cell lipid FA, we envisage the following 2 primary pathways. (a) The first is conversion of plasma VLDL-TGFA directly to FFA (e.g., by LPL activity in the capillary endothelium or by an hepatic lipase), thereby providing a source of FFA for tumor cell PLFA synthesis that would by-pass the tumor ECF-TG pool. Any FFA that formed in this way should enter the rapidly turning over ECF-FFA pool of the tumor (19, 22, 28). (b) The second primary pathway is transport of VLDL-TG from plasma to tumor ECF as an intact lipoprotein molecule followed by the incorporation of VLDL-TGFA in the ECF of the tumor into tumor cell PLFA. The radioactivity in the ECF-FFA pool of the tumor was too low to measure reliably, but it was not negligible. Most of the labeled FA transferred from the host to the tumor could have traversed this pathway. Radioactivity in the tumor ECF was almost entirely in the form of intact TG molecules, presumably VLDL-TG (21). We were unable to evaluate how much of the VLDL-TG that entered the tumor fluid from blood plasma was utilized by the tumor cells. However, our multicompartamental analyses indicate that, in contrast to an earlier study in vitro (11), VLDL-TGFA in the tumor ECF was a minor source of tumor cell lipid FA.

The present study was not designed to evaluate the turnover rate and sources of tumor ECF-TGFA. However, we have estimated the rate of VLDL-TGFA transport from the circulation to the tumor fluid. This transport rate (0.5 nmol TGFA per min per 7-ml tumor), although slow compared to the turnover of plasma VLDL-TGFA, is about an order of magnitude faster than the net rate of TGFA accumulation in tumor ECF (about 0.04 nmol TGFA per min per 7-ml tumor). It is probable that plasma VLDL particles are entering the tumor ECF as part of the well-known process of ultrafiltration through the liver (30). The concentration of VLDL-TG in the tumor ECF is maintained at a lower level than in the blood plasma (16, 17). This could be due, in part, to (a) VLDL-remnant-TG clearance by liver cells as the ascitic fluid is formed and, in part, to (b) net entry of water into the ascitic fluid by other pathways. For example, we know that there is a pathway by which blood plasma water can exchange very rapidly with ascitic fluid water (24). We assume that net entry of water into the ascitic fluid could occur by this pathway, without significant concomitant transfer of plasma VLDL-TG. Thus, the ECF-TG concentration remains at about 10% that of plasma but responds to changes in plasma VLDL-TG concentrations elicited by alterations in patterns of feeding and fasting (16, 17, 20). This would be expected for an ultrafilterate of plasma. A detailed understanding of the quantitative aspects of ECF-TG turnover and uptake by the tumor cells will require studies of different design and longer duration.

Essentially, all of the label in the tumor cells lipids was found in PL, as expected both from our modeling studies of FFA metabolism by these tumor cells in vivo (19, 22) and from the earlier studies of Spector (28). Only trace amounts of radioactivity were found in the tumor cell TG fraction. This finding indicates that the large uptake of intact TG molecules by these cells in vitro that was reported by Brenneman and Spector (11)

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4 M. Ookhtens and N. Baker, unpublished observations.
may have been an artifact of the in vitro incubation and of the particular conditions used.

Finally, we estimated the contribution of plasma VLDL-TGFA to the overall FA requirements for growth and oxidation of this tumor. We have established previously that a 7-ml Ehrlich ascites tumor is growing at a net rate that requires about 10 nmol FA per min (22). The requirements for oxidation are uncertain. However, the tumor exists in an anaerobic environment (27), and we suspect, based upon recent studies, that all values previously published (see Ref. 24) are gross overestimates. Nevertheless, we may relate the net FA needs for tumor growth, given above, to the rates of (a) FFA transport from the plasma (10 nmol FFA per min per 7-ml tumor) (6); (b) de novo lipogenesis (maximal rate of 7.5 nmol FA synthesized per min per 7-ml tumor) (18); and (c) plasma TGFA incorporation into tumor cell TLFA reported here, namely 1.5 nmol TGFA per min per 7-ml tumor. Compared to the other sources of FA, plasma TGFA seems to be a minor, but not insignificant source, representing about 8% \((1.5)/(10 + 7.5 + 1.5) \times 100\) of the total FA influx, including de novo FA synthesis by the tumor cells. The combined influx (19 nmol FA per min per 7-ml tumor) probably accounts for both the growth and oxidative needs of the tumor.

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