Differential Effects of Delivery of Omega-3 Fatty Acids to Human Cancer Cells by Low-Density Lipoproteins versus Albumin

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ABSTRACT

Purpose: Omega-3 (n-3) fatty acids (FA) have been proposed to confer tumor-inhibitory properties. In vivo, dietary FA are delivered to tumor cells by two main routes: low-density lipoproteins (LDL) and albumin complexes. High FA concentration in LDL and up-regulation of LDL receptors in tumor cells suggest that the LDL receptor pathway may be the major route for FA delivery. We compared effects of n-3FA delivered to human cancer cells by LDL and albumin.

Experimental Design: LDL was isolated from plasma of African Green monkeys fed diets enriched in fish oil (n-3 FA) or linoleic acid (n-6FA) and used to deliver FA to MCF-7 and PC3 cancer cells. Cell proliferation, apoptosis, and changes in global gene expression were monitored.

Results: Both LDL and albumin were effective in delivering FA to tumor cells and modifying the composition of cell phospholipids. The molar ratio of 20:4 (n-6) to 20:5 (n-3) in phosphatidylcholine and phosphatidylethanolamine was profoundly decreased. Although cell phospholipids were similarly modified by LDL and albumin-delivered FA, effects on cell proliferation and on transcription were markedly different. LDL-delivered n-3 FA were more effective at inhibiting cell proliferation and inducing apoptosis. Expression microarray profiling showed that a significantly higher number of genes were regulated by LDL-delivered than albumin-delivered n-3 FA with little overlap between the two sets of genes.

Conclusions: These results show the importance of the LDL receptor pathway in activating molecular mechanisms responsible for the tumor inhibitory properties of n-3FA.

INTRODUCTION

Dietary fat intake may be an important factor in the development of several human cancers, notably breast, prostate, and colon. Of particular interest are studies indicating that the potential risk may relate to the type rather than the amount of dietary fat, with saturation of the fatty acid (FA) being the critical discriminator. Diets rich in animal fat (high in saturated FA) have been compared with those enriched in vegetable (n-6 polyunsaturated FA), olive (monounsaturated FA), and fish oil (n-3 polyunsaturated FA). In human population studies, an inverse relationship has been observed between breast cancer incidence and dietary intake of saturated FA and n-6 polyunsaturated FA and a negative relationship with fish oil consumption (3).

FAs are present in the diet as triacylglycerols or triglycerides. After dietary intake, triglycerides are packaged in the intestinal epithelium into chylomicrons, which are secreted into the lymphatic system and enter the circulation via the thoracic duct. Lipolysis of these particles, initially in tissues such as heart and lungs by the enzyme lipoprotein lipase, produces free FAs that quickly associate with serum albumin. Remnant particles return to the liver where their triglycerides are assembled with apolipoprotein B 100 (apoB) for secretion as very LDL particles. In the circulation, lipolysis of very LDL produces LDL, which in turn is taken up by peripheral tissues. Thus, FAs are delivered to mammary cells by two major routes: by uptake and intracellular hydrolysis of internalized LDL and by albumin complexes formed after lipolysis. Hormone-sensitive lipase hydrolysis of triglycerides stored in adipose tissue also contributes to the FA-albumin complement, but the molar concentration of FA in lipoprotein triglycerides is an order of magnitude higher than that of FA-albumin (4) and may be the primary source of FA in many tissues. Many studies have confirmed the observation that LDL receptors are up-regulated in tumor cells (5). Therefore, the LDL receptor pathway is likely to be a major route for FA delivery to these cells.

Studies to date that have addressed mechanisms related to dietary fat and breast cancer at the cellular level have been limited to FA delivery either by albumin or liposome incorporation (6–9). We hypothesized that FA delivery from the lysosomal degradation of LDL would, through production of regulatory metabolites, present far greater potential for regulation of...
growth and transcription than the albumin-associated FA delivery pathway. The present study shows that n-3FA delivered by the LDL receptor-mediated process has profoundly greater effects on cell growth, apoptosis, and gene regulation than n-3 FAs delivered by albumin.

**MATERIALS AND METHODS**

**Low-Density Lipoprotein Isolation and Characterization**

LDL were isolated from adult male African Green monkeys fed n-3 or n-6FA–enriched diets for 3 to 5 years (n = 12 each group) whose maintenance and clinical procedures are published (10–12). Diet compositions are shown in supplementary Table 1. Blood samples were drawn from the femoral vein of anesthetized animals after an overnight (18 hours) fast and placed into chilled tubes containing 0.1% EDTA, 0.02% NaN₃, 0.04% 5,5′-dithiobis(2-nitrobenzoic acid) [final concentrations] at pH 7.4. Plasma was immediately isolated by low-speed centrifugation, and LDL was isolated from plasma by sequential density gradient ultracentrifugation (10). LDL was filter sterilized, then stored at 4°C under argon, and used within 3 months of isolation. Alternatively, isolated LDL was cryopreserved in 10% sucrose under argon at −70°C for up to 6 months before use (13). LDL protein was measured by the method of Lowry (14). LDL FAs were determined after lipid extraction, saponification, and methylation, and FA methyl esters were quantified by gas-liquid chromatography as described previously (15). Coefficients of variation for the major FA are <15%.

**Preparation of Fatty Acid/Bovine Serum Albumin Complexes**

Linoleic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) were obtained as sodium salts from Sigma Chemical Company (St. Louis, MO) and used to prepare 600-μmol/L stocks. A 125-μmol/L solution of FA-free BSA (Sigma) was prepared in DMEM/Ham’s F-12. FA salts were solubilized in the BSA-media at 37°C for 30 to 60 minutes. FA-BSA stocks were filter-sterilized and stored in aliquots at −20°C under argon.

**Cell Culture**

MCF-7 cells were obtained from the American Type Culture Collection (Rockville, MD) and routinely maintained and grown in DMEM/F12 supplemented with 5% fetal bovine serum (FBS), 10 μg/mL porcine insulin (Sigma), penicillin/streptomycin, and t-glutamine.

**Fatty Acid Delivery to Cells**

Cells were grown in 75-cm² flasks until ~50% confluent, then the growth media was replaced with fresh media containing 0.5% FBS supplemented with LDL or BSA-FA. At the end of each experiment (24 to 72 hours), cell monolayers were washed twice with balanced salt solution (137 mmol/L NaCl, 2.7 mmol/L KCl, 1.45 mmol/L KH₂PO₄, and 20.3 mmol/L Na₂HPO₄), and lipids were extracted with isopropanol for 24 hours at 4°C. Lipid extracts were phased into chloroform, saponified, and FAs were methylated and separated by gas-liquid chromatography (15). In some experiments, chloroform extracts were separated into individual lipid classes by thin-layer chromatography, before FA analysis.

**Determination of Cholesterol, Triglyceride, and Phospholipid Content of Cells**

Aliquots of chloroform extracts were evaporated to dryness under nitrogen and exchanged into aqueous solution by addition of 2 mL of 1% Triton X-100 in chloroform, re-evaporation and solubilization of the detergent residue in 0.5 mL dH₂O. Total cholesterol, triglycerides, and phospholipids were measured with standard enzymatic and chemical procedures (10). To determine free and esterified cholesterol, aliquots of chloroform extracts were dried under nitrogen, dissolved in 50 μL of dichloromethane, and free and total cholesterol were determined by gas-liquid chromatography (16). Total and free cholesterol were quantified with a stigmasteryl internal standard, and esterified cholesterol was calculated as the difference between total and free cholesterol.

**Phospholipid Analysis**

Lipid extracts were analyzed for the phospholipid subclasses phosphatidyicholine and phosphatidylethanolamine (PE) with a Quattro II electrospray triple quadrupole tandem mass spectrometer (Waters/Micromass) as described previously (17). Phosphatidylcholine was analyzed by monitoring the precursors of 184 m/z in the positive ion mode. PE was analyzed in the positive ion mode by monitoring the neutral loss of 141 Da. The FA distribution of individual molecular species was determined in the negative ion mode by product ion analysis of the [M-CH₃]+ ions from phosphatidycholine and the [M-H]− ions from PE. The ion intensity of each spectrum was corrected for isotope effects and transmission losses. The recovery of phospholipids was quantified with internal standards of unnatural phospholipid subclasses.

**Cell Proliferation Assays**

**DNA Synthesis.** MCF-7 cells were plated in 24-well cluster dishes (1.3 × 10⁵ cells/well) in media containing 5% FBS. After 24 hours, the media was replaced with media containing 0.5% FBS, 5μCi/mL [methyl ³H] thymidine, and supplemented with LDL or BSA-FA. Control cells were treated with medium alone (for LDL-FA) and medium with different concentrations of BSA (for BSA-FA). At the end of a 24-hour treatment period, cell monolayers were washed with balanced salt solution, dislodged with 0.25% trypsin, −0.5% EDTA, and adjusted to 5% trichloroacetic acid to precipitate the DNA at −20°C overnight. After thawing, the trichloroacetic-acid precipitates containing [³H]-DNA were pelleted by centrifugation at 450 × g for 10 minutes. The pellets were washed three times with ice-cold trichloroacetic acid, dissolved in 0.5 mL of 0.5N sodium hydroxide, and aliquots were measured for radioactivity by scintillation counting.

**Cell Growth.** MCF7 cells in DMEM plus 0.5% FCS were seeded (1 × 10⁴/200 μL) in 96-well plates, incubated for 24 hours, and treated with FAs for 24 hours. Cell growth was measured with CellTiter96 AQueous One Solution Cell Proliferation Assays (Promega, Madison, WI).
RESULTS

LDL was isolated from plasma of African Green Monkeys fed diets enriched in n-3 or n-6 polyunsaturated FAs. Details of diet composition are presented in supplementary Table 1. The FA content of LDL isolated from plasma of African Green monkeys fed diets enriched in n-3 or n-6 polyunsaturated FAs. LDLs were isolated by sequential density ultracentrifugation, and FAs were measured as methyl esters by gas-liquid chromatography. Data represent triplicate pools of LDL isolated from three different groups of n-3 (n = 3, 4, 5) or n-6 (n = 3, 5, 5) animals; bars, SEM. 14:0 myristic acid; 16:0 palmitic acid; 18:0 stearic acid; 18:1 oleic acid; 18:2 linoleic acid; 20:4 arachidonic acid; 20:5 eicosapentaenoic acid; 22:6 docosahexaenoic acid.

Incubation of human breast cancer MCF-7 cells with n-3 polyunsaturated FA or n-6 polyunsaturated FA-enriched LDL resulted in delivery of the respective FA to the cells. Table 1 shows the cell FA percentage distribution after 48-hour treatment with either the polyunsaturated FA-enriched LDL or BSA-bound n-3 polyunsaturated FA (EPA) or n-6 polyunsaturated FA (linoleic acid). No n-3 polyunsaturated FAs were detected in cells incubated in control media without exogenous polyunsaturated FA. Cells incubated with either n-3 LDL or EPA-BSA showed an increased content of n-3 polyunsaturated FA (EPA + DHA) to 8.6% and 13.1% of total cell FA, respectively. Similarly, cells incubated with either n-6 LDL or linoleic acid-BSA showed an increased content of n-6 polyunsaturated FA (linoleic acid) to 16.9% and 14.2%, respectively. Thus, both the LDL and albumin were effective in delivering polyunsaturated FA into the cells. Longer incubation times (up to 5 days with the polyunsaturated FA-BSA) did not change this distribution.

In control cells, phospholipids comprised 76 ± 15%, triglycerides 14% ± 4%, and cholesterol 10% ± 1% of the total cell glycolipid plus cholesterol content (Fig. 2). The cell cholesterol was predominantly (>95%) free cholesterol (data not shown). Treatment with albumin-bound EPA or linoleic acid did not change the cell lipid distribution. LDL treatment, however, resulted in an increase in cholesterol to 24% ± 6% and 29% ± 5% for n-3 LDL-treated and n-6 LDL-treated cells, respectively, representing mainly an increase in cholesteryl esters.

Both n-3 LDL and EPA-BSA were highly effective in modifying the composition of tumor cell phospholipids (Table 2). After 24 hours of treatment, the ratio of 20:4 (n-6) to 20:5 (n-3) was profoundly decreased in both phosphatidylserine and PE, two major phospholipids in cells. This was accomplished through an increase in EPA-containing phospholipids without changes in arachidonic acid-containing phospholipids. Parallel experiments were conducted with human prostate cancer PC-3...
cells, and similar effects on cell phospholipids were observed (Supplemental Table 6).

Although cell phospholipids were similarly modified by LDL- and BSA-delivered FA, the two pathways resulted in marked differences in effects of n-3 FA on cell growth and survival. DNA synthesis, as measured by incorporation of [3H]thymidine over a 24-hour period, was inhibited by n-3 but not n-6–enriched LDL (Fig. 3A). Inhibition was dose dependent (200 g/mL n-3 LDL resulting in a 31% change from control). EPA-BSA had a lesser inhibitory effect (Fig. 3A). A >70% reduction in cell growth was observed at 100 μg/mL n-3 LDL, whereas n-6 LDL seemed to induce a slight increase in cell growth (Fig. 3B). Consistently, both EPA-BSA and linoleic acid-BSA treatment caused a slight reduction in cell growth, but the effect was far less robust than that of n-3 LDL (Fig. 3B). Similar results were obtained in human prostate carcinoma PC-3 cells (data not shown).

The finding that the effect of n-3 LDL on cell growth was greater than on DNA synthesis suggested that another process may be modified by n-3 LDL. Apoptosis analysis, as measured by the production of PARP cleavage product, reduction in procaspase 3, and microscopic counting of apoptotic nuclei, showed that n-3 LDL but not n-6 LDL, EPA-BSA, or linoleic acid-BSA induced apoptosis in the MCF-7 cells (Fig. 3C). Percentage total cell death, as measured by trypan blue exclusion assay, additionally supported this observation (Fig. 3D).

To additionally determine differences of effects on cells between LDL- and BSA-delivered FA, we monitored the global changes in gene transcription by DNA microarray. A significantly higher number of genes were affected by LDL-delivered FA compared with BSA-delivered FA (Fig. 4). The majority of genes affected by EPA-BSA did not overlap with those affected by n-3-LDL (Fig. 4A; Supplemental Table 2). A similar effect was also seen in PC-3 cells (Supplemental Fig. 1). This differential effect on transcription between LDL- and BSA-delivered n-3FA was related to the FA content rather than the LDL per se, because n-6 LDL had a distinct expression profile from n-3 LDL (Fig. 4; Supplemental Table 4). To validate the microarray data, real-time RT-PCR was used to confirm the expression of a set of genes that had a consistent change as a result of n-3 LDL treatment in both MCF-7 and PC-3 cells (Supplemental Fig. 2).

**DISCUSSION**

The novelty and uniqueness of our study is that we have compared the two main physiologic routes for delivery of dietary FA to tumor cells: LDL and albumin. We tested the hypothesis that FA delivered by the LDL receptor pathway would have different effects on cells than FA delivery by albumin. LDL was isolated from monkeys fed diets enriched in either n-3 or n-6 polyunsaturated FA and used in comparison to albumin to deliver FA to human breast (MCF-7) and prostate (PC-3) cancer cell lines that express the LDL receptor (19, 20). Our data showed effective delivery of the respective FA to the cells and similar levels of incorporation into cell phospholipids by both methods (Fig. 2; Table 1; Supplemental Fig. 1). However, LDL delivery of n-3 FA resulted in markedly greater effects on cell growth and apoptosis and on gene expression profiles than did

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**Table 1** Percentage of fatty acid composition of MCF-7 cells

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MA (14:0)</th>
<th>PA (16:0)</th>
<th>SA (18:0)</th>
<th>OA (18:1)</th>
<th>LA (18:2)</th>
<th>AA (20:4)</th>
<th>EPA (20:5)</th>
<th>DHA (22:6)</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.79</td>
<td>20.96</td>
<td>3.85</td>
<td>34.98</td>
<td>0.84</td>
<td>2.20</td>
<td>ND</td>
<td>ND</td>
<td>34.38</td>
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<tr>
<td>EPA-BSA</td>
<td>4.68</td>
<td>33.27</td>
<td>6.67</td>
<td>13.39</td>
<td>0.67</td>
<td>1.63</td>
<td>11.49</td>
<td>1.66</td>
<td>26.54</td>
</tr>
<tr>
<td>LA-BSA</td>
<td>2.87</td>
<td>26.30</td>
<td>6.03</td>
<td>15.39</td>
<td><strong>14.23</strong></td>
<td><strong>8.25</strong></td>
<td>ND</td>
<td>ND</td>
<td>26.93</td>
</tr>
<tr>
<td>n-3 LDL</td>
<td>1.88</td>
<td>26.28</td>
<td>9.14</td>
<td>25.25</td>
<td>3.28</td>
<td>3.00</td>
<td>5.63</td>
<td><strong>2.94</strong></td>
<td>22.60</td>
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<tr>
<td>n-6 LDL</td>
<td>1.65</td>
<td>24.93</td>
<td>10.55</td>
<td>25.06</td>
<td><strong>16.98</strong></td>
<td><strong>1.93</strong></td>
<td>ND</td>
<td>ND</td>
<td>18.90</td>
</tr>
</tbody>
</table>

*Abbreviations: MA, myristic acid; PA, palmitic acid; SA, stearic acid; OA, oleic acid; LA, linoleic acid; AA, arachidonic acid; ND, not detectable.*

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**Table 2** Percentage of the total fatty acids in each phospholipid class

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Phospholipid</th>
<th>AA/EPA ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA (20:4)</td>
<td>EPA (20:5)</td>
</tr>
<tr>
<td>Control</td>
<td>PC</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>24.3</td>
</tr>
<tr>
<td>EPA-BSA</td>
<td>PC</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>18.2</td>
</tr>
<tr>
<td>n-3 LDL</td>
<td>PC</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td>27.4</td>
</tr>
</tbody>
</table>

*Abbreviations: AA, arachidonic acid; PC, phosphatidylcholine.*
albumin-delivered n-3 FA. This is, to our knowledge, the first study to examine LDL-FA delivery to tumor cells in this manner. In previous in vitro studies examining effects of n-3 FA on cancer cells, FA were delivered by albumin or liposomes (6–9, 21). Our data emphasize the importance of the LDL receptor pathway as a critical delivery route for studying effects of n-3 FA on cell regulation.

It has been understood for many years that ingestion of specific dietary FA leads to LDL enrichment in those FA (22). This results from modification in the acyl chains of both the core cholesteryl esters and surface phospholipids. The animals used as LDL donors for the present study had been receiving polyunsaturated FA–supplemented diets for >3 years. LDL FA content was therefore stable, reflecting the steady state of the whole body FA pools including those of liver and adipose tissue. As shown in Fig. 1, LDL contains a mixture of the major FA, thus LDL delivery of n-3 FA to cells takes place in the presence of that mixture. However, the growth inhibitory and apoptotic effect appeared to be mainly attributed to n-3 FA, because n-3 LDL and n-6 LDL have a similar mixture of FAs with the
Fig. 4  Hierarchical clustering of FA treatment experiments. MCF-7 cells were treated with 0, 30 μmol/L of EPA-BSA, linoleic acid-BSA, or 100 μg/mL of n-3 LDL, n-6 LDL for 24 hours. Total RNA was isolated and used for microarray analysis with Affymetrix HGU133 chip set. Three independent experiments were done. Microarray data were processed with the dCHIP software.  

Differentially expressed transcripts were identified with PM/MM difference model. Hierarchical clustering was done with the Genesis software.  

A. Diagram of hierarchical clustering of FA treatment experiments based on differentially expressed genes.  

B. Pairwise comparison of common and different alterations within sets of genes affected by treatments. (LA, linoleic acid)

Web address: http://biosun1.harvard.edu/complab/dchip/.

Web address: http://genome.tugraz.at/.
exception of linoleic acid enrichment in n-6 LDL and EPA-DHA enrichment in n-3 LDL (Fig. 1).

Our data show that human cancer cells rapidly become enriched with polyunsaturated FA by both LDL and albumin routes, with stable changes in lipids achieved in 24 hours. Subsequent studies have shown effects of LDL on gene regulation as early as 8 hours. Although the FA content of the cells was similarly modified by both LDL and albumin-delivered FA, LDL also changed the composition of cell lipids. Not surprisingly, cholesterol delivered to the cells by LDL was esterified, and cholesteryl esters contributed to the increased cholesterol content of LDL-treated cells (Fig. 2). It is not clear at present how great a role, if any, the cholesteryl esters may play in the observed effects of the n-3 LDL on proliferation, apoptosis, or gene regulation. In vascular smooth muscle cells, the cholesteryl ester pathway has been shown to regulate signal transduction pathways that control the cell cycle at the G1-S transition (23). However, our data show that cholesteryl esters were increased to a similar extent in both n-6 LDL- and n-3 LDL-treated cells, suggesting that the discriminating factor was FA composition rather than amount of cell cholesteryl ester.

It is clear that cell phospholipids, the prime candidates for involvement in lipid signaling pathways, were successfully modified in 24 hours by both LDL and albumin-delivered FA. Of particular interest was the decrease in ratio of n-6 to n-3 FA. In a multinational European case control study of adipose tissue, in four of five of the study centers, the ratio of n-3 to n-6 FA was inversely associated with breast cancer (24). This ratio is proposed to be more important than the absolute levels of the two classes because of competitive inhibition for the desaturases and elongases required for the generation of eicosanoids (25). Our data also show that the MCF-7 cells used were able to elongate and desaturate the exogenous FA by forming arachidonate acid from linoleic acid and DHA from EPA. This is in contrast to a previous study that reported defects in the desaturase activity.5 Although these changes were only ~2-fold at 24 hours, the level of PDEF mRNA increased significantly after 24 hours in n-6 LDL-treated cells. Expression of PDEF has been shown to correlate with invasive potential of human breast cancer (36). PDEF interacts with the androgen receptor (37) and the putative prostate tumor suppressor NKKX3.1 (38) and activates prostate-specific antigen gene expression.

The potential importance of dietary FA in carcinogenesis has been strongly supported by studies in rodents in which diets rich in n-6 polyunsaturated FA are tumor-promoting, whereas those rich in n-3 polyunsaturated FA are protective (39–45). Study models include dietary supplementation in chemically induced rat carcinogenesis (39–41) and modulation of human breast cancer cell xenografts in athymic mice (43–45). Primary tumors as well as metastases were inhibited by n-3 polyunsaturated FA and promoted by n-6 polyunsaturated FA dietary supplementation. The results with n-6 polyunsaturated FA are particularly disturbing in view of the increased use in the United States of n-6–enriched vegetable oils, and they confound dietary recommendations regarding substitution of polyunsaturated FA for saturated FA to reduce cancer risk. A potential use for n-3 polyunsaturated FA as a nutritional adjuvant therapy was suggested by studies with a xenograft model in mice in which metastases were inhibited by dietary supplementation with n-3 polyunsaturated FA initiated both before and after surgical removal of the primary tumors (46). In the same model, dietary n-3 polyunsaturated FA was shown to increase the efficacy of doxorubicin in inhibiting tumor growth (47). Similarly, the growth of human mammary carcinoma MX-1 implants in athymic mice was more sensitive to inhibition by mitomycin C when animals received fish oil-enriched diets (48). These studies not only suggest potential benefits of n-3 polyunsaturated FA dietary supplementation for breast cancer patients but also emphasize the importance of developing an understanding of mechanisms by which these FA exert their beneficial effects.

Despite continuous interest in the tumor-inhibitory role for n-3 dietary FAs, molecular mechanisms remain poorly understood. Our study may establish a paradigm for the design of future studies aimed at elucidating molecular pathways of cell modification by dietary FA. In addition, our data draw attention to the usefulness of LDL as a reagent for monitoring polyunsaturated FA intake by clinical trial subjects. Whereas this is widely accepted by the cardiovascular research community, it has been mostly ignored by the cancer researchers.

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