Elevated Uptake of Low Density Lipoproteins by Human Lung Cancer Tissue in Vivo[1]

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ABSTRACT

In order to explore new treatment modalities for cancer, it is important to identify qualitative or quantitative differences in metabolic processes between normal and malignant cells. Previous *in vitro* and *in vivo* studies have shown that acute myelogenous leukemia cells have elevated receptor-mediated uptake of low density lipoproteins (LDL), compared to normal WBC. High receptor-mediated uptake of LDL by certain cancer cells in tissue culture and experimental tumors in animals *in vivo* has also been demonstrated. The present study was undertaken to compare the *in vivo* assimilation of LDL by human lung cancer tissue with that by surrounding lung tissue. Ten patients with newly diagnosed lung tumors, scheduled for surgery, received an i.v. injection of [^{14}C]sucrose-labeled LDL. Following cellular uptake and degradation of the LDL particle, the radiolabeled sucrose moiety remains trapped in the lysosomal compartment, making this labeling technique useful for *in vivo* studies of tissue uptake of LDL. Radioactivity was determined in plasma and in tissue biopsies obtained at surgery 1–3 days after injection. The uptake of radioactivity in lung cancer tissue was elevated (1.5–3.0-fold), compared to surrounding tissue, in 7 of 9 patients with primary lung cancer. The most rapid preoperative disappearance of radioactivity from plasma was found in 2 patients with large tumors exhibiting high LDL uptake, relative to normal lung tissue. These findings support the hypothesis that the selectivity of cytotoxic agents can be enhanced also in nonhematological malignancies by administering the drugs incorporated in LDL particles.

INTRODUCTION

In order to design new anticancer agents or to develop new treatment modalities for cancer it is important to identify and take advantage of qualitative or quantitative differences in metabolic processes between normal and malignant cells. Previous studies have provided evidence that some malignant cells possess elevated receptor-mediated uptake of LDL[3] (see Ref. 1 for review). LDL is the major cholesterol-carrying lipoprotein in human plasma, containing two thirds of plasma cholesterol (2). Each LDL particle contains approximately 1500 molecules of cholesteryl ester surrounded by a polar shell of phospholipids, free cholesterol, and apolipoprotein-B. Cells can fulfill their cholesterol requirements by receptor-mediated uptake of LDL from plasma and/or endogenous synthesis of cholesterol (2). Once bound to its cell surface receptor, LDL is internalized and degraded in lysosomes, and the subsequently released cholesterol may be used for membrane synthesis, steroid hormone production, or bile acid production in the various tissues.

It has been shown that freshly isolated leukemic cells from patients with acute myelogenous leukemia have elevated LDL receptor activities, compared to normal WBC and nucleated bone marrow cells (3, 4). Hypocholesterolemia is a frequent finding in patients with acute leukemia (5, 6) and cholesterol levels are inversely correlated with the LDL receptor activities of the leukemic cells (5). This suggests that the mechanism behind the hypocholesterolemia is high LDL catabolism by the leukemic cells (5). *In vitro* catabolism of LDL can be determined from the cellular degradation of ^{125}I-labeled LDL (3, 4). This labeling technique is, however, not suitable for determination of *in vivo* catabolism of LDL since the radioactive degradation fragments are rapidly released by the cells into the blood and excreted by the kidneys. Using [^{14}C]sucrose-labeled LDL, we have recently demonstrated that the uptake of LDL by leukemic cells is elevated in leukemic patients *in vivo* (7). This labeling technique is suitable for *in vivo* studies of LDL catabolism since the [^{14}C]sucrose moiety is retained in lysosomes following cellular uptake (8).

Hypocholesterolemia is also associated with nonhematological malignancies like lung cancer (9, 10). Previous studies have shown elevated LDL receptor activity in gynecological cancer cells in tissue culture, compared to the corresponding normal cells (11), and high LDL uptake in experimental animal tumor models *in vivo* (12–14). Until now, there has been no demonstration of high uptake by solid tumors *in vivo* in humans. In the present study, therefore, we investigated the *in vivo* accumulation of radiolabeled LDL in human lung cancer tissue after i.v. injection before surgery. We employed the same labeling technique with [^{14}C]sucrose-LDL as used in the previous study in patients with leukemia (7). If the uptake of LDL is similarly elevated in lung cancer tissue, this would suggest that selective chemotherapy could be achieved by administering cytotoxic drugs incorporated in LDL particles.

MATERIALS AND METHODS

Patients. Clinical characteristics of the patients are given in Table 1. The study was approved by the Ethics Committee at the Karolinska Hospital. Informed consent was obtained from each subject entering the study.

Materials. [U-^{14}C]Sucrose (specific activity, >5550 GBq/mmol) was purchased from Amersham and cyanuric chloride was purchased from Sigma. Other materials were from previously reported sources (7).

Lipoproteins. LDL (density, 1.020–1.063 g/ml) was isolated from serum of healthy blood donors by sequential ultracentrifugation (15). [^{14}C]Sucrose-LDL (specific activity, 5–19 cpm/ng of protein) was prepared as described by Pittman *et al.* (16). The purity of LDL preparations was checked by agarose gel electrophoresis. Autoradiography after agarose gel electrophoresis of [^{14}C]sucrose-LDL showed that all radioactivity was present in a single band with mobility similar to that of native LDL. The preparations of [^{14}C]sucrose-labeled LDL were filtered through a Millipore 0.22-μm HA filter under aseptic conditions and were stored at 4°C for <3 weeks. Immediately before the i.v. injection, the preparation was refiltered.

***In Vivo* Studies with [^{14}C]Sucrose-LDL.** Patients with an operable lung tumor received an i.v. injection of 2.2–3.7 MBq of [^{14}C]sucrose-LDL, in a volume of 1.3–2.8 ml of 0.15 M NaCl/0.3 mM Na$_2$EDTA, 1–3 days prior to surgery. At different times thereafter blood samples were collected from a peripheral vein and plasma was separated by low speed centrifugation. At surgery, tissue specimens (500–1200 mg wet weight)

Table 1 *Clinical data*

Patient	Sex/age (yr)	Wt (kg)	RBW[a] (%)	Total	LDL	HDL[c]	Triglycerides	Histopathological diagnosis	Size (cm)	Tumor cells (%) [mean (range)]
				Plasma lipids (mmol/liter)[b]				**Tumor data**		
				Cholesterol						
1	M/44	66	89	5.7	ND[d]	ND	1.0	Large cell undiff.[e] carcinoma, pleural infiltration	3 × 3.5 × 3	40 (20–80)
2	F/62	58	84	4.8	3.4	1.2	1.6	Poorly diff. adenocarcinoma, metastasis to the lung and lymph nodes	10 (largest diameter) + 7 × 3	75 (60–90)
3	M/70	80	110	5.6	3.9	1.0	1.6	Poorly diff. squamous cell carcinoma	7 × 6	55 (30–85)
4	M/80	57	81	5.1	3.1	1.4	1.4	Moderately diff. squamous cell carcinoma	7 × 4	35 (15–60)
5	M/65	76	100	6.2	4.4	1.4	1.1	Poorly diff. squamous cell carcinoma	2.5 × 3	30 (10–70)
6	M/65	68	89	5.9	5.5	1.0	1.1	Poorly diff. mixed squamous cell and adenocarcinoma	3 × 3.5	70 (40–90)
7	M/74	66	106	6.4	4.0	1.3	2.4	Poorly diff. mixed squamous cell and adenocarcinoma	2 × 1.5	40 (25–65)
8	F/58	65	110	4.9	2.9	0.6	3.0	Chordoma metastases	3.2 × 1.7 (largest)	95 (90–100)
9	F/62	46	79	4.8	3.0	1.3	1.1	Poorly diff. mixed squamous cell and adenocarcinoma, pleural and thoracic wall infiltration	5 × 5 × 3	60 (45–85)
10	M/74	70	85	3.9	2.5	0.9	1.0	Intermediately diff. adenocarcinoma	6 × 6 × 4	90 (75–95)

[a] RBW, relative body weight, calculated as body weight (kg)/[height (cm) − 100] × 100%.
[b] To convert mmol/liter to mg/dl for cholesterol, multiply by 38.7. To convert mmol/liter to mg/dl for triglycerides, multiply by 88.5.
[c] HDL, high density lipoproteins.
[d] ND, not determined.
[e] diff., differentiated.

were taken from the tumor, avoiding macroscopically necrotic material, and from surrounding lung tissue. The specimens were collected in ice-cold 0.15 M NaCl solution, rinsed extensively, and cut into 2–8 pieces of about 200–400 mg, which were treated with 500 µl of 2 M NaOH by incubation at 60°C for 2–4 h. The solubilized tissue samples were neutralized with 5 M HCl and the pH was stabilized by the addition of 1 M Tris-HCl, pH 7.4, as described previously (7). Finally, the ^{14}C radioactivity was determined in a Packard liquid scintillation counter with appropriate quench correction, after the addition of 10 ml of Picofluor 15. It was verified that an increase in the amount of counted material gave rise to a linear increase in the radioactivity. The results were expressed as the sum of the radioactivities of the pieces divided by the total weight of the tissue assayed. The radioactivity in plasma was determined by the direct addition of 500 µl of plasma to 10 ml of Picofluor 15 and subsequent counting.

Histopathological Examination. The primary histopathological diagnoses of the lung tumors were confirmed upon reexamination of the original histological slides, which had been prepared from the surgical material. The proportion of tumor cells in individual tumors was also determined (Table 1).

Other Assays. Plasma total cholesterol, LDL cholesterol, and triglyceride concentrations were determined using enzymatic techniques (Merck, Darmstadt, Germany). The protein concentrations of LDL preparations were determined by the method of Lowry et al. (17), with bovine serum albumin as a standard.

Statistical Analysis. Significance levels were derived from Student's *t* test for paired observations.

RESULTS

No side effects were seen following the administration of [^{14}C]sucrose-LDL i.v. to the patients with different lung tumors. Plasma radioactivity decay curves for 9 of the 10 patients are presented in Fig. 1. After injection, plasma radioactivity declined in a bimodal fashion, with terminal half-lives in the range of 35–50 h.

The uptake of [^{14}C]sucrose-LDL in tumor tissue and surrounding lung tissue has been plotted in Fig. 2. All but one patient (patient 8) had a primary lung cancer. Patient 8 had four metastases of a chordoma which showed a low uptake of radioactivity, compared with surrounding tissue. In 7 of the 9 patients with primary lung cancer, the uptake in tumor tissue was higher (range, 1.5–3.0-fold) than in surrounding tissue. Con-
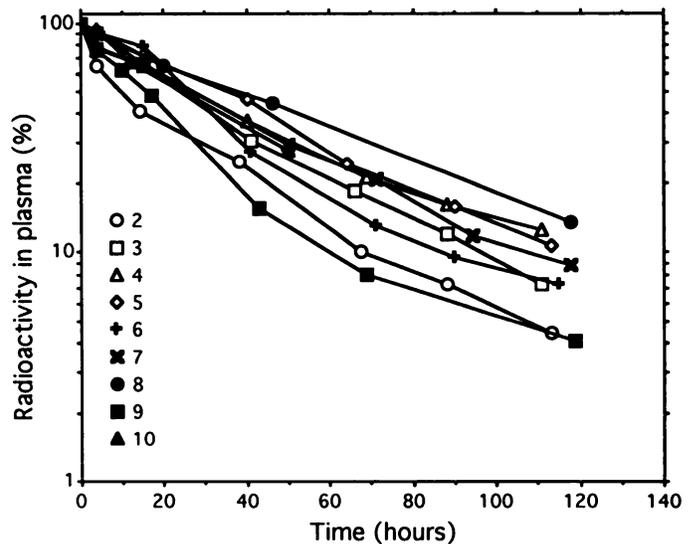

Fig. 1. Radioactivity remaining in plasma after i.v. injection of [^{14}C]sucrose-LDL in 9 patients with lung tumors. Radioactivity in plasma 10 min after injection was set to 100%. For identification of patients, see Table 1. Patient 1 was omitted due to missed sampling at 10 min.

sidering all patients, the mean LDL uptake (expressed as LDL protein) was 150.4 ± 66.6 ng/g (mean ± SD) for normal tissue and 251.8 ± 146.8 ng/g for tumor tissue ($P = 0.011$). Patient 1, a 44-year-old male with a large cell undifferentiated carcinoma, had a tumor uptake approximately 3 times the uptake of surrounding tissue. In patient 3, a 70-year-old male with a poorly differentiated squamous cell carcinoma, the uptake was approximately 2.5 times higher in the tumor, compared with the surrounding tissue. In contrast, in patient 5, with a poorly differentiated squamous cell carcinoma, and in patient 7, with a poorly differentiated mixed squamous cell carcinoma and adenocarcinoma, the uptake in tumor and surrounding tissue was very similar.

Patients 2 and 9 had large tumor burdens. Patient 2 had a poorly differentiated adenocarcinoma with metastasis to the lung and regional lymph nodes and patient 9 had a poorly
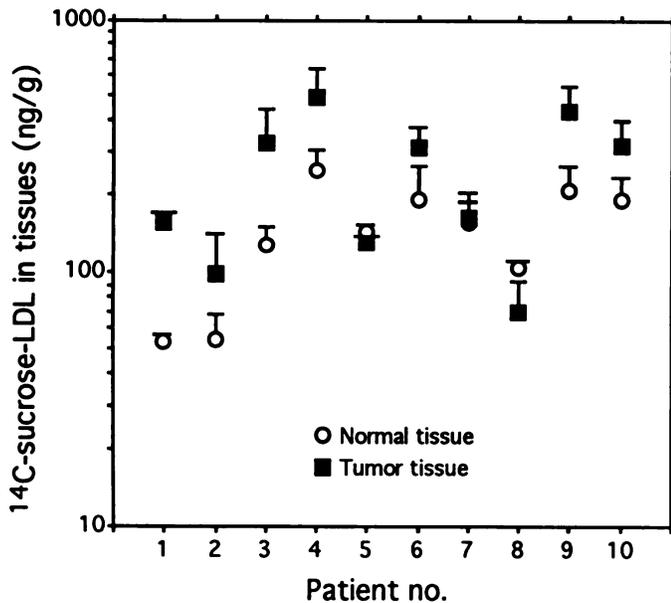
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Fig. 2. *In vivo* uptake of [¹⁴C]sucrose-LDL by normal tissue and tumor tissue from 10 patients with lung tumors, 1–3 days after injection. *Numbers* refer to individual patients (Table 1). *Bars*, SD.

differentiated mixed squamous cell carcinoma and adenocarcinoma with pleural and thoracic wall infiltration. Interestingly, both these patients had the most rapid preoperative decay of plasma radioactivity.

Tumor tissue exhibited a more heterogeneous uptake of radioactivity, compared to normal lung tissue. The mean coefficient of variation for the 2–8 pieces into which the tumor biopsies were subdivided was 31.6% (range, 1.6–54.6%), compared with normal lung tissue in which 2–5 pieces had a mean coefficient of variation of 19.1% (range, 1.9–48.2%).

DISCUSSION

The present study demonstrates that lung cancer tissue has a higher *in vivo* assimilation of LDL than does surrounding lung tissue. Recently, Henriksson *et al.* (18) demonstrated in prostatic cancer patients that the plasma clearance of LDL was more rapid in patients with metastases, compared to patients without metastases, indicating that an increased tumor burden increases the elimination of LDL from blood. Several investigators have also demonstrated high LDL uptake by solid tumors *in vivo* in animals (12–14).

Epidemiological studies have also given indirect support for high LDL uptake by cancer tissue, from the inverse correlation found between cancer mortality and serum cholesterol concentration (19, 20). Few studies have been performed on cholesterol or lipoprotein levels in patients with newly diagnosed lung cancer. Chao *et al.* (9) made serial measurements of cholesterol levels in lung cancer patients and found that in several patients cholesterol levels declined rapidly during the course of the disease. This was seen in patients with either adenocarcinomas or squamous cell carcinomas. Alexopoulos *et al.* (21) measured cholesterol and lipoprotein levels in 103 cancer patients. Cancer patients as a group had significantly lower total cholesterol and LDL cholesterol levels, compared with control patients. In 31 patients with lung cancer the mean total cholesterol and LDL cholesterol levels were not significantly different, compared with controls. On the other hand, a significantly lower mean value of pre-β-lipoproteins (very low density lipoproteins)

was found among the lung cancer patients, compared with controls. In the present study we also determined cholesterol levels, but the cholesterol levels were not remarkably low and none of the patients exhibited a marked hypocholesterolemia. Of particular interest is the rapid preoperative disappearance of radioactivity from blood of the patients (patients 2 and 9) with advanced tumors with high LDL uptake. In contrast, patients 5 and 8, with small tumors and low uptake of radioactivity, exhibited slow preoperative clearances of radioactivity.

What then is the mechanism for the elevated tumor uptake of LDL? As estimated from the uptake of ¹²⁵I-labeled LDL and cyclohexanedione-modified ¹³¹I-labeled LDL, which is not recognized by the LDL receptor, Hynds *et al.* (12) reported that the receptor-mediated uptake of LDL by a virus-induced parotid adenoma in mice was very high. When expressed per gram of tissue, it was surpassed only by uptake in the adrenals (12). With the same technique, Norata *et al.* (13) found that the receptor-mediated uptake of LDL by a transplantable fibrosarcoma tumor in mice was much higher than that in liver, spleen, and muscle. However, they also found evidence for increased nonspecific uptake of LDL by the tumor. Lombardi *et al.* (14) found that several experimental tumors in mice had a higher relative uptake of LDL, compared to the liver, and that the *in vivo* uptake correlated well with *in vitro* specific binding of ¹²⁵I-β-very low density lipoproteins to tumor membranes. Further support for high receptor-mediated uptake of LDL by tumor cells as a mechanism for LDL assimilation by tumor cells can be found in studies with patients with acute leukemia who were given i.v. injections of [¹⁴C]sucrose-LDL (7). A strong correlation was found between the *in vivo* uptake of [¹⁴C]sucrose-LDL by leukemic cells and the *in vitro* rate of receptor-mediated degradation of ¹²⁵I-LDL by the isolated leukemic cells. Rudling *et al.* (22) determined LDL receptor densities in crude tissue homogenates of normal and malignant human tissues obtained at surgery, using a binding assay based on the ability of heparin to specifically release receptor-bound LDL. They found that the adrenal gland and the ovary had the highest receptor densities and that, in certain cases, tumors from the stomach and parotid gland expressed very high LDL binding.

The reason for elevated LDL receptor activity in certain malignant cells is not known and can only be speculated upon. The findings of low cholesterol content (3, 23–25) and high levels of endogenous cholesterol synthesis (3, 26, 27) in acute myelogenous leukemia cells indicate that the enhanced cellular uptake of cholesterol is a compensatory response to mechanisms that lower the cholesterol content of the cell. Increased cholesterol demand for membrane synthesis in rapidly proliferating cells is one possibility. Indeed, LDL receptor activity in cultured cells is very much dependent on the growth rate (28). Another possibility is that tumor cells need more cholesterol because of rapid membrane turnover. A defect in the regulation of the LDL receptor in tumor cells could be another explanation for the elevated receptor activity. However, Ho *et al.* (3) showed that LDL receptors in leukemic cells are subject to regulation by LDL similar to that in normal cells.

The largest difference in LDL uptake between normal and malignant tissues in the present study was about 3-fold. It can be argued that such a difference is not enough if LDL is to be considered as a targeting vehicle for cytotoxic agents. However, we observed that in most cases the biopsies from normal lung tissue macroscopically appeared to contain more blood than the tumor specimens, which could mean that the difference between tumor and normal lung was underestimated, especially when

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account is taken of the fact that surgery was performed 1–3 days after injection of radiolabeled LDL and blood radioactivity was still considerable at surgery. Even if the true difference in LDL uptake between nomal cells and cancer cells is at most 2–3-fold, this could have a major impact on the outcome of LDL-mediated chemotherapy and could lead to an increased therapeutic index and cure of the patient.

Previous studies have shown that cytotoxic agents can be incorporated into LDL and delivered to tumor cells both *in vitro* and *in vivo* (29). The organs most likely to suffer from the cytotoxic effects of drug-LDL complexes are those with a high LDL uptake, such as the adrenals and the liver. As indicated by animal studies, it may be possible to circumvent this problem by pretreatment with steroids and bile acids (12). Further *in vivo* studies of LDL uptake in different human solid tumors are needed in order to better characterize and understand cholesterol turnover in normal and malignant tissue.

In conclusion, we have shown that lung cancer tissue *in vivo* assimilates more LDL than does surrounding normal lung tissue. Hence, LDL should be considered as a potentially interesting drug carrier for treatment of lung cancer.

ACKNOWLEDGMENTS

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