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Uptake of low density lipoproteins by human leukemic cells *in vivo*: Relation to plasma lipoprotein levels and possible relevance for selective chemotherapy

(cholesterol/low density lipoprotein receptors/sucrose labeling/acute leukemia)

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ABSTRACT **The success of cancer chemotherapy is dependent on the possibility to utilize biological differences between malignant and normal cells to selectively destroy the tumor cells. One such difference may be that of receptor-mediated cellular uptake of low density lipoproteins (LDLs). Previous studies have shown that leukemic cells from patients with acute myelogenous leukemia have elevated receptor-mediated uptake and degradation rates of plasma LDL *in vitro* compared to normal white blood and bone marrow cells, and that plasma cholesterol levels at diagnosis are inversely correlated with the LDL receptor activity of the malignant cells. An important question is whether the uptake of LDL by the leukemic cells is also increased *in vivo*. To evaluate the *in vivo* uptake of LDL, 11 adult patients with newly diagnosed acute myelogenous leukemia received an i.v. injection of [^{14}C]-sucrose-labeled LDL. On degradation of [^{14}C]sucrose–LDL, the radiolabeled sucrose moiety is known to remain trapped in the lysosomal compartment of the cells. After injection, radioactivity accumulated progressively for at least 12 hr in the leukemic cells. The uptake of radioactivity *in vivo* correlated with the rate of receptor-mediated degradation of ^{125}I-labeled LDL by the leukemic cells assayed *in vitro* ($r = +0.88$, $P < 0.001$). An inverse correlation between plasma LDL cholesterol concentrations and the *in vivo* cellular uptake of [^{14}C]sucrose–LDL in whole blood ($r = -0.76$, $P < 0.01$) indicates that the hypocholesterolemia is due to elevated LDL uptake by the leukemic cells. Postmortem biopsies from virtually all tissues were obtained from one patient, and the distribution of radioactivity revealed that the liver and bone marrow had accumulated most radioactivity; the adrenals had the highest uptake of label per gram of tissue weight. The results indicate that LDL may be used as a carrier targeting lipophilic cytotoxic drugs to leukemic cells.**

Low density lipoprotein (LDL) is the major cholesterol-carrying lipoprotein in human plasma, representing ≈70% of total plasma cholesterol (1, 2). Each LDL particle contains ≈1500 molecules of cholesteryl ester surrounded by a polar shell of phospholipids, free cholesterol, and apolipoprotein (apo) B. LDL particles enter cells predominantly by receptor-mediated endocytosis, the first event in this process being the binding of LDL to specific cell-surface receptors, the LDL receptors (1). The bound LDL is then internalized and degraded in lysosomes, and the subsequently released free cholesterol may be used for membrane synthesis, steroid hormone production, or bile acid production in the various tissues. Cells can also supply their cholesterol needs by *de novo* synthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase being the rate-limiting enzyme (1, 2).

Previous studies have shown that freshly isolated leukemic blood and bone marrow cells from patients with acute myelogenous leukemia (AML) have elevated LDL receptor activities as compared to normal white blood and nucleated bone marrow cells (3, 4). Hypocholesterolemia is a frequent finding in patients with acute leukemia. The plasma cholesterol levels are inversely correlated with the LDL receptor activities of the leukemic cells assayed *in vitro*, suggesting that the hypocholesterolemia may be a consequence of high LDL catabolism by the leukemic cells (4, 5). If the leukemic cells have an increased uptake of LDL *in vivo*, this might be of therapeutic importance. Thus, it may be possible to target LDL-bound lipophilic toxic drugs to malignant cells with high expression of LDL receptors (6–9).

In the present study, we have examined the *in vivo* accumulation of radiolabeled LDL in leukemic cells after i.v. injection in patients with acute leukemia. Specifically, we asked the questions: (*i*) Is the LDL receptor activity of leukemic cells increased also *in vivo*?; (*ii*) If so, how is the *in vitro* LDL receptor activity related to the *in vivo* activity of the LDL receptor?; and (*iii*) Can the uptake of LDL by the leukemic cells on a quantitative basis explain the reduction in plasma LDL frequently observed in these patients? To avoid the rapid excretion of radioactivity from the cells that is seen after uptake and degradation of ^{125}I-labeled LDL, we have administered LDL coupled to [^{14}C]sucrose. Detailed studies in cultured cells and animals have shown that the [^{14}C]sucrose moiety is retained within the cells in the lysosomes, and this technique is thus suitable for determining *in vivo* tissue catabolism of LDL (10, 11).

Our results show that accumulation of radioactivity occurs for at least 12 hr in leukemic cells after a bolus injection of [^{14}C]sucrose–LDL, that the cellular *in vivo* uptake of radioactivity correlates with the receptor-mediated degradation of LDL as assayed *in vitro*, and that the plasma concentration of LDL in the patients with leukemia is inversely related to the rate of *in vivo* uptake of radioactivity in the leukemic cells. Postmortem tissue biopsies from one patient revealed that a considerable amount of the administered LDL was retained in the bone marrow, lending further support to the

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Abbreviations: AML, acute myelogenous leukemia; apo, apolipoprotein; LDL, low density lipoprotein.

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concept of targeted drug therapy with LDL-bound drugs in acute leukemia.

MATERIALS AND METHODS

Patients. Clinical characteristics of the 11 patients with AML are given in Table 1. Classification of the AML was performed according to the FAB (French-American-British subclassification) system (12). Informed consent was obtained from each individual, and the study was approved by the Ethics Committee of the Karolinska Institute.

Materials. Na ^{125}I (carrier free, pH 7–11) and [U-^{14}C]sucrose (specific activity >350 Ci/mol; 1 Ci = 37 GBq) were purchased from Amersham. Cyanuric chloride was purchased from Sigma. Other materials were from reported sources (4).

Lipoproteins. LDL (density 1.020–1.060 g/ml) and lipoprotein-deficient serum (density >1.215 g/ml) were isolated from the serum of healthy blood donors by sequential ultracentrifugation (13). ^{125}I-labeled LDL (specific activity 150–380 cpm/ng of protein) and [^{14}C]sucrose–LDL (specific activity, 8–15 cpm/ng of protein) were prepared as described by Langer *et al.* (14) and Pittman *et al.* (10), respectively. The purity of LDL preparations was checked by agarose electrophoresis. Less than 1% of radioactivity was present as free iodide in the ^{125}I-labeled LDL preparations. Autoradiography of [^{14}C]sucrose–LDL after agarose electrophoresis showed that all radioactivity was present in a single band with β mobility. All LDL preparations were immediately filtered through a Millipore 0.45-μm HA filter under aseptic conditions. Sterile human albumin (Kabi, Stockholm) was added to [^{14}C]sucrose–LDL, and the preparation was stored at +4°C for <3 wk. A few hours before the i.v. injection, the [^{14}C]sucrose–LDL preparation was refiltered.

***In Vivo* Studies with [^{14}C]Sucrose–LDL.** Each patient with acute leukemia received an i.v. injection of $\approx 220 \times 10^6$ dpm of [^{14}C]sucrose–LDL in a volume of 2–3 ml of 0.15 M NaCl/0.3 mM Na_2EDTA. At different time intervals after the injection, blood samples were drawn from a peripheral vein and immediately put on ice, and leukemic cells were isolated by centrifugation on Lymphoprep (Nyegaard, Oslo), as described (4). The yield of leukemic cells was 90–95% of those originally present in the blood sample. The washed cell pellets were dissolved in 500 μl of 2 M NaOH for 3–5 hr at 50°C. The protein concentration was determined on an aliquot by the Lowry technique (15), and 250 μl of the solubilized cells were neutralized with 100 μl of 5 M HCl, and 300 μl of 1 M Tris·HCl was added as buffer. Finally, the ^{14}C radioactivity was determined in a Packard β-liquid scintillation counter after the addition of 10 ml of Picofluor-15.

Uptake of [^{14}C]Sucrose–LDL in Tissues. From one patient tissue samples were taken from different organs at autopsy for the determination of ^{14}C radioactivity. The tissue specimens were collected in ice-cold physiologic saline and rinsed extensively. Pieces of 200–400 mg (wet weight) of the tissues were dissolved in 500 μl of 2 M NaOH by incubation at 60°C for 2–4 hr. Neutralization and radioactivity determination were carried out as described for cells above.

LDL Receptor Determination on Leukemic Cells *in Vitro*. The rate of high-affinity degradation of ^{125}I-labeled LDL by isolated leukemic cells was used as measure of LDL receptor activity as described (4). In brief, 3×10^6 leukemic cells were incubated at 37°C in 1 ml of RPMI 1640 medium supplemented with 30% lipoprotein-deficient serum with 25 μg of ^{125}I-labeled LDL in the absence and presence of a 20-fold excess of unlabeled LDL. Cellular degradation of ^{125}I-labeled LDL was determined from the formation of acid-soluble noniodide radioactivity in the incubation medium. The high-affinity degradation rate of ^{125}I-labeled LDL was calculated by subtracting the degradation of ^{125}I-labeled LDL in the presence of excess unlabeled LDL (unspecific degradation) from the degradation in the absence of unlabeled LDL in excess (total degradation).

Analysis of Plasma Lipoproteins. Plasma total and LDL cholesterol and triglyceride concentrations were determined enzymatically by using Merckotest (Merck). Plasma LDL

Table 1. Basal data on the patients

Patient no.	Sex/age in yr	Weight, kg	Plasma lipids, mmol/liter*			Hematological data				
			Cholesterol		Triglycerides	WBC × 10^{-9}/liter	Leukemic cells, %†		^{125}I-LDL degraded, ng/hr/cell × 10^{-6}	FAB diagnosis
			Total	LDL			PB	BM		
1	M/70	84	1.5	1.3	1.2	28.9	62	60	7.00	M2
2	F/78	65	5.2	4.5	2.4	68.8	89	95	0.56	M2
3	F/43	67	4.3	3.3	1.7	200.0	60	49	0.56	M4
4	F/82	63	5.1	4.3	3.7	28.8	100	91	1.90	M5A
5	M/82	86	5.3	4.6	1.8	16.1	10	86	2.96	M2
6	F/75	67	3.8	2.7	1.2	18.8	50	73	0.50	M2
7	M/63	49	3.8	3.1	1.3	11.5	98	76	1.20	M2
8	M/39	83	2.7	2.0	2.0	106.4	90	81	3.36	M4
9	F/77	52	2.8	2.2	1.4	31.8	70	42	1.98	AUL
10	F/71	43	3.0	2.4	2.1	44.2	84	80	4.90	M2
11	F/73	71	3.8	2.7	1.9	33.6	78	79	3.13	M5B

Patients: 1, Colon resection 3 yr before study due to diverticulitis, febrile, abdominal surgery due to ileus on day 2, died on day 8, received no cancer chemotherapy; 2, TAD started on day 1; 3, Febrile (40°C), MEA started 8 hr after injection of [^{14}C]sucrose–LDL; 4, pernicious anemia, on steroids due to polymyalgia rheumatica, febrile (40.4°C), Ara-C + daunorubicin started on day 1; 5, emphysema, pneumonia 1 week before study, low-dose Ara-C started on day 1; 6, chronic respiratory insufficiency, on warfarin due to deep venous thrombosis and pulmonary embolism, digitalis and diuretics, Ara-C + daunorubicin on day 2; 7, AML 8 mo before study, previous chemotherapy with different protocols including anthracyclines, antimetabolites, and steroids with minor effect. One week before study on low-dose Ara-C, febrile (38.7°C), high-dose Ara-C started on day 2; 8, liver affection (toxic?), febrile, MEA started 12 hr before injection of [^{14}C]sucrose–LDL; 9, febrile, TAD started on day 1; 10, oligoblastic leukemia transformed into AML, prior treatment low-dose Ara-C, low-dose epirubicin on day −4, −1, and +1; 11, hypertension, gallstone disease, MEA started on day 5. M, male; F, female; WBC, white blood cell count; PB, peripheral blood; BM, bone marrow; Ara-C, cytosine arabinoside; TAD, thioguanine plus Ara-C plus daunorubicin; MEA, mitoxantrone plus etoposid plus Ara-C; day 0 denotes the day for injection with [^{14}C]sucrose–LDL.

*To convert mmol/liter to mg/dl, multiply cholesterol by 38.7 and triglycerides by 88.5.

†Leukemic cells, blast cells plus promyelocytes/promonocytes. Cellularity of bone marrow was ≥90% in all patients.

cholesterol concentrations were determined with a citrate/heparin precipitation method (16).

RESULTS

The administration of [^{14}C]sucrose–LDL was without side effects in all patients. After injection of [^{14}C]sucrose–LDL, the plasma radioactivity declined in a bimodal fashion (Fig. 1). Concomitantly, there was a progressive accumulation of radioactivity in the leukemic cells for at least 12 hr, until a plateau was reached (Fig. 2). The magnitude of this *in vivo* accumulation of ^{14}C radioactivity in the leukemic cells correlated strongly with parallel LDL-receptor determinations on the cells *in vitro* ($r = +0.88$, $P < 0.001$). This is illustrated in Fig. 3, where the cellular high affinity *in vitro* degradation rates of ^{125}I-labeled LDL have been plotted against the *in vivo* uptake of [^{14}C]sucrose–LDL 4 hr after injection.

To further test the hypothesis that leukemic cells lower plasma cholesterol through their high LDL uptake, plasma LDL cholesterol concentrations in the 11 patients were correlated with the *in vivo* uptake of ^{14}C radioactivity by the leukemic cells. It was found that the plasma LDL cholesterol concentrations in the 11 patients showed an inverse correlation ($r = -0.76$, $P < 0.01$) with the cellular uptake of ^{14}C radioactivity per volume of blood (Fig. 4).

One patient (no. 1) died from septicemia and acute intestinal obstruction 1 week after the injection of [^{14}C]sucrose–LDL. He was never treated with cytostatic agents, and hence his bone marrow was still leukemic. Radioactivity determinations of tissue biopsies obtained at autopsy revealed that the adrenals and the liver were the two organs with the highest uptake per g of tissue (Fig. 5). Also bone marrow had a considerable accumulation of radioactivity. Based on the organ weights, it can be estimated that ≈10% of the injected radioactivity was present in the body at this time.

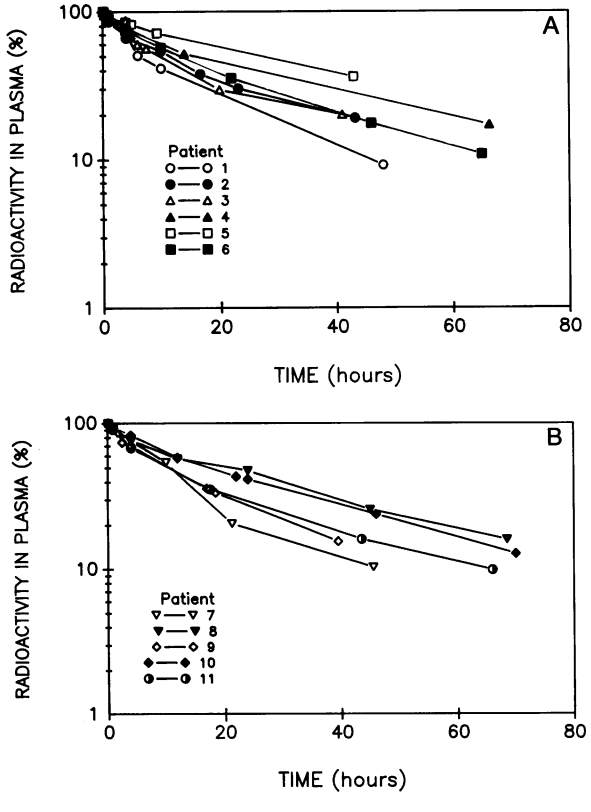

FIG. 1. Radioactivity remaining in plasma after i.v. injection of ≈220 × 10^6 dpm of [^{14}C]sucrose–LDL in 11 patients with acute leukemia. Radioactivity in plasma 10 min after injection was set to 100%. For identification of patients, see Table 1.

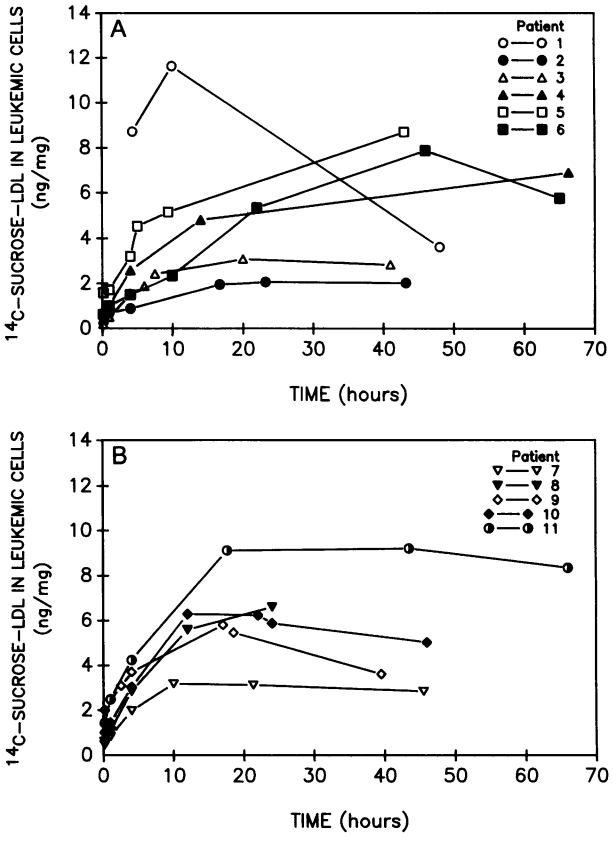

FIG. 2. Accumulation of [^{14}C]sucrose–LDL in leukemic cells after i.v. injection of ≈220 × 10^6 dpm in 11 patients with acute leukemia. Data are expressed as ng per mg of cell protein. Symbols are the same as for Fig. 1.

DISCUSSION

In the present work, we have administered [^{14}C]sucrose–LDL to patients with acute leukemia to study the LDL receptor activity in the leukemic cells *in vivo*. [^{14}C]sucrose–LDL has been shown (10) to bind to LDL receptors *in vitro* with the same affinity as iodinated LDL. After endocytosis and lysosomal hydrolysis, [^{14}C]sucrose is trapped in the lysosomes leading to cellular accumulation of radioactivity.

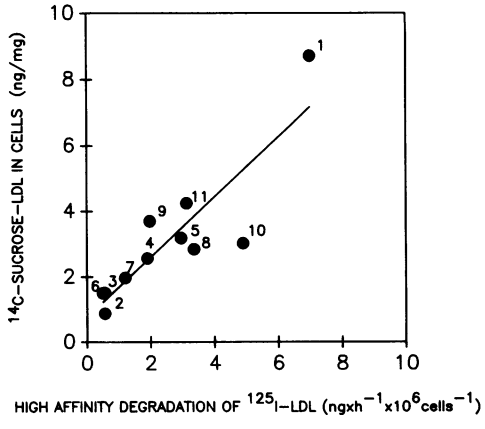

FIG. 3. *In vivo* uptake of [^{14}C]sucrose–LDL by the leukemic cells 4 hr postinjection in relation to rates of high-affinity degradation of ^{125}I-labeled LDL by the leukemic cells assayed *in vitro*. Data are expressed as ng per mg of protein. Numbers refer to individual patients (Table 1).

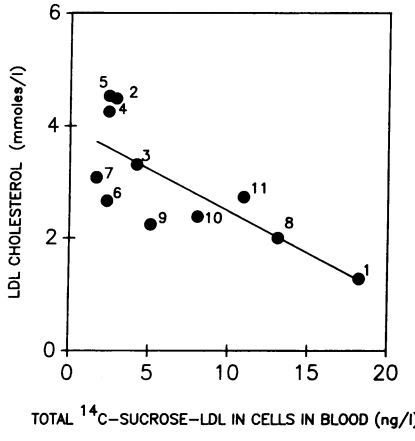

FIG. 4. Plasma LDL cholesterol concentrations in the 11 patients with acute leukemia in relation to the *in vivo* uptake of [^{14}C]sucrose-LDL by the leukemic cells in 1 ml of blood. Numbers refer to individual patients (Table 1).

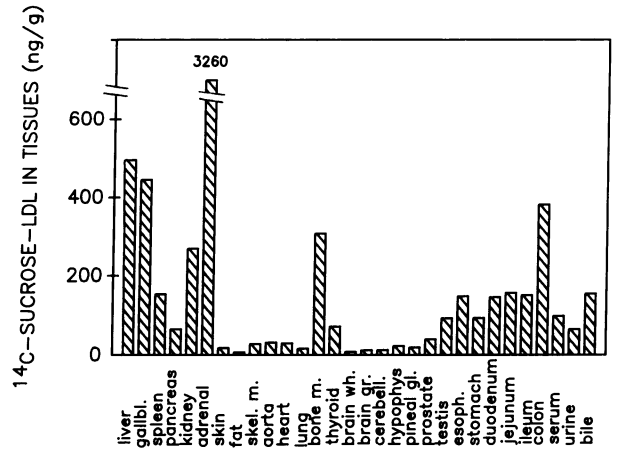

FIG. 5. Postmortem content of [^{14}C]sucrose-LDL in different organs of patient no. 1, 1 week after injection of [^{14}C]sucrose-LDL. Data are expressed as ng of [^{14}C]sucrose-LDL per g (wet weight) of tissue. gallbl., gallbladder; skel. m., skeletal muscle; bone m., bone marrow; brain wh., white matter of brain; brain gr., grey matter of brain; hypophys., hypophysis; pineal gl., pineal gland; esoph., esophagus; cerebell., cerebellum.

Direct comparisons on cultured cells have shown that there is a high concordance between the cellular accumulation of [^{14}C]sucrose and the cellular uptake and degradation of ^{125}I-labeled LDL, demonstrating that the former behaves like a trapped ligand (10). The strong correlation seen between *in vitro* degradation rates of LDL in leukemic cells and the *in vivo* accumulation of ^{14}C radioactivity in the present study (Fig. 3) lends support to the use of [^{14}C]sucrose-LDL to evaluate LDL catabolism also in humans.

Studies in animals have shown similar plasma clearance rates for [^{14}C]sucrose-LDL and ^{125}I-labeled LDL (11, 17). Considering the difficulties inherent in studies of patients with acute leukemia, the present investigation was not primarily designed to obtain detailed information on the kinetics of plasma LDL in this situation. Nevertheless, it is of interest to note that the estimated rate of disappearance from plasma of [^{14}C]sucrose-LDL in leukemic patients in our study was considerably faster than that of ^{125}I-labeled LDL in normal humans of similar age (Table 2), indicating that the elimination rate of LDL from plasma was increased in the leukemic patients. Although we do not have comparable data from [^{14}C]sucrose-LDL turnover studies in normals, further support for this concept was gained when the leukemic patients were compared with two patients with gastric cancer given [^{14}C]sucrose-LDL: the elimination rate of LDL seen in the latter patients was clearly less rapid than that observed in the present study (Table 2). To perform the studies immediately after diagnosis, we used homologous LDL for our [^{14}C]sucrose-LDL studies. The use of nonautologous LDL as a tracer may give a better estimation of true LDL receptor activity because the LDL that remains in the circulation of a leukemic patient with rapid clearance and low levels of LDL might be a fraction that binds poorly to the LDL receptor. A reduced affinity of LDL for its receptor in situations with an increased receptor-mediated elimination of LDL has, indeed, been demonstrated recently (18, 19), indicating that the use of autologous LDL in such situations may lead to an underestimation of LDL catabolism.

The death of one patient in intercurrent disease 1 week after the injection of the [^{14}C]sucrose-LDL provided a unique possibility to determine tissue sites of LDL degradation *in vivo* in the human (Fig. 5). The adrenals and the liver were the two organs with the highest content of radioactivity per g of tissue 1 week after the injection. Other organs with a relatively high uptake were kidney, spleen, and intestine (although the fact that the patient had intestinal obstruction may have affected the relative distribution of radioactivity in the colon). The radioactivity in gallbladder and bile most likely represents [^{14}C]sucrose that is being excreted from the body. When the absolute organ weights were considered, the liver—which was somewhat enlarged but without leukemic infiltration—contained almost 40% of the remaining radioactivity. This is in agreement with previous reports on the binding of ^{125}I-labeled LDL to isolated membranes (20) or crude tissue homogenates from animal tissues (20, 21) as well as tissue uptake of [^{14}C]sucrose-LDL in animals (11, 17). The overall organ uptake profile in the current human study is, in fact, very similar to the *in vitro* binding data from a recent study of human tissues (22). Of particular interest is the fact that a substantial amount of radioactivity was present in the (leukemic) bone marrow. Because the weight of this organ is at least 3 kg, it may be estimated that an amount of [^{14}C]sucrose-LDL almost equivalent to that in the liver was taken up into the bone marrow.

Table 2. Estimations of plasma LDL kinetics in patients with leukemia

Subject group	*n*	Age, yr	Plasma LDL cholesterol, mmol/liter	Estimated LDL fractional catabolic rate, pools/day	Radioactivity remaining at 24 hr, %
Leukemic patients*	11	68 ± 4	3.2 ± 0.3 (2.0–4.6)	0.95 ± 0.08 (0.55–1.27)	32 ± 2 (28–52)
Gastric cancer patients*	2	65, 71	2.2; 2.3	0.58; NP	47; 55
Healthy subjects†	12	68 ± 2	4.1 ± 0.1 (2.8–4.9)	0.30 ± 0.01 (0.25–0.34)	68 ± 2 (50–80)

The fractional catabolic rate of plasma LDL was calculated from the slope of the plasma radioactivity decay curve using a two-compartment model as described (14, 18). Analysis was not possible in patient 5. For comparison, data are given for two patients with gastric cancer who were injected with a similar dose of [^{14}C]sucrose-LDL and for 12 age-matched male healthy volunteers injected with 30–60 μCi of autologous ^{125}I-labeled LDL (S.E., M. Eriksson, S.V., K. Einarsson, L. Berglund, and B.A., unpublished work). Data are presented as means ± SEM; ranges are in parentheses. NP, analysis not possible.

*[^{14}C]sucrose-LDL.

†^{125}I-labeled LDL.

We have hypothesized that the hypocholesterolemia in acute leukemia might be the result of a high receptor-mediated uptake of LDL by the leukemic cells (5). In the present study, there was an inverse correlation between the cellular high-affinity degradation rates of ^{125}I-labeled LDL *in vitro* and plasma LDL cholesterol concentrations. Moreover, an even stronger inverse correlation was obtained between the *in vivo* uptake of [^{14}C]sucrose–LDL per volume of blood and the plasma LDL cholesterol concentration. Because the latter correlation reflects *in vivo* conditions and also takes the white blood cell count into consideration, this finding further fortifies our hypothesis. Hypocholesterolemia has been reported also in patients with myeloproliferative disease (23). With the objective of identifying the sites of LDL catabolism, Vallabhajosula *et al.* (24) have recently studied the distribution of ^{99}Tc-labeled LDL in such patients by gamma camera imaging. Their results indicate that the spleen and the bone marrow are the major sites of LDL catabolism in this situation; this result would agree with our present data.

It should be emphasized, however, that we cannot presently exclude that additional effects on LDL uptake in other tissues are induced by the leukemic cells (e.g., via the release of humoral growth-stimulating factors). It is of particular interest to consider the fact that the estimated amount of cholesterol being delivered to the malignant blood cells appears to be in great excess of that which can be utilized for cell growth, even if the turnover of cells is increased. The previous findings of a low cholesterol content (3) and a high endogenous cholesterol production (25) in AML cells clearly indicate a cellular deficiency in cholesterol which, in the presence of an increased uptake of LDL, may suggest that an enhanced loss of sterol from the cells takes place. Thus, the exact mechanism behind the enhanced expression of LDL receptors in AML cells still remains obscure; nevertheless, the results of the present study have clearly demonstrated that a considerable fraction of LDL is taken up by the leukemic cells in AML.

Our study provides strong support for the concept of using LDL as a drug carrier in treating AML. The progressive accumulation of LDL in leukemic cells could be favorable if the lipoprotein carries a cytotoxic drug. The drug would be directed preferentially to leukemic cells with high LDL uptake. Compared with the nonselective distribution of most lipophilic cytotoxic drugs used today, the high incorporation of LDL into the leukemic bone marrow (Fig. 5) should offer an advantage. Furthermore, animal studies have indicated that downregulating the high LDL uptake in the adrenals with steroids is possible, which could reduce the potential risk for toxicity in this organ (26). Clinical studies using LDL–drug complexes in the treatment of leukemia should hence be considered.

It is possible that the mechanism for the low cholesterol levels frequently also seen in nonhematologic malignancies (27, 28) is increased LDL-receptor activity in the tumor cells. Previous studies have indeed shown elevated LDL-receptor activities in certain tumor cells in both tissue culture and *in vivo* as compared to the corresponding normal cells (22, 29). *In vivo* studies on animals with experimental tumors have also shown a high LDL uptake in the tumor (26, 30), and a recent study has demonstrated an enhanced elimination of LDL in metastatic cancer of the prostate (31). If increased LDL receptor expression is common in malignant disease, the principle of selective drug delivery also may be of interest in the therapy of solid tumors.

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