³¹P-Nuclear Magnetic Resonance Studies of the Effect of Recombinant Human Interleukin 1α on the Bioenergetics of RIF-1 Tumors[1]

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ABSTRACT

The effect of a single injection of human recombinant interleukin 1α (IL-1α) on s.c. RIF-1 tumors in mice was studied by *in vivo* ³¹P nuclear magnetic resonance spectroscopy. Spectra were obtained before and up to 24 h after IL-1α. At 2, 4, 6, and 8 h after IL-1α injection, RIF-1 tumors exhibited a reduction in bioenergetic status compared to untreated controls. The P_i to β-nucleoside triphosphate and the phosphomonoester to β-nucleoside triphosphate ratios increased, while the phosphocreatine to P_i and phosphodiester to phosphomonoester ratios decreased. Tumor blood flow, estimated by ⁸⁶RbCl uptake, decreased within 30 min after IL-1α treatment. Minimum perfusion was detected at 4 h, with recovery between 6 and 12 h after IL-1α treatment. Histological sections of the RIF-1 tumors revealed intravascular congestion by 2 h, extravascular hemorrhage by 4 h, and necrosis by 12 h after treatment with IL-1α. The time course of bioenergetic changes in RIF-1 tumors determined by ³¹P-NMR spectroscopy was found to parallel the reduction and subsequent recovery of tumor blood flow.

INTRODUCTION

Recombinant human IL-1α[3] is a multifunctional cytokine with significant antitumor activity in experimental models (1, 2). Although IL-1α may be directly cytotoxic to some cell lines *in vitro* (3), it is not toxic to RIF-1 cells in culture (2). However, when administered to *in vivo* RIF-1 tumors, IL-1α produces vascular congestion, extravascular hemorrhage, hemorrhagic necrosis, and tumor cell kill (2).

In vivo ³¹P-NMR spectroscopy provides useful information on the status of phosphorus metabolites in solid tumors before and after therapeutic intervention (4–8). In the RIF-1 murine tumor model, age- and volume-dependent reductions in tumor blood flow (9) are accompanied by an increase in the P_i/β-NTP ratio and a decrease in the PCr/P_i ratio (8). In addition the P_i resonance exhibits an upfield shift indicative of tumor acidification. These changes are consistent with a growth associated decrease in relative levels of high energy phosphates. When increases in tumor blood flow are seen after chemotherapy (10), NMR spectroscopy has demonstrated an improvement in the apparent bioenergetic status of the tumor (7, 8).

In the present study *in vivo* ³¹P-NMR spectroscopy was used to determine the effect of a single IL-1α treatment on the bioenergetic status of s.c. implanted RIF-1 tumors. In addition, ⁸⁶RbCl uptake experiments were conducted to determine the time-dependent changes in tumor blood flow following a single IL-1α treatment.

MATERIALS AND METHODS

Tumor Model. RIF-1 tumor cells were propagated *in vitro* in RPMI 1640 medium (Mediatech, Washington, DC) supplemented with 10% fetal bovine serum (Irvine Scientific, Santa Ana, CA), 2 mM glutamine (GIBCO, Grand Island, NY) and antibiotics, as previously described (2, 8–10). Female C3H/HeJ mice (The Jackson Laboratories, Bar Harbor, ME), 6–10 weeks old, were inoculated in the right flank with a subdermal injection of 5×10^5 tissue culture cells. Studies were initiated 14 days later when tumors were approximately 1.0 g. Because IL-1α activity appears to be modified by levels of steroid hormones and because of concern over possible diurnal variations in levels of these hormones, special care was taken with respect to animal handling. All mice were quarantined for 2 weeks prior to entering studies. Randomly selected mice were tested and found to be free of adventitious murine viruses. All mice were housed, four to five per cage, in a temperature and humidity controlled, American Association for the Accreditation of Laboratory Animal Care approved facility with a 12-h light-dark cycle (lights on at 0600 h local time). Mice were provided standard mouse chow and water *ad libitum*. For both blood flow and NMR studies, IL-1α treatments were routinely administered between 0700 and 0900 h local time.

Interleukin 1α. Recombinant human IL-1α was generously provided by Dr. Peter Lomedico (Hoffmann-LaRoche, Nutley, NJ). The IL-1α used in these studies was highly purified (2.5×10^9 D_{10} units/mg protein) and essentially free of endotoxin contamination (<0.125 Eu/mg protein). The IL-1α was diluted in nonpyrogenic 0.9% NaCl containing 0.05% bovine serum albumin and a dose of 25 μg/kg (6.25×10^7 D_{10} units/kg) was administered in a total volume of 0.2 ml by i.p. injection. We have previously shown that this dose is two to three times smaller than the dose required to stimulate murine hematopoiesis (11).

Tumor Blood Flow. Tumor blood flow was estimated by the ⁸⁶RbCl distribution assay described by Sapirstein (12) and used by us in studies of the RIF-1 tumor model (2, 9, 10). Briefly, approximately 200,000 cpm of ⁸⁶RbCl (NEN, Boston, MA) were injected via the lateral tail vein. The mice were killed 45 s later by cervical luxation, and tissue samples quickly collected and weighed. Radioactivity was measured using a gamma well scintillation spectrometer (Packard Instruments, Downers Grove, IL) and expressed as a fraction of the injected dose. Drug distribution is proportional to the distribution of the cardiac output to the tissue (12). In order to minimize variations due to animal size, the injected dose per gram was multiplied by the body weight (2, 9, 10).

Spectroscopy. ³¹P-NMR spectra of s.c. tumors were obtained with a Bruker AM-360 WB NMR spectrometer (8.5 Tesla/8.9-cm bore) interfaced to an Aspect 3000 computer. A home-built probe containing a three-turn solenoidal radiofrequency coil, 1.5 cm in diameter, double tuned to ¹H and ³¹P was used (13). The homogeneity of the magnetic field was optimized for each tumor by shimming to obtain a H_2O resonance with a maximum linewidth of 100 Hz. Each spectrum was obtained by accumulating 200 scans using a 60° flip angle (8 μs), 1024 data points, and 8-kHz spectral width. A repetition of 3 s was employed, which results in only a small partial saturation of the PME, P_i, and PCr resonances. Resolution was enhanced by the convolution difference method using 1000-Hz and 20-Hz exponential multiplication (14). Chemical shifts are reported with respect to the α-NTP resonance, which was assigned to −10 ppm as an internal reference (15). Integrated resonance areas were obtained using a Lorentzian line fitting program (GLINFIT, Bruker Users Society). Two Lorentzian curves were used to fit the PME and P_i peaks, and three for the PDE peaks. The reported

areas are of the composite peaks. The average P_i chemical shift weighted by the area of each P_i resonance was used to calculate pH (4).

Thirty animals, divided into five groups of six animals each, were used for the NMR studies. The first group was used as an untreated control, while Groups 2–5 were treated with a single dose of IL-1α (25 μg/kg). ^{31}P-NMR spectra were obtained at 2 and 4 h (Group 2), at 6 and 8 h (Group 3), at 12 h (Group 4), and at 24 h (Group 5) after IL-1α administration. Immediately prior to spectroscopy all animals were anesthetized with an i.p. injection of ketamine (50 mg/kg)/aceproma-zine (5 mg/kg).

Statistical Analysis. Analysis of variance was used to evaluate the overall variation and significance of posttreatment responses. The significance between group means in the time course study was determined by the Newman-Keuls multiple-range test. A P value of less than or equal to 0.05 was sufficient to reject the null hypothesis.

RESULTS

Interleukin 1α produced distinct histological changes in RIF-1 tumors. Although focal necrosis is occasionally observed, the well vascularized RIF-1 tumor model does not exhibit central necrosis (Fig. 1A). By 2 h after IL-1α, vasodilation and marked intravascular congestion were routinely observed (Fig. 1B). By 4 h after IL-1α, capillary destruction and extravascular hemorrhage were observed (Fig. 1C). All tumor samples obtained at 12 h after IL-1α exhibited large areas of necrosis (Fig. 1D).

The uptake of [86]RbCl in RIF-1 tumors was significantly reduced ($P < 0.05$) within 30 min after IL-1α treatment, and by 4 h the [86]RbCl uptake was reduced by approximately 60% (Fig. 2). Recovery was evident by 6 h after treatment. At 12 h and later after injection of IL-1α, the mean [86]RbCl uptake was not significantly different from that in controls.

Representative ^{31}P-NMR spectra of control and treated tumors are shown in Fig. 3. The spectra obtained from the control group are typical of untreated RIF-1 tumors of this size, with a $P_i/β$-NTP ratio of 1.16 ± 0.28 and pH of 6.90 ± 0.15. The energy status of the tumors was significantly decreased for at least 8 h after IL-1α treatment (Table 1). Two h after IL-1α administration, PCr/P_i was reduced by 78% and $P_i/β$-NTP increased by approximately 400%. A marked decrease in PDE/PME ratio and an increase in the PME/$β$-NTP ratio were also noted. These ratios remained different from control values for 8 h. At 12 and 24 h posttreatment, metabolite ratios were not significantly different from those of controls. Tumor pH did not change significantly throughout the time of the experiment (Table 1). The reenergization of the tumors followed the same time course as the recovery of [86]RbCl uptake.

DISCUSSION

A marked decrease in the apparent bioenergetic status of RIF-1 solid tumors was seen within 2 h after treatment with human recombinant IL-1α. A significant increase in $P_i/β$-NTP and a decrease in PCr/P_i and PDE/PME were observed for at least 8 h after treatment. Changes were reversed, and the
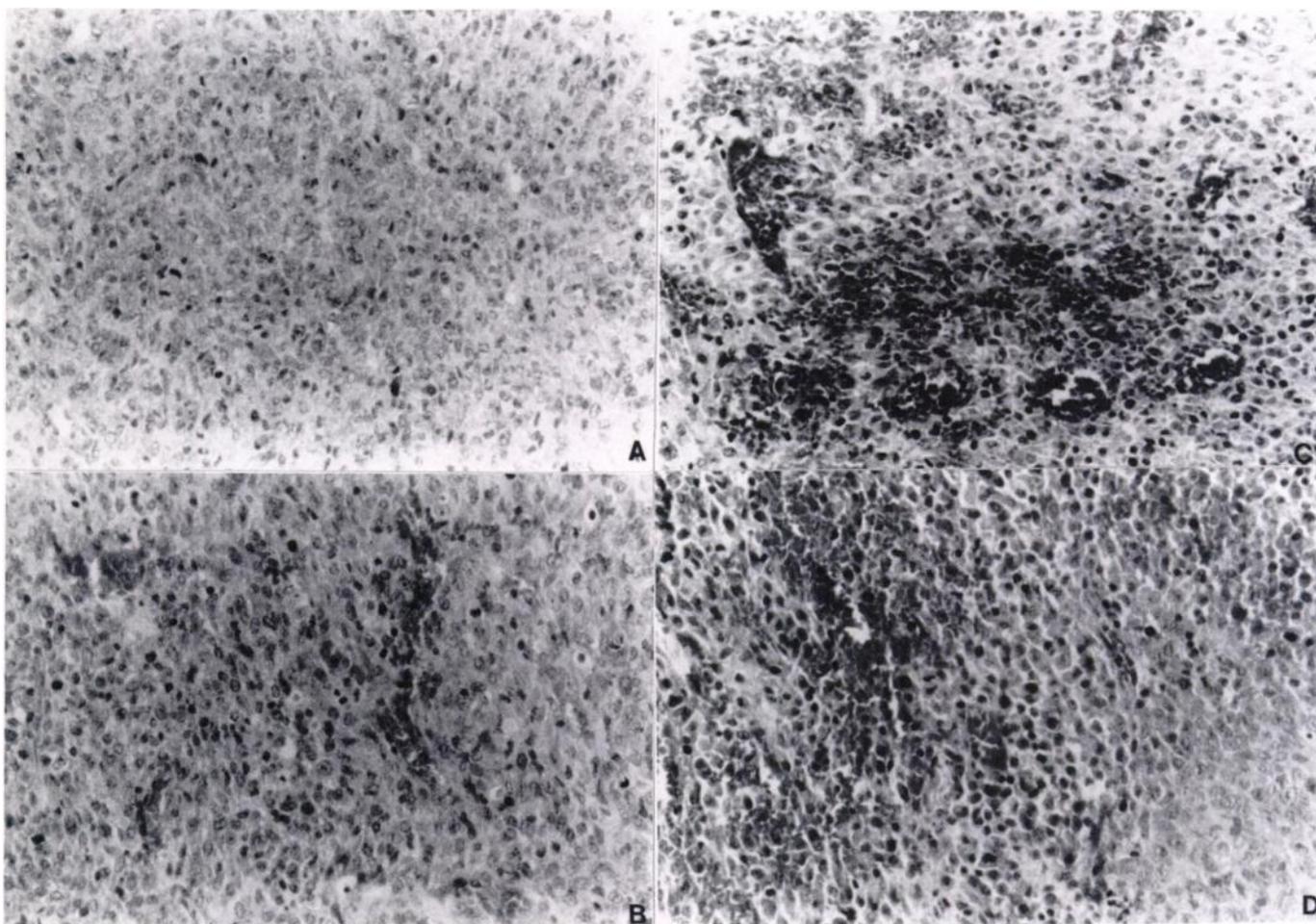

Fig. 1. Histological sections from representative control (A) and IL-1α-treated (B–D) RIF-1 tumors. Control tumors (A) exhibited a typical fibrosarcoma histology. Central necrosis was absent and focal necrosis was only rarely seen. Vasodilation and intravascular congestion were seen at 2 h (B) and by 4 h (C) vascular breakdown and extravascular hemorrhage were seen. At 12 h (D) hemorrhagic responses were still apparent near areas of viable tumor tissue. Large areas of necrosis were also seen at this time. All sections were stained with hematoxylin & eosin. Magnification, 80 ×.
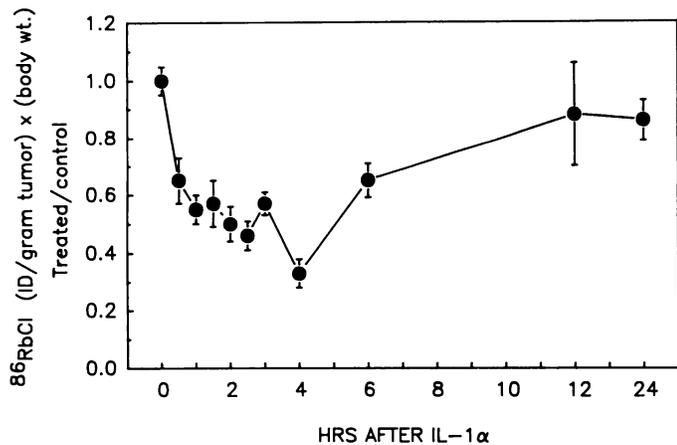
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Fig. 2. The effects of IL-1α (25 μg/kg) on the distribution of [86]RbCl in subcutaneous RIF-1 tumors. A total of 148 tumors were used in these studies. Each point is the mean ± 1 SEM for at least 10 tumors per study interval. Analysis of variance indicated highly significant ($P < 1.0 \times 10^{-4}$) treatment effects. All points up to 6 h were significantly ($P < 0.05$) different from controls (Newman-Keuls multiple range tests), while points starting at 12 h were indistinguishable from controls.
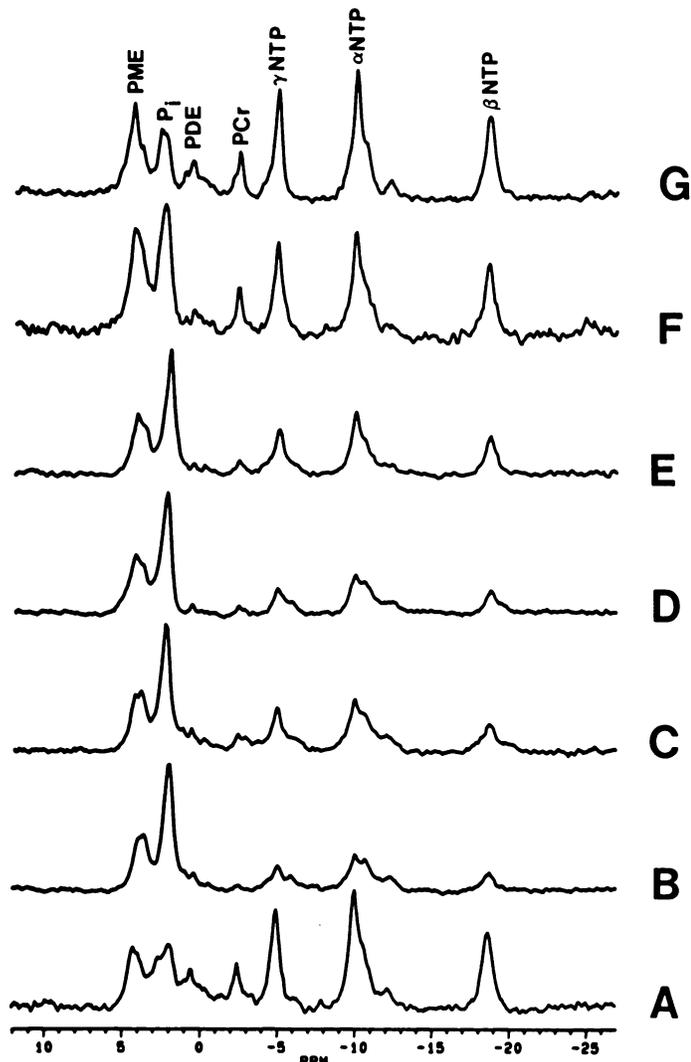
Table 1 *Effects of IL-1α on the RIF-1 tumor*

Mean metabolite ratios determined from the integrated areas of the resonances fitted by Lorentzian curves. Errors indicated are standard deviations of the mean.

Time (h)	PDE/PME	PCr/Pi	Pi/β-NTP	PME/β-NTP	pH
0	0.46 ± 0.24	0.32 ± 0.12	1.17 ± 0.28	1.15 ± 0.41	6.89 ± 0.15
2	0.15 ± 0.10	0.07 ± 0.07	5.61 ± 2.73	3.35 ± 1.41	6.97 ± 0.07
	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	NS[a]
4	0.14 ± 0.06	0.08 ± 0.05	3.66 ± 2.17	2.08 ± 0.39	6.94 ± 0.05
	$P < 0.01$	$P < 0.01$	$P < 0.05$	NS	NS
6	0.15 ± 0.10	0.13 ± 0.08	3.84 ± 1.28	2.56 ± 0.51	7.02 ± 0.09
	$P < 0.01$	$P < 0.01$	$P < 0.05$	$P < 0.01$	NS
8	0.12 ± 0.09	0.16 ± 0.08	2.36 ± 0.24	1.78 ± 0.24	6.84 ± 0.10
	$P < 0.01$	$P < 0.01$	NS	NS	NS
12	0.37 ± 0.27	0.28 ± 0.19	1.92 ± 0.87	1.74 ± 0.52	7.03 ± 0.15
	NS	NS	NS	NS	NS
24	0.48 ± 0.13	0.32 ± 0.07	1.20 ± 0.36	1.19 ± 0.24	7.12 ± 0.09
	NS	NS	NS	NS	NS

[a] NS, not significant.

Fig. 3. Representative *in vivo* ^{31}P-NMR spectra of s.c. RIF-1 tumors before (*A*), 2 h (*B*), 4 h (*C*), 6 h (*D*), 8 h (*E*), 12 h (*F*), and 24 h (*G*) after IL-1α (25 μg/kg). In the RIF-1 tumor approximately 60% of the NTP resonance is due to ATP (15).

apparent bioenergetic status of the tumors improved to that of control by 12 h after IL-1α administration. The response of RIF-1 tumors after IL-1α, determined by NMR, differed from that seen after either chemotherapy (5, 8) or radiation (5, 16), but resembled that seen after hyperthermia (4, 5), TNF (17) or physical clamping of the tumor (17).

Reduced [86]RbCl uptake within 30 min after IL-1α treatment (Fig. 2) suggests prompt inhibition of blood flow. The time course of reduced [86]RbCl uptake after IL-1α coincided with that of reduced high energy phosphates, while subsequent increases in the uptake of the radiolabeled probe paralleled improvement in the bioenergetic status of the tumor.

The [86]RbCl distribution method provides an indirect measure of tumor blood flow (12). Since the uptake of the indicator reflects cardiac output distribution (12), determination of perfusion by the uptake of [86]RbCl can be complicated by treatment-mediated changes in cardiac output. A decrease in [86]RbCl uptake in the tumor after IL-1α could result from reduced cardiac output. However, in previous studies IL-1α had little or no effect on the [86]RbCl distribution, and presumably blood flow, in femoralis muscle or skin from RIF-1 tumor-bearing mice (2). The histological findings of vasodilation, intravascular congestion, and hemorrhagic necrosis, together with the findings from the [86]RbCl uptake studies, imply that in RIF-1 tumors the reduction in NTP relative to Pi following IL-1α treatment is due to reduced vascular perfusion secondary to IL-1α-mediated tumor vascular injuries.

Previous studies have shown that tumor bioenergetics, as measured by ^{31}P-NMR spectroscopy, is directly related to tumor blood flow (18). Decreases in RIF-1 tumor blood flow with increasing tumor size have been observed using the [86]RbCl method (9). In other studies, the peripheral vasodilator hydralazine, which reduces tumor blood flow (19), lowered high energy phosphate levels and decreased tumor pH in FSaII tumors (20). At 12 h, when tumor blood flow was restored to its pretreated value, all metabolite ratios and pH returned to pretreated values even though histologically the tumor showed large areas of necrosis. The observation that the highly necrotic tumors showed a high apparent bioenergetic status suggests that the NMR signal originated only from viable cells.

The mechanism by which IL-1α causes vascular injuries in RIF-1 and in other tumor models (2) is not well understood. Although IL-1α is known to stimulate endothelial cells to produce procoagulant activity (21), proteolytic enzymes (22), and vasoactive prostaglandins (23), IL-1α may also stimulate the production of TNF (24). Vascular injury induced in RIF-1 tumors by IL-1α is similar to that previously reported for the more proximal cytokine TNF (17, 25). Intratumoral TNF treat-

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ments have been shown by ^{31}P-NMR to decrease PDE resonances and increase PME resonances in excised solid tumor tissues and extracts (26) In the present study, large decreases in the PDE/PME ratio were observed during the first 6 h after IL-1α. Using *in vivo* ^{31}P-NMR spectroscopy, it was not possible to determine if the PME resonance after IL-1α treatment reflected an increase in glycerol-3-phosphate as was observed in the TNF extract study (26). Treatment of Meth-A tumors with an i.p. dose of 15 μg/kg of TNF (17) induced changes in the *in vivo* ^{31}P-NMR spectra similar to those reported here for IL-1α. At this time, the extent to which TNF participates in the IL-1α-mediated hemorrhagic responses in solid tumor models is unknown.

The pathophysiological effects of IL-1α in solid tumors can be exploited for the design of treatment strategies combining IL-1α and other therapeutic modalities. For example, IL-1α-mediated vascular and metabolic responses observed in the present study with RIF-1 tumors may increase the *in vivo* thermal sensitivity of tumors. In this regard, TNF has been shown to enhance the efficacy of hyperthermia in model systems (27), and in preliminary studies (28) combined treatment with IL-1α and hyperthermia induced greater than additive antitumor response in the RIF-1 tumor model.

Our results indicate that *in vivo* ^{31}P-NMR spectroscopy could be a useful tool for monitoring metabolic responses in tumors during cytokine therapy and may provide important information for the design of new cytokine-based therapeutic strategies.

ACKNOWLEDGMENTS

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