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Promotion of Angiogenesis by Low Energy Laser Irradiation

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ABSTRACT

The effect of low energy laser (He-Ne) irradiation (LELI) on the process of angiogenesis in the infarcted rat heart and in the chick chorioallantoic membrane (CAM), as well as the proliferation of endothelial cells in tissue culture, was investigated. Formation of new blood vessels in the infarcted rat heart was monitored by counting proliferating endothelial cells in blood vessels. In the CAM model, defined areas were laser-irradiated or nonirradiated and blood vessel density was recorded in each site in the CAM at various time intervals. Laser irradiation caused a 3.1-fold significant increase in newly formed blood vessels 6 days post infarction, as compared with nonirradiated rats. In the CAM model, a slight inhibition of angiogenesis up to 2 days post irradiation and a significant enhancement of angiogenesis in the laser-irradiated foci as compared with control nonirradiated spots were evident. The LELI caused a 1.8-fold significant increase in the rate of proliferation in endothelial cells in culture over nonirradiated cells. It is concluded that LELI can promote the proliferation of endothelial cells in culture, which may partially explain the augmentation of angiogenesis in the CAM model and in the infarcted heart. These results may have clinical significance by offering therapeutic options to ameliorate angiogenesis in ischemic conditions. *Antioxid. Redox Signal.* 4: 785–790.

INTRODUCTION

TWO PROCESSES are responsible for the formation of new blood vessels, both of which result in formation of simple, endothelium-lined, capillary-like tubes. The first is vasculogenesis, which is the primary differentiation of mesodermal precursors to endothelial cells, and their subsequent organization into a primary capillary plexus. The second is angiogenesis, which is defined as formation of new blood vessels by a process of sprouting of preexisting vessels. Angiogenesis occurs during development and postnatal life, whereas vasculogenesis is limited to early embryogenesis. In addition to its role during development, angiogenesis is required for maintenance of functional and structural integrity of the organism during postnatal life, like wound healing, inflammation, ischemia. The regulatory mechanisms associated with the process of angiogenesis have been well documented in particular cytokines that are involved in the phase of activation of the endothelial cells (19). Angiogenesis and its significance in the ischemic heart have also been extensively investigated in laboratory animals and humans (9, 13, 21).

Low energy laser irradiation (LELI) has been found to modulate various biological processes (6, 10, 11), such as increasing mitochondrial respiration and ATP synthesis (15, 26), facilitating wound healing (6), and promoting the process of skeletal muscle regeneration and angiogenesis (3–5, 24). We have recently shown that laser irradiation induces synthesis of cell cycle regulatory proteins in satellite cells from skeletal muscles due to activation of early cell cycle regulatory genes (1) and mitogen-activated protein kinase (MAPK) extracellular signal-regulated kinase (ERK) cascade (20). Recently, in an experimental model of infarcted heart in rats and dogs, we have established the optimal power density for LELI to affect the complex process of scar tissue formation (17). Based on these recent data, we have demonstrated a profound cardioprotective effect of LELI on chronic infarcted myocardium in rats and dogs, resulting in a 50–70% reduction in infarct size 4–6 weeks after left descending coronary artery chronic occlusion (18). This phenomenon was partially attributed to a three- and six-fold significant elevation in the number of undamaged mitochondria and ATP content, respectively, in the cardiomyocytes in the ischemic zone in the

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myocardium of the laser-irradiated rats as compared with nonirradiated rats (18).

In the present study, we report the effect of LELI on the process of angiogenesis in the infarcted heart and on the chorioallantoic membrane (CAM) of the chick during development. The effect of LELI on endothelial cell proliferation in culture was investigated as well.

MATERIALS AND METHODS

Infarcted rat heart model

Myocardial infarction was induced in 11 8–10-week-old (250–350 g) male Sprague–Dawley rats, as described by us previously (17). In brief, occlusion of the left anterior descending (LAD) coronary artery was carried out after thoracotomy. The LAD was occluded 3 mm distally from where it branches off the aorta, using 5/0 polypropylene thread (Ethicon Inc., Cincinnati, OH, U.S.A.). Post operation, food and water were supplied *ad libitum*. A diode (Ga-As) laser, wavelength 804 nm with a power output of 38 mW and a beam diameter of 1.5 × 3.5 mm after collimation, was used (Lasotronic Inc., Zug, Switzerland). The laser device was equipped with a blunt tip (1.5 mm diameter) and placed directly on the intercostal muscles (after removal of the skin) at a perpendicular angle to the medial and lateral side of the left chest wall at the point above the beating heart. Rats were randomly assigned to either control non–laser-irradiated (five rats) or laser-irradiated (six rats) groups. The above laser irradiation did not cause elevation of the temperature in the irradiated tissue as has already been determined previously in skeletal muscles (3). Furthermore, no elevation of temperature was noticed in the myocardium of rats that were irradiated with the above laser for 3 min as measured by a sensitive (±0.1°C) thermocouple with a probe inserted in the irradiated area of the myocardium. A NOVA power-energy laser monitor equipped with a special detecting probe (Ophir Optronics Ltd., Jerusalem, Israel) was used to measure the power output of the laser and the power of the laser irradiation after penetration through the chest muscles. The measured power of irradiation in the above area was 5.0 ± 0.7 mW; thus, the power density of the irradiation on the myocardium was 4.5 ± 0.6 mW/cm^2. It could be assumed, therefore, that the dispersed laser beam would cover the infarcted area, including most of the lateral wall of the left ventricle (LV) of the rats. Laser irradiation was performed as described above 10–15 min after LAD occlusion, for duration of 1 min after the rats were breathing regularly. Total energy given to the tissue thus comprised 0.27 J/cm^2. On day 3 post LAD occlusion, the rats were lightly anesthetized with halothane (ICI, Cheshire, U.K.), the skin sutures over the chest were removed, and the intercostal muscles below were exposed. Laser irradiation was performed as above, but time of exposure was lengthened to 3 min. Based on the above data, the total energy given on the third day was 0.81 J/cm^2. Control infarcted sham-operated rats underwent the same process as the treated rats (anesthetized and chest exposed), and the laser was applied to the chest, but was not connected to a power source.

For determination of angiogenesis, the rats were lightly anesthetized with halothane 5 days post LAD occlusion, and 40 mg/kg body weight 5-bromo-2-deoxyuridine (BrdU; Sigma Chemical Co., St. Louis, MO, U.S.A.) in saline was injected intraperitoneally three times every 4 h in order to label proliferating cells. The rats were killed on day 6 post LAD occlusion. The hearts were excised, and 3-mm transverse sections from the middle of the infarcted area were processed for histology as described above. The above regime and time points were chosen in order to trace the effect of the second laser irradiation and to follow neoformation of blood vessels that commenced in the infarcted area at 3 days post LAD occlusion. Two histological sections from each heart were randomly selected for analysis of blood vessel formation in the infarcted area. The sections were viewed at a direct ×400 magnification using a Zeiss microscope equipped with a video screen. Two observers analyzed the blood vessels in the entire area of the LV of the infarcted rats. The total number of capillaries (<10 μm in diameter) and arterioles (20–100 μm in diameter) were counted in the LV area. On the same section, the newly formed blood vessels were also counted (Fig. 1). These vessels were defined as vessels that contained more than one endothelial cell positively immunolabeled (see above) for BrdU (see Fig. 1). The total number of BrdU-labeled (dividing cells) endothelial cells (confined to blood vessels) in the LV area were counted as well. The results were expressed per LV area of each microscopic section in the heart due to low variability in the area at risk (25) and similar heart size of the rats (Fig. 2). Furthermore, they express the newly formed blood vessels in both the perinfarcted and infarcted regions of the LV at this particular time point (6 days) post LAD ligation. The results were statistically analyzed using ANOVA (22).

Chick embryo CAM model

Fertilized chicken eggs were supplied from a local farm and were kept in a well ventilated incubator at 37°C through-

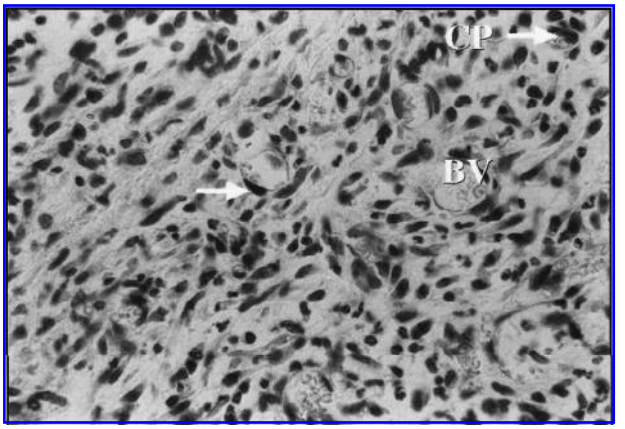

FIG. 1. Representative light micrographs of neoformation of blood vessels in infarcted rats. Note blood vessels (BV) and BrdU-immunostained endothelial cells (arrows) indicating newly formed blood vessels. BrdU immunostaining and hematoxylin counterstaining. ×220. CP, capillary.

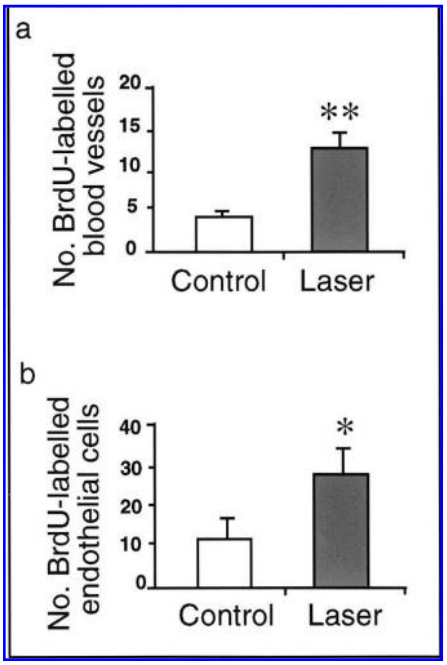

FIG. 2. Histograms of the number of BrdU-labeled blood vessels (a) and BrdU-labeled endothelial cells (b) in the area of the LV in a histological section of the LV of non–laser-irradiated (open columns) and laser-irradiated (shaded columns) rats 6 days post LAD occlusion. Each point is the mean ± SEM of 12 and 10 histological sections in control and laser-irradiated rats, respectively. *$p < 0.05$ or **$p < 0.01$, significantly different from non–laser-irradiated rats.

out the experiment. On day 4 after fertilization, 2–3 ml of the egg albumin was removed from the egg by suction through the eggshell, with a syringe under sterile conditions. On day 5 post fertilization, a "window" (1 cm × 1 cm) was cut in the dorsal part of the eggshell under sterile conditions. The eggs were then transferred to 37°C until day 12 when the laser was applied. Four to six plastic discs (5-mm diameter) were placed at various regions of the CAM under sterile conditions. In a preliminary experiment, it was found that these rings do not enhance or inhibit the regular angiogenic process in the CAM.

Laser irradiation was performed through the "window" created in the eggshell directly on the regions in the CAM that were coated by the discs. On the same egg, half of the regions in the CAM encircled by the plastic discs were laser-irradiated (randomly selected) and the other half served as control nonirradiated regions. The laser source (He-Ne laser, 632.8 nm, 5.5 mW power output; Ealing Electro-Optics, Holliston, MA, U.S.A.) was placed perpendicular to the window in the chicken eggshell and 15 cm from it. Under the above conditions, the energy density was 180 mW/cm^2, and duration of irradiation was 10 s (1.8 J/cm^2, respectively). The entire area on the CAM within each disc was completely covered by four to six irradiations, because the diameter of the disc was larger (5 mm) than the laser beam.

Extent of angiogenesis in the defined regions of the CAM was recorded daily from the first day post irradiation by observation through the CAM under a stereoscope. The extent

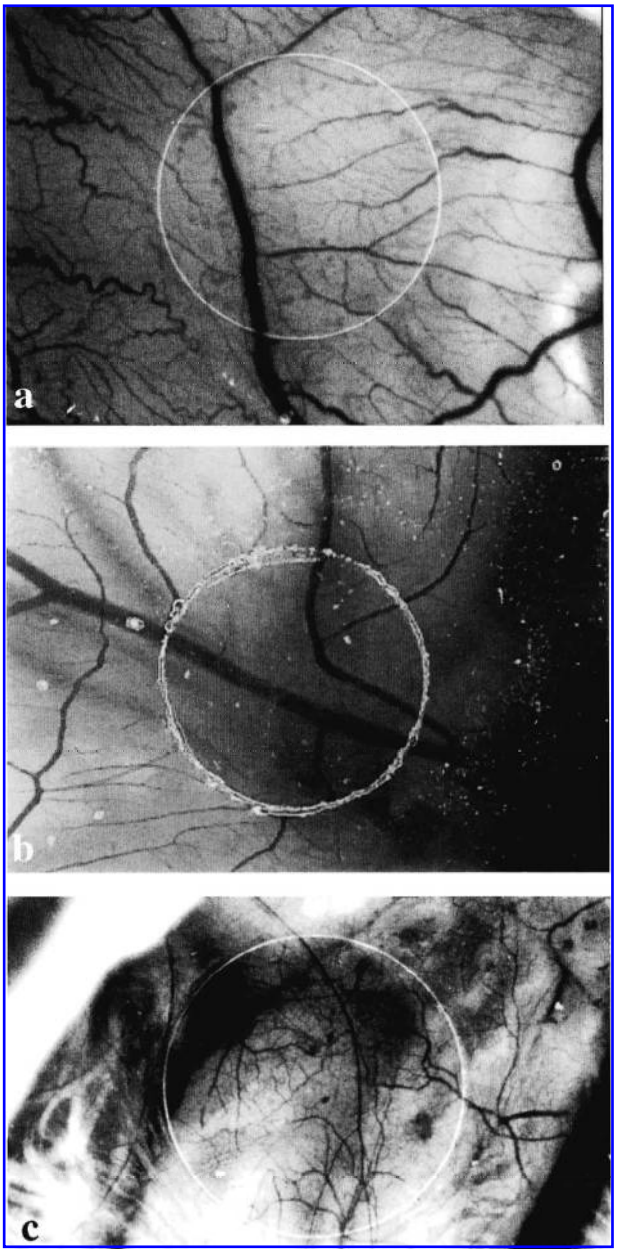

FIG. 3. Representative foci in the chick CAM of control (a) and laser-irradiated areas 2 (b) and 5 (c) days post laser irradiation. Note similar concentration of blood vessels within discs and surrounding area in (a) and inhibition and enhancement of angiogenesis in the disc area in (b) and (c), respectively. ×5.

of angiogenesis relative to the vicinity of each of the regions around the disc was graded from +1 (mild) to +3 (maximum) enhanced angiogenesis (relative to the vicinity) by two separate observers (Fig. 3). Zero level of angiogenesis was considered as angiogenesis to the same extent as its vicinity in the CAM. Inhibition of angiogenesis relative to the vicinity was also scored from −1 (mild) to −3 (maximum). Finally, the extent of promotion or inhibition of angiogenesis was calculated as an average resulting from combined scores of all irradiated discs divided by the number of irradiated discs.

Endothelial cells in culture

The endothelial cells in culture (ABAE cells, kindly donated by Prof. G. Neufeld from the Technion Institute of Technology, Israel), were grown in Dulbecco's modified Eagle's medium low-glucose medium. The cells were irradiated using the same laser with the same power output as described above for the CAM experiments. The laser irradiation of the cell culture was carried out essentially as described by us previously for myogenic cells in culture (1). In brief, the plated cells were irradiated through a grid composed of 1.8 mm × 1.8 mm squares to ensure precise irradiation over the entire tissue-culture plate. Each square was irradiated for various time periods with the same He-Ne laser used for the CAM experiments. Nonirradiated cells were kept under the same conditions as the irradiated ones, but the laser was not turned on.

The colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (16) was used to assess cell survival and proliferation. The culture medium was removed, and 100 µl of fresh culture medium (without serum) containing 10 µl of MTT (5 mg/ml) was added to each well. The cells were then incubated at 37°C for 3 h. The reaction was terminated by adding 0.04 *M* HCl in isopropanol. The absorbance of the medium was then determined at 570 nm and 630 nm, using the laboratory spectrophotometer, and the difference in absorbance was calculated.

RESULTS

The number of newly formed blood vessels, as manifested by BrdU-labeled vessels (Fig. 1) counted in the histological sections of the LV of the laser-irradiated rat heart, was 62 ± 10 (mean ± SEM) as compared with 27 ± 4 in the control, nonirradiated rats (Fig. 2). Thus, a 3.1-fold significantly ($p < 0.01$) higher new vascularization was evident in the laser-irradiated rats than in the non–laser-irradiated ones. The number of dividing (BrdU-labeled) endothelial cells in histological sections of the LV of laser-irradiated rats comprised 28 ± 6, which was significantly higher than the value (11 ± 5) in the non–laser-irradiated rats (Fig. 2).

In the chick CAM model, it can be seen that when laser was applied on day 12 after fertilization on the first 2 days post irradiation, the angiogenesis process in the irradiated areas was inhibited relative to surrounding areas (Figs. 3 and 4) that were not laser-irradiated. On days 4–8 post irradiation, the formation of new blood vessels in the irradiated area was enhanced by ~1.5-fold.

The effect of LELI on the rate of endothelial cell proliferation is presented in Fig 5. It can be seen that there is ~80% significant ($p < 0.01$) increase in the rate of proliferation and survival of the laser-irradiated (in energy densities of 0.54 J/cm^2 and 1.08 J/cm^2) cells 2 days post irradiation as compared with nonirradiated cells.

DISCUSSION

The results of the present study are in accordance with our previous findings that formation of blood vessels in the regenerating zone following skeletal muscle injury is enhanced twofold by applying laser irradiation (5). The results clearly indicate that LELI significantly promotes angiogenesis in infarcted heart and in the chick CAM model and also increases rate of proliferation of endothelial cells in culture and in the chicken CAM. The fact that endothelial cell proliferation in culture could be enhanced by LELI corroborates the results of promotion of angiogenesis by LELI in the infarcted heart and the chick CAM model. Furthermore, it indicates that at least part of the enhanced angiogenesis could be attributed to the direct effect of LELI on endothelial cells within the CAM that are activated to proliferate. In another

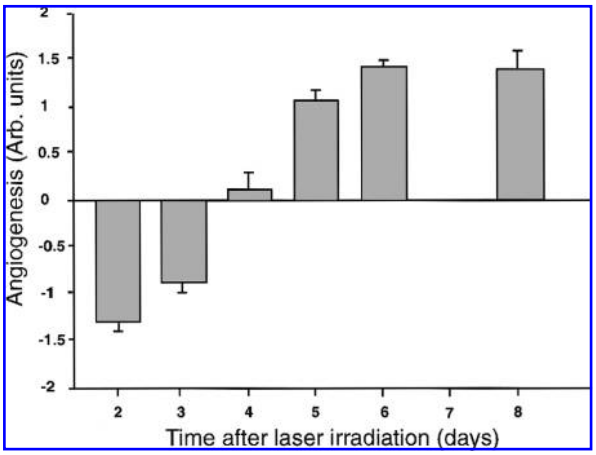

FIG. 4. Attenuation of the angiogenesis process in discs in the chick CAM by LELI. Note inhibition of angiogenesis 2 and 3 days post laser irradiation (12 days post fertilization) and enhanced angiogenesis from day 5 on post irradiation. Each column is the mean ± SEM of 30–40 discs (in seven to 10 chick CAM).

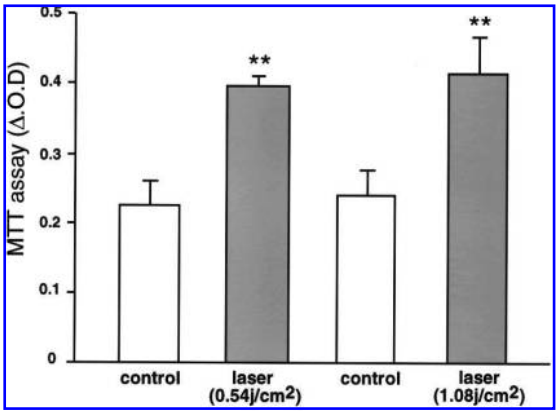

FIG. 5. Enhancement of cell survival and proliferation as revealed by MTT assay of control (open columns) and laser-irradiated (shaded columns) endothelial cells in culture. Cells were irradiated at two different energy densities as indicated. Each column is the mean ± SEM of six to 10 tissue culture wells. $^{**}p < 0.01$.

cell culture (satellite cells from skeletal muscle origin), we also demonstrated a twofold promotion of cell proliferation by LELI (1). This phenomenon was further supported by our recent study using the same tissue culture demonstrating the specific effect of LELI on the MAPK ERK cascade that is associated with cell proliferation (20). In that study, we also demonstrated that the receptor on these cells is phosphorylated by the laser irradiation similarly to the phosphorylation of the receptor of hepatic growth factor, which also has mitogenic activity.

It should be noted that on the first 2 days post laser irradiation there was a transient inhibitory effect of the laser on the process of angiogenesis relative to control areas in the chick CAM. Only after this delay period was the enhancement in angiogenesis noticed, peaking at 8 days post irradiation when its extent was 1.5-fold that of control nonirradiated areas in the CAM.

The results of the present study may also have clinical relevance. Based on our previous results showing that direct LELI on myoblasts in culture does not affect their differentiation *in vitro* (1) and that the use of LELI in humans has no known deleterious effects (7), it can be postulated that the use of LELI would appear to be safe. In the case of the ischemic heart, for example, LELI can be delivered to the myocardium in humans via fiber optics in the catheter of the nonfluoroscopic *in vivo* navigation and mapping technology currently in use in experimental animals and in humans (2, 8, 12). The LELI energy can also be applied during or after the procedure of balloon angiography, using a catheter with a central canal bearing a fiber optic, through which the laser energy can be transversely delivered (360°) to the infarcted area. As an adjunct procedure to other, increasingly popular approaches to repairing ischemic myocardium (angioplasty, stenting, grafting, transmyocardial revascularization, etc.), the cardioprotective effects of LELI may likewise be beneficial at minimal or no additional risk.

In conclusion, the results of the present study demonstrate that LELI causes a profound enhancement of angiogenesis in the chick CAM model and following myocardial infarction. However, the precise molecular mechanisms associated with the above phenomenon remain to be further investigated.

Perspective section

Lubart *et al.* (14) have shown that laser irradiation causes an elevation in hydrogen peroxide and postulated that induction of processes in the cell may take place via reactive oxygen species ROS). Indeed, it was recently shown by Suzuki *et al.* (23) that even a small amount of ROS in cells may cause activation of signal transduction. It may, thus, be speculated that a minor elevation of ROS content in cells by the laser irradiation, in turn, may also cause induction of antioxidant synthesis in the cells. In infarcted dogs, there was indeed a significantly higher concentration of catalase in the blood 24 h post myocardial infarction of the laser-irradiated dogs as compared with control (18). Thus, the link between laser irradiation, ROS elevation, and activation of specific signal transduction pathways cannot be ruled out. The precise mechanisms associated with this interesting phenomenon remain to be elucidated by further studies.

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ABBREVIATIONS

BrdU, 5-bromo-2-deoxyuridine; CAM, chorioallantoic membrane; ERK, extracellular signal-regulated kinase; LAD, left anterior descending; LELI, low energy laser irradiation; LV, left ventricle; MAPK, mitogen-activated protein kinase; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; ROS, reactive oxygen species.

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