Acta Histochemica 116 (2014) 1185–1191

Contents lists available at ScienceDirect

Acta Histochemica

journal homepage: www.elsevier.de/acthis

Infrared LED light therapy influences the expression of fibronectin and tenascin in skin wounds of malnourished rats—A preliminary study

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ARTICLE INFO

Article history:
Received 11 April 2014
Received in revised form 23 June 2014
Accepted 24 June 2014

Keywords:
Malnourishment
Undernourishment
Wound healing
Light therapy
LED phototherapy
Tenascin
Fibronectin

ABSTRACT

The aim of this investigation was to evaluate the effect of infrared (λ 846 ± 20 nm) LED irradiation on the expression profile of the extracellular matrix protein components, tenascin and fibronectin on skin wounds induced in well nourished and malnourished rats. Eighteen albino rats (21 days old) were randomly divided into a well-nourished group (standard diet) and a malnourished group (regional basic diet). After receiving the diet for 70 days, skin wounds were created and the animals were subdivided into three groups: well-nourished control ($n = 6$), malnourished control ($n = 6$), and malnourished + LED irradiated (λ 846 ± 20 nm, 100 mW, 4 J/cm^2) ($n = 6$). The animals were sacrificed 3 and 7 days after injury and histological sections were immunostained for both proteins. They were examined for the presence, intensity, distribution and pattern of immunolabeling. At 3 days, the distribution of tenascin was shown to be greater in the wound bed of malnourished animals compared to the well-nourished group. The intensity and distribution of tenascin was shown to be lower in the malnourished LED irradiated group compared to the malnourished control. There was a significant difference regarding the presence of fibronectin in the malnourished and well-nourished groups after 7 days ($p = 0.03$). The intensity of fibronectin was slight (100%) in the irradiated group and moderate to intense in the malnourished control group. The results of the present study indicate that infrared LED irradiation modulates positively the expression of tenascin and particularly fibronectin.

Introduction

Tissue repair is a dynamic process that involves the interaction of soluble mediators, blood components, parenchymatous cells and extracellular matrix (Kumar et al., 2005). Among the extracellular matrix components, the non-collagen proteins fibronectin and tenascin are the largest glycoproteins that have known adhesion properties and play an important role in the tissue repair process (Mackie et al., 1988; Chiquet-Ehrismann and Tucker, 2000). Proper tissue repair requires an adequate environment. In this respect, several clinical factors can significantly compromise tissue repair including: hypoxia, infection, tumors, metabolic disorders, presence of debris and necrotic remnants, some medications, and a diet deficient in proteins, vitamins or minerals. In addition, the inflammatory process and increased cellular activity during wound healing increase the demand for proteins or amino acids, vitamins, and minerals (Mackay and Miller, 2003).

Malnutrition is a common condition in developing countries and is generally associated with low-income families with a larger number of household members, poor education, low development, poor housing conditions, and limited access to healthcare and food. The two main factors responsible for limited access to food are global

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http://dx.doi.org/10.1016/j.acthis.2014.06.006
0065-1281/

food shortage or an unequal distribution of food in certain regions, which more frequently deprives poor families of food (Gopalan, 2000).

The use of light therapies for tissue repair is less invasive, less costly and less time-consuming when compared to many of the other therapeutic modalities, in addition to being a practical method (Vinck et al., 2005). Irradiation with low-intensity light of the red and near-infrared spectrum (λ 630–1000 nm) has been shown to modulate various biological processes *in vitro* and *in vivo* (Karu, 1999; Pinheiro et al., 2004; Sousa et al., 2013). Since the introduction of the light-emitting diode (LED), it has been studied as an alternative source of photons for wound healing, pain relief and treatment of other pathological conditions (Weiss et al., 2005; Al-Watban and Andres, 2006).

The objective of the present study was to evaluate the effect of infrared LED light irradiation on the expression profile of the extracellular matrix protein components, tenascin and fibronectin, on skin wounds induced in well nourished and malnourished rats.

Materials and methods

The study was approved by the Ethics Committee of the School of Dentistry of the Federal University of Bahia. Eighteen male albino Wistar rats (*Rattus norvegicus*) 21 days old were obtained from the Animal House of the Faculty of Veterinary Medicine, Federal University of Bahia. The animals were kept at a controlled temperature of 22 °C under natural light conditions in individual cages covered with wood shavings that were changed daily. The animals were fed according to the experimental groups.

The animals were randomly divided into three groups ($n = 6$ per group): (1) a well-nourished control group consisting of animals fed standard Labina® chow (Purina); (2) a malnourished control group ($n = 6$) consisting of animals fed a regional basic diet (RBD) (Laboratory of Food Biochemistry, School of Nutrition, Federal University of Bahia, Salvador, Bahia, Brazil); and (3) a malnourished group fed RBD and irradiated with infrared (λ 846 ± 20 nm) LED light at 4 J/cm^2. The RBD consists of 37.1 g *Phaseolus vulgaris* (common bean), 13.9 g beef jerky, 32.0 g *Ipomoea batatas* (sweet potato), 67.4 g *Manihot esculenta* (manioc flour), 7.88% proteins, 69.96% carbohydrates, 0.60% fat, 1.27% minerals, and 7.70% fiber. Animals of all groups had access to water *ad libitum*.

After receiving the diet for 70 days, anesthesia was induced in the well-nourished and malnourished animals by intraperitoneal injection of 60 mg/kg ketamine hydrochloride (Ketalar®, Parke-Davis, Guarulhos, SP, Brazil) and 10 mg/kg xylazine (Rompum®, Bayer S.A., São Paulo, SP, Brazil). After anesthesia, the mid-region of the animal's back was shaved and antisepsis was performed with 2% chlorhexidine digluconate. Standard skin wounds measuring 1.0 cm × 1.0 cm were created in all animals and the flap obtained was excised. The wound was created with an instrument specifically developed for this purpose, which consisted of two scalpel handles joined together with screws and plugs in order to maintain a distance of 1.0 cm between blades and exact parallelism between them and the wound area corresponded to 1 cm^2. No sutures were performed in order to permit natural healing.

Next, animals of the experimental group only were irradiated with LED light. Animals of the control groups were handled in the same way as animals of the experimental group to standardize the level of stress caused by handling. A LED device was used for LED irradiation (FISIOLED, MMOptics® Equipment, São Carlos, Brazil). LED irradiation parameters are shown in Table 1.

Irradiation was performed in the contact mode. In each session, the wound area was irradiated only once, since the probe diameter of these LED prototypes is sufficient to cover the full extent of the wound. The protocol consisted of irradiation immediately after creation of the wound and subsequent irradiation sessions over a period of 3 or 7 days at intervals of 48 h. A spatial average energy fluence (SAEF) of 4 J/cm^2 per session was calculated based on the tissue area (1 cm^2) that was irradiated. This corresponded to a total SAEF of 8 and 16 J/cm^2 in the groups treated for 3 and 7 days, respectively, as the group treated for three days received two irradiation sessions and group treated for seven days received four irradiation sessions. In addition, energy density and energy values were 2 J/cm^2 and 4 J per session, respectively.

Table 1
Irradiation parameters used for the groups irradiated for 3 and 7 days.

Experimental period	Infrared LED	
	3 days	7 days
Wavelength (nm)	846 ± 20	846 ± 20
Energy fluence per session (J/cm^2)	4	4
Power output (mW)	100	100
Irradiated area (cm^2)	1.0	1.0
Spot area (cm^2)	2.0	2.0
Power density (mW/cm^2)	79.12	79.12
Irradiation time per session (s)	40	40
Total irradiation time (s)	80	160
Total energy fluence (J/cm^2)	8	16

After each treatment period, the animals were sacrificed by CO_2 inhalation and wound specimens were removed. The wound was excised with margins of 0.5 cm and stored for 24 h in a plastic flask containing 10% neutral buffered formalin. The specimen was divided into two parts in the medial portion and the fragments were processed for routine wax embedding and immunohistochemistry.

Immunohistochemistry was performed on 3 μm thick sections paraffin wax-embedded. The tissue sections were routinely deparaffinized and rehydrated. For antigen retrieval of tenascin (Clone 4C8MS, Novus Biologicals, Littleton, CO, USA, dilution 1:50), the tissue sections were treated with a 1% trypsin solution at 37 °C for 30 min, but no antigen retrieval was used for fibronectin (Clone AB23751, Abcam, Cambridge, UK). Endogenous peroxidase activity was blocked using hydrogen peroxide solution for 10 min. Next, the sections were incubated with the primary antibodies diluted in antibody diluent in addition to background-reducing components (Dako, Carpinteria, CA, USA) for 60 min for tenascin and 20 for fibronectin. The EnVision™ Polymer (Dako) was applied for 30 min at room temperature. The reaction was developed with diaminobenzidine (DAB; Dako, Glostrup, Denmark) as a chromogen. Finally, the sections were washed in distilled water and counterstained with Mayer's hematoxylin.

Sections of human placenta tissue with known tenascin and fibronectin immunostaining were used as positive controls. The negative control consisted of replacement of the primary antibody with non-immune bovine serum albumin.

The immunostained sections were analyzed in a blind fashion under a light microscope at 400× magnification (Zeiss Axiostar Plus, Göttingen, Germany). Up to five immunostained fields, in each case, were analyzed and the images were recorded with a digital camera (Zeiss Axiocam ICC3, Göttingen, Germany) using specific software (AxioVision, ver. 4.8, Carl Zeiss Microimaging, Göttingen, Germany). The slides were analyzed regarding the presence or absence, intensity (absent, slight, moderate, intense), distribution (absent, present in less than 25%, between 25% and 50%, more than 50%) and pattern of immunostaining (absent, fibrillar, reticular and both) in the wound bed. From each group 18 histological tissues were assessed for tenascin and fibronectin immunohistochemical reaction. The slides were assessed by an expert pathologist who was unaware of the experimental group or immunostainings.

Table 2
Semi-quantitative analysis of the presence, intensity, distribution and pattern of tenascin C expression in the wound bed according to the number and percentage of specimens per category.

Criteria	Group, *n* (%)					
	Nourished control 3 days	Nourished control 7 days	Undernourished 3 days	Undernourished 7 days	Undernourished + LED λ 846 nm 3 days	Undernourished + LED λ 846 nm 7 days
Presence						
Absent		1 (33%)				1 (33%)
Present	3 (100%)	2 (67%)	3 (100%)	3 (100%)	3 (100%)	2 (67%)
Intensity						
Absent		1 (33%)				1 (33%)
Discrete		2 (67%)			1 (33%)	
Moderated				1 (33%)	2 (67%)	
Intense	3 (100%)		3 (100%)	2 (67%)		2 (67%)
Distribution						
Absent		1 (33%)				1 (33%)
Less than 25%	2 (67%)	1 (33%)				1 (33%)
25–50%	1 (33%)	1 (33%)		1 (33%)	2 (67%)	
Over 50%			3 (100%)	2 (67%)	1 (33%)	1 (33%)
Expression pattern						
Absent		1 (33%)				1 (33%)
Fibrillar	1 (33%)	1 (33%)		1 (33%)	1 (33%)	1 (33%)
Reticular	2 (67%)	1 (33%)	3 (100%)	2 (67%)	2 (67%)	1 (33%)
Both						

Results

Semi-quantitative analysis of tenascin C and fibronectin immunostaining in skin wounds of well-nourished control and malnourished control rats, respectively are shown in Tables 2 and 3.

Intragroup analysis

Well-nourished controls (3 and 7 days)

At 3 days, all specimens of the well-nourished control group exhibited intense immunostaining for tenascin (Fig. 1A), whereas absent or slight staining was observed after 7 days (Fig. 1B). However, the difference between the two time points was not statistically significant ($P > 0.05$, Fischer exact test).

With respect to immunostaining for fibronectin staining, a significant difference was observed between the two time points ($P = 0.03$, Fischer exact test), with moderate expression of this protein in 100% of the specimens at 3 days after injury (Fig. 2A) and absent expression in all specimens at 7 days (Fig. 2B).

Malnourished controls (3 and 7 days)

No significant difference in the expression of fibronectin or tenascin was observed between malnourished control animals at 3 and 7 days (Figs. 1C and D and 2C and D). A reticular pattern of fibronectin expression was seen in all specimens at 3 and 7 days.

Table 3
Semi-quantitative analysis of the presence, intensity, distribution and pattern of fibronectin expression in the wound bed according to the number and percentage of specimens per category.

Criteria	Group, *n* (%)					
	Nourished control 3 days	Nourished control 7 days	Undernourished 3 days	Undernourished 7 days	Undernourished + LED λ 846 nm 3 days	Undernourished + LED λ 846 nm 7 days
Presence						
Absent						
Present	3 (100%)	100% (b) (a,b)	3 (100%)	3 (100%)(e) (b,e)*	3 (100%)	100% (f) (b,f)*
Intensity						
Absent		3 (100%)(d) (c,d)*				
Discrete			1 (33%)		1 (33%)	3 (100%) (g) (d,g)*
Moderate	3 (100%)(c)		1 (33%)	1 (33%)	1 (33%)	
Intense			1 (33%)	2 (67%)	1 (33%)	
Distribution						
Absent		3 (100%)				
Less than 25%	1 (33%)		1 (33%)	1 (33%)		2 (67%)
Between 25 and 50%	1 (33%)		1 (33%)			
More than 50%	1 (33%)		1 (33%)	2 (67%)	3 (100%)	1 (33%)
Expression pattern						
Absent		3 (100%)				
Fibrillar						2 (67%)
Reticular	2 (67%)		3 (100%)	3 (100%)	2 (67%)	
Both	1 (33%)				1 (33%)	1 (33%)

(a and b)*Statistical difference between Nourished Control 3 days and Nourished Control 7 days ($P = 0.03$); (c and d)*Statistical difference between Nourished Control 3 days and Nourished Control 7 days ($P = 0.03$); (b and e)*Statistical difference between Nourished Control 7 days and Undernourished 7 days ($P = 0.03$); (b and f)*Statistical difference between Nourished Control 7 days and Undernourished + LED λ 846 nm 7 days ($P = 0.03$); (d and g)*Statistical difference between Nourished Control 7 days and Undernourished + LED λ 846 nm 7 days ($P = 0.03$).

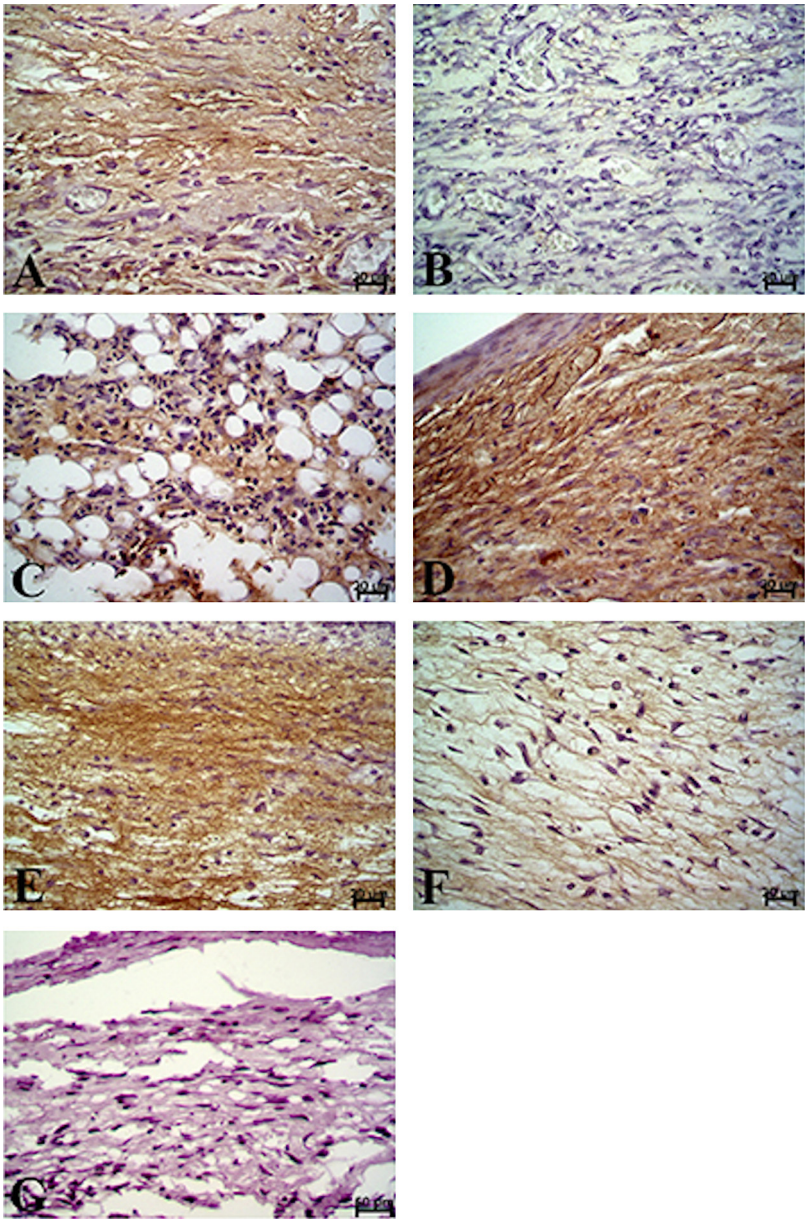

Fig. 1. Tenascin: (a) control specimen at 3 days. (b) Control specimen at 7 days. (c) Malnourished specimen at 3 days. (d) Malnourished specimen at 7 days. (e) Malnourished + LED irradiated specimen at 3 days. (f) Malnourished + LED irradiated specimen at 7 days. (g) Negative control.

With respect to tenascin, intense staining and a reticular pattern of expression predominated at the two time points.

Malnourished + LED (λ 846 nm ± 20 nm; 3 and 7 days)

There was no significant difference in fibronectin or tenascin expression between malnourished + LED λ 846 nm for 3 and 7 days ($P > 0.05$, Fisher exact test) (Figs. 1E and F and 2E and F). However, fibronectin staining was more slight and sparsely distributed at 7 days, in addition to exhibiting a fibrillar or mixed pattern, although this difference was not statistically significant.

Intergroup analysis

Well-nourished and malnourished control

Intense tenascin staining was observed in the well-nourished and malnourished control groups at 3 days after injury (Fig. 1A and C). Fibronectin staining was reticular in all specimens of the malnourished control group at 7 days (Fig. 2D), whereas no staining was observed in any of the specimens of the well-nourished control group (Fig. 2B). This difference was statistically significant ($P = 0.03$, Fischer exact test).

Malnourished + LED (λ 846 ± 20 nm) × well-nourished control

No difference in tenascin staining was observed between the malnourished group irradiated with infrared LED light and the well-nourished control group (Fig. 1A and E, B and F) ($P > 0.05$, Fisher exact test). Slight fibronectin staining was seen in all specimens of the irradiated group, whereas staining was absent in all specimens of the well-nourished control group (Fig. 2F and B) ($P = 0.03$).

Malnourished + LED (λ 846 ± 20 nm) × malnourished control

Comparison of both proteins showed no significant difference between irradiated malnourished + LED λ 846 nm animals (Figs. 1E and F and 2E and F) and malnourished animals (Figs. 1C and D and 2C and D) at either time point ($P > 0.05$, Fisher

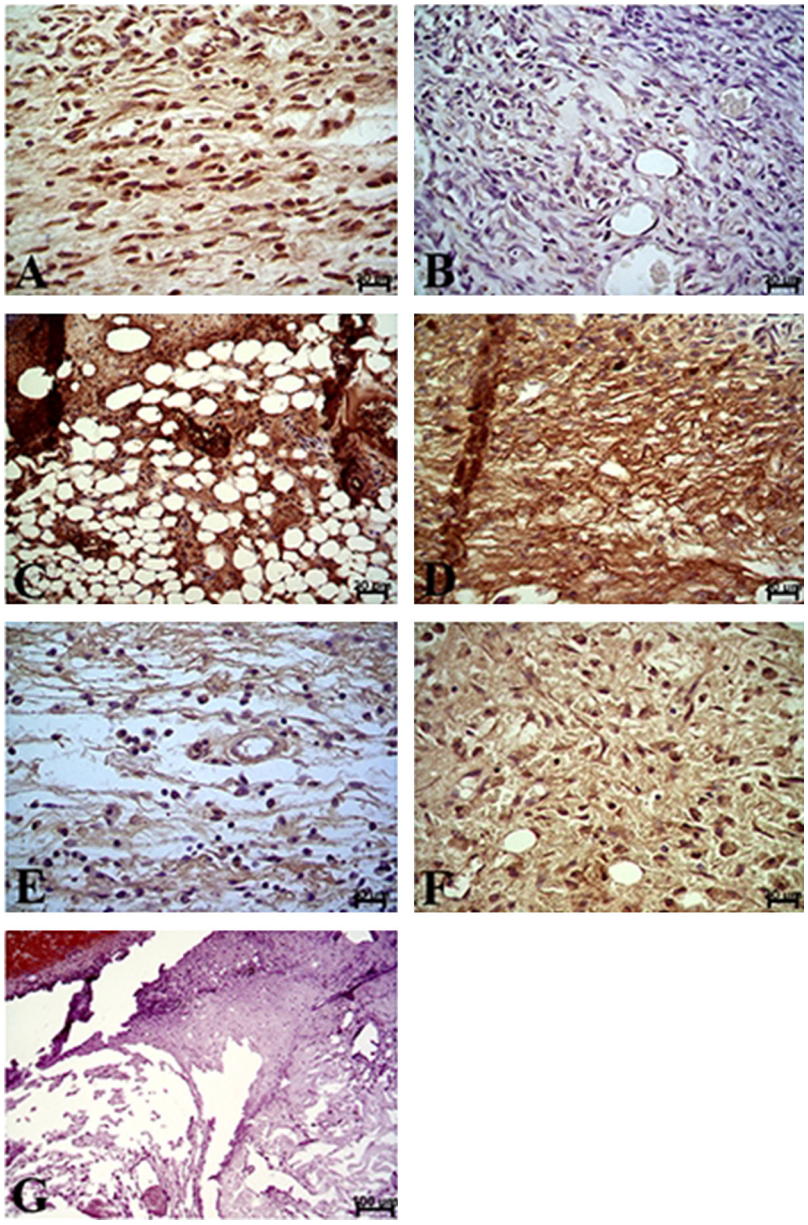

Fig. 2. Fibronectin: (a) control specimen at 3 days. (b) Control specimen at 7 days. (c) Malnourished specimen at 3 days. (d) Malnourished specimen at 7 days. (e) Malnourished + LED irradiated specimen at 3 days. (f) Malnourished + LED irradiated specimen at 7 days. (g) Negative control.

exact test). There was a less intense and sparsely distributed expression of tenascin in the malnourished + LED λ 846 nm group at 3 days (Fig. 1E), as well as sparsely distributed expression of fibronectin, although this difference was not statistically significant. At 7 days, moderate to intense fibronectin expression was seen in the malnourished control group (Fig. 2D), but slight in all specimens of the LED irradiated group (Fig. 2F). Also regarding fibronectin expression, although there was a significant difference ($P = 0.03$) in the intensity of expression between the malnourished + LED λ 846 nm group (100% slight) and the well-nourished control group (100% absent), the LED irradiated group (Fig. 2F) more closely resembled the well-nourished control group (Fig. 2B) than the malnourished group (moderate to intense).

Discussion

Our results showed that tenascin and fibronectin were expressed during the early phase of skin wound healing in all specimens, irrespective of systemic condition, whereas a reduction in the expression of these proteins was seen in the well-nourished group at the end of the period studied. These findings are in agreement with other studies that show transient expression of tenascin (Mackie et al., 1988; Betz et al., 1993; Willems et al., 1996; Chiquet-Ehrismann and Chiquet, 2003; Tamaoki et al., 2005; Midwood and Orend, 2009) and fibronectin (Mackay and Miller, 2003; Lenselink, 2013; To and Midwood, 2011) in the wound bed during tissue repair under normal metabolic conditions, with the expression of these proteins decreasing with progression of wound healing (Mackay and Miller, 2003; Tamaoki et al., 2005).

Previous studies have demonstrated an association between the lack of expression of tenascin C and deficient and fibrotic repair of different tissues in an animal model (Tamaoki et al., 2005; Okamura et al., 2010). In contrast, marked transient expression of this protein has been observed during the repair of different types of tissues such as infarcted myocardium (Willems et al., 1996; Dobaczewski et al., 2010), injured cartilage (Okamura et al., 2010),

and skin wounds in animals (Mackie et al., 1988; Fassler et al., 1996; Midwood and Orend, 2009). Similarly, we also observed intense expression of tenascin in the well-nourished group 3 days after injury and a reduction of expression at 7 days.

Like tenascin, fibronectin is expressed specifically during the early phase of wound healing in animal models (To and Midwood, 2011), as also demonstrated in the present study. In the well-nourished group, moderate expression of fibronectin was observed during the early phase of wound repair, whereas expression was absent in the final stage of wound healing and this difference was significant. With respect to the chronology of wound healing, studies have shown that fibronectin is deposited within a few minutes (Ortiz-Rey et al., 2003) to several hours after injury (Igisu, 1986), forming a scaffold of serum and tissue fibronectin (Gopalan, 2000; Kumar et al., 2005; To and Midwood, 2011). According to Midwood and Orend (2009), the systemic condition of the organism can influence the activity of these extracellular matrix proteins in the wound bed. In the present study, expression of tenascin and fibronectin was still observed in all specimens from malnourished animals 7 days after injury. Separate analysis showed a wider distribution of tenascin at 3 days and a marked intensity and wider distribution of this protein at 7 days in the malnourished group when compared to well-nourished animals, but the difference was not significant. Tenascin expression has been associated with chronic wounds in different tissues and *in vivo* models (Midwood and Orend, 2009; Chowdhury et al., 2010; Goh et al., 2010; Brissett et al., 2013).

Immunostaining for fibronectin was absent in all specimens from the well-nourished group 7 days after injury, but was still present in all specimens from the malnourished group, with this difference being significant. Persistence of fibronectin has also been observed in the presence of other chronic injuries (McDermott et al., 2003; Zack et al., 2006; Arslan et al., 2011; Stoffels et al., 2013). However, the prolonged presence of fibronectin, even when structurally altered, contributes to the failure of regeneration as a result of persistent chronic inflammation mediated by different mechanisms, increasing the degradation of injured tissue and compromising its repair (Summers et al., 2009; Stoffels et al., 2013). Fibronectin therefore needs to be degraded and removed to make room for collagen deposition, which will provide tensile strength to the final scar (Enoch and Leaper, 2005; Singh et al., 2010).

In the present study, immunostaining for fibronectin was less intense than immunostaining for tenascin with no significant difference. This finding might be attributed to the regulatory role of tenascin in the deposition and activity of fibronectin. In this respect, Chiquet-Ehrismann et al. (1988) demonstrated that tenascin interferes with the fibroblast attachment activity of fibronectin, inhibiting the *in vitro* migration of these cells. Matsuda et al. (2005) observed reduced deposition of fibronectin in corneal sutures of animals that did not express tenascin.

Analysis of the expression pattern showed a reticular pattern of fibronectin expression in all specimens from malnourished animals at 3 and 7 days after injury. Similar findings have been reported by Ortiz-Rey et al. (2003) who observed a reticular pattern in 90% of cases expressing fibronectin and in 80% of cases expressing tenascin 15 min after tissue injury. It is possible to suggest that malnutrition prolongs the deposition of fibronectin over days in patterns similar to those seen during the early phase of normal wound healing.

With respect to the role of infrared LED light therapy, we hypothesize that this therapy exerts a biomodulatory effect on extracellular matrix proteins in malnourished rats. However, no significant difference in the expression of tenascin or fibronectin was observed between the irradiated and untreated malnourished groups at any of the time points studied. It is possible that malnutrition, induced in the animals of this study had a constitutive effect on wound healing, which was not overcome by LED phototherapy (λ 846 nm ± 20 nm). Nevertheless, the irradiated malnourished group more closely resembled the well-nourished group and differed from untreated malnourished animals. At 7 days after injury, a reduction in the presence, intensity, and distribution of tenascin expression was observed in the irradiated malnourished group, whereas high expression of this protein was seen in untreated malnourished animals, although the difference was not significant. This finding impairs speculation about the influence of infrared light therapy on this protein, although the qualitative differences mentioned above suggest a possible biomodulatory effect on the expression of tenascin in malnourished rats. With respect to fibronectin, despite a significant difference in the intensity of expression between the irradiated malnourished group and well-nourished control, the former was qualitatively more similar to the well-nourished than to the malnourished control, suggesting a positive biomodulation of fibronectin expression.

There appears to be no study of LED phototherapy in malnourished animals focusing on tenascin and fibronectin. However, a few studies have reported beneficial effects of laser and/or polarized light phototherapies in improving wound healing in malnourished animals (Pinheiro et al., 2004, 2009). Pinheiro et al. (2004) showed that laser phototherapy (λ 630 nm, 20 J/cm^2) and polarized light (λ 400–2000 nm, 20 J/cm^2) can improve wound repair in RBD-induced malnourished rats, and Pinheiro et al. (2009) showed that laser exerts a biomodulative effect on fibroplasia of malnourished animals (λ 635 nm, 20 J/cm^2 and λ 780 nm, 40 J/cm^2) more than nourished ones. In this study, we hypothesized that tenascin and fibronectin expression in wounds of malnourished animals could be two of the major components of the stromal scaffold in wound healing.

Finally, the present study suggests that infrared (λ 846 ± 20 nm) LED light therapy, using the present parameters, modulates positively the expression of tenascin and particularly fibronectin. However, further studies are needed to elucidate the mechanisms of this therapy that underlie wound healing in malnourished animals.

Acknowledgment

The authors gratefully thank the Coordenação de Pessoal de Nível Superior (CAPES) for financial support.

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