

A Possible Role of Endoneurial Fibroblast-Like Cells in the Resolution of Endoneurial Oedema Following Nerve Crush Injury

El Posible Rol de los Fibroblastos Endoneurales en la Resolución del Edema Endoneural Después de una Lesión por Aplastamiento Nervioso

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SUMMARY: Endoneurial oedema is a salient feature of all types of neuropathy. Its elimination is crucial during the complications of nerve recovery. The objective was to study a possible role of the endoneurial fibroblasts in the resolution of nerve edema. Forty-two albino male rats aged between 30 and 40 days (weight 200 g to 250 g) were used in this study. The left sural nerves of 36 rats were subjected to crush injury at one to three-week intervals with six animals per interval. The right and left sural nerves of the remaining six rats were used as controls. At the end of the second week after crush injury, the endoneurium showed channel-like spaces that were lined by fibroblast-like cells and collagen bundles that contained degenerated myelin, and were connected to the subperineurial spaces. Flattened fibroblast-like cells were arranged in several layers in the subperineurial, forming barrier-like cellular sheets localizing to the endoneurial oedema in the space. Fibroblast-like cells also wrapped around the regenerating nerve fibres with their branching cytoplasmic processes. During the third week, the flattened fibroblast-like cells formed nearly continuous cellular sheets in the subperineurial spaces. Macrophages were frequently observed between these cellular barrier-like sheets and in the subperineurial. The endoneurial fibroblast-like cells form barrier-like cellular sheets that probably localise the endoneurial oedema in the subperineurial space. It also appear to create endoneurial channel-like spaces containing degenerated myelin and endoneurial oedema, which may be helpful in localizing and resolving such oedema.

KEY WORDS: Sural Nerve; Endoneurial Fibroblast-Like Cells; Endoneurial Oedema; Barrier-Like And Channel-Like Spaces.

INTRODUCTION

Fibroblast-like cells play a central role in various diseases of different organs, including the synovial membranes of diseased joints (Kontoyiannis & Kollias, 2000; Mor *et al.*, 2005), the myocardium (Takemura *et al.*, 1998; Hayakawa *et al.*, 2003; Yano *et al.*, 2005), and the liver (Jodon de Villeroché & Brouty-Boyé, 2008). These cells are mostly differentiated into different types, such as neurons, corneal cells, osteoblasts, chondrocytes, adipocytes, cardiomyocytes, hepatocytes, and pancreatic islet cells. Despite originating from a non-embryonic source, they express stem cell markers that are important for maintaining an undifferentiated state. This multipotent property makes these cells a promising therapeutic target (Dravida *et al.*, 2005; Giovannini *et al.*, 2008). In rheumatoid arthritis, fibroblast-like cells, called fibroblast-like synovial cells (FLS) stimulate the inflammatory process and directly attack the cartilage and bones. Moreover, FLS modulate the

autoimmune response, and are crucial in the pathogenesis of rheumatoid arthritis (Kontoyiannis & Kollias; Mor *et al.*). Fibroblast reorganisation is associated with neoplastic progression, and is associated with the inflammatory process, and macrophage recruitment is associated with neoplasia (Coussens & Werb, 2002; Allinen *et al.*, 2004; Amatangelo *et al.*, 2005).

Fibroblasts control local and distant angiogenesis mediated by bone marrow stem cells; however, they are transformed into invasive types and myofibroblasts (De Wever & Mareel 2003; Orimo *et al.*, 2005) within the stroma of invasive cancers of the breast, colon, ovaries, pancreas and prostate (Kalluri & Zeisberg, 2006). After wound injury, fibroblasts are activated and help recruit mesenchymal stem cells that play a role in wound healing (McGee *et al.*, 2013). Cardiac fibroblasts are transformed into myo-fibroblasts,

which are important in tissue contraction and repair after myocardial infarction (Takemura *et al.*; Yano *et al.*). Moreover, they can be converted into a myogenic phenotype, which may be helpful for the treatment or prevention of myocardial infarction (Salvatori *et al.*, 1995; Wise *et al.*, 1996; Etzion *et al.*, 2002; Goldsmith *et al.*, 2004; van Tuyn *et al.*, 2007). The biliary tract and hepatic epithelial cells arise from the portal tracts surrounding ducts, where fibroblasts are abundant (Crosby *et al.*, 2001; Libbrecht *et al.*, 2002; Li *et al.*, 2013; Lemoine *et al.*, 2013). In vitro studies using fibroblasts from different tissues showed that fibroblasts display distinct behaviour according to the anatomic site and the disease status (Chang *et al.*, 2002; Parsonage *et al.*, 2003).

Endoneurial oedema is a prominent feature in most types of neuropathies (McManis *et al.*, 1986; Olsson, 1989; Pedowitz *et al.*, 1991; Gabreëls-Festen *et al.*, 1993; Eaton *et al.*, 1996; Maxfield *et al.*, 1997). It has a major role in reducing the endoneurial blood flow and subsequent degeneration of the nerve fibres (Maxfield *et al.*). During nerve regeneration, the endoneurial oedema subsides, leading to decreased endoneurial pressure and increased blood flow (Low *et al.*, 1985; Gonda *et al.*, 2010; Kobashigawa *et al.*, 2011). In diabetic neuropathy, the progressive nerve fibre loss may be attributed to the persistent nature of the endoneurial oedema (Low *et al.*). Endoneurial oedema accumulates primarily in the subperineurial and perivascular spaces (Pedowitz *et al.*; Gabreëls-Festen *et al.*). The reason for this localisation and fate of the accumulated endoneurial oedema in different types of neuropathies remains unclear. The question remains, do fibroblast-like cells have a role in nerve regeneration and the localisation or resolution of endoneurial oedema following nerve injury. Therefore, the present study assessed endoneurial fibroblast-like cells and their possible role in the localisation and resolution of endoneurial oedema.

MATERIAL AND METHOD

Forty-two albino adult male Sprague-Dawley rats were used in this study, weighing 200 to 250 g and aged 30-40 days. A total of 36 rats were initially anaesthetised by ether inhalation, followed by an intraperitoneal injection of penta-barbitone sodium (Sagatal; 60 mg/ml) at a dose of 30 mg/kg body weight. Anaesthesia was maintained during surgery by repeated intraperitoneal injection of penta-barbitone sodium. The left sural nerves were exposed and subjected to crush injury just distal to its origin from the tibial nerve using non-toothed forceps for 10 seconds. The right and left sural nerves of the remaining 6 rats were used as a control group. At set intervals ranging from 1 to 3 weeks

after the nerve crush, 12 animals were re-anaesthetised initially by ether inhalation, and then weighed and injected with penta-barbitone sodium according to their weight. The crushed nerves were re-exposed and collected. A 2.5 mm segment at the site of the crush was discarded. The remaining nerve was segmented into 2.5 mm segments, fixed in 2.5 % glutaraldehyde then post-fixed in 2 % osmium tetroxide. The nerve segments were dehydrated in graded concentrations of ethanol and embedded in Araldite resin. Semithin sections of 1 µm were obtained and stained with toluidine blue in borax for light microscopy. Ultrathin sections of 0.07 µm were stained with uranyl acetate and lead citrate for electron microscopy. Sural nerve segments were also collected from the normal nerves and processed similarly.

Light Microscopic Study

Light Microscopic Study of Normal Sural Nerves. The endoneurium contained myelinated nerve fibres with different diameters and thicknesses of their myelin sheaths. There were few scattered endoneurial fibroblasts with short cytoplasmic processes throughout the endoneurium without special arrangement. The subperineurial space contained myelinated nerve fibres (Fig. 1A).

Light Microscopic Study of Crushed Nerves. One week after the crush injury, the endoneurium showed a significant increase of the number of endoneurial fibroblasts and fibroblast-like cells with long cytoplasmic processes. Some were scattered in the endoneurium, whereas others surrounded the regenerating nerve fibres. Fibroblast-like cells surrounded the regenerating nerve fibres. There was an increase in degenerated myelin and endoneurial macrophages (Fig. 1B).

Two weeks after the crush injury, the flattened fibroblast-like cells were arranged in multiple cellular layers in the subperineurial space. The flattened cytoplasmic processes of the fibroblast-like cells were attached in the majority of layers, forming subperineurial barrier-like cellular sheets. Fibroblast-like cells also surrounded the regenerated nerve fibres, isolating them in special compartments. The spaces between the fibroblast-like cellular sheets and perineurium contained accumulated endoneurial oedema, in addition to some of the endoneurial macrophages carrying degenerated myelin (Fig. 1C).

Three weeks after the crush injury, the fibroblast-like cells were arranged in a nearly continuous cellular sheet in the subperineurial space, forming a cellular barrier-like structure. Other cells surrounded the regenerating groups of nerve fibres. The subperineurial space contained endoneurial oedema and endoneurial macrophages (Fig. 2).

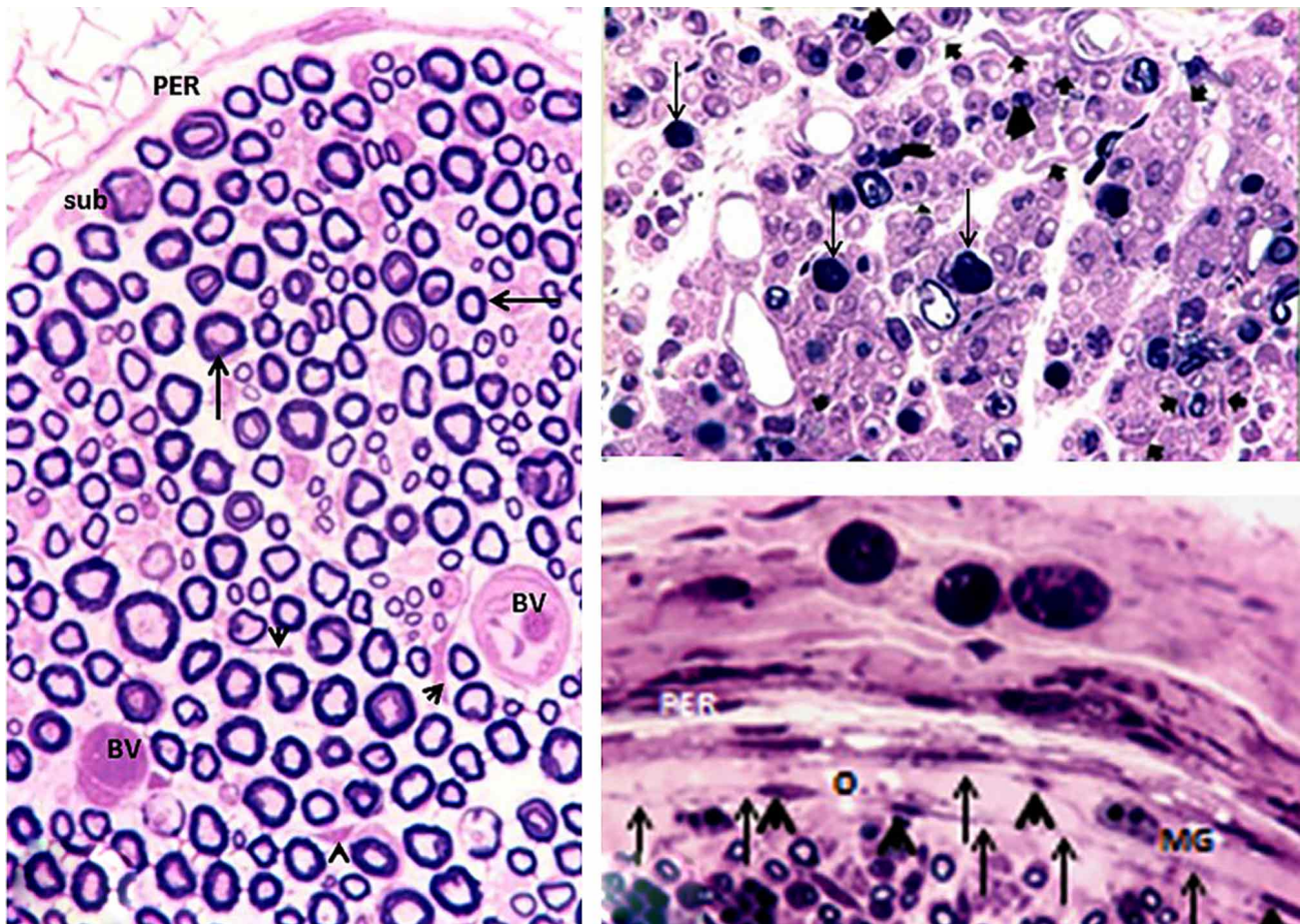


Fig. 1A. A normal sural nerve showing the perineurium (PER), endoneurium containing myelinated nerve fibres (long arrows), few scattered fibroblasts (arrow heads) and the endoneurial blood vessels (BV). B. One week after the crush, there are increased degenerated myelin (long arrows), increased number of endoneurial fibroblasts (short arrows). C. After two weeks of the crush injury, the endoneurial fibroblast-like cells form several cellular sheets in the subperineurial space (arrows) forming barrier-like sheets. O, subperineurial oedema, MG; macrophages, PER; perineurium, BV; blood vessels. X 400.

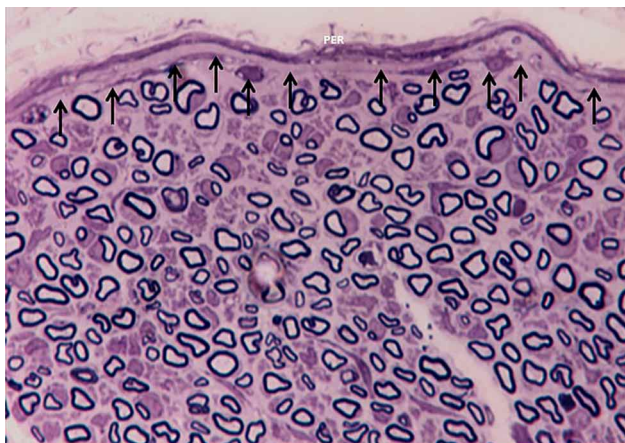


Fig. 2. After three weeks after the crush injury, the endoneurial fibroblast-like cells form a nearly continuous cellular sheet in the subperineurial space (arrows) localizing the subperineurial oedema. PER; perineurium. X 400.

Electron Microscopic Study

Normal Sural Nerves. The endoneurium showed myelinated and non-myelinated nerve fibres along with collagen bundles together with the endoneurial blood vessels. Endoneurial fibroblasts were few and scattered in the endoneurium, and a few had longer cytoplasmic processes. The subperineurial spaces were filled with collagen bundles and nerve fibres (Fig.3A).

Crushed Sural Nerve. One week after the crush injury, the endoneurium showed the accumulation of endoneurial oedema indicated by the wide separation of collagen fibrils. It showed an increased number of flattened endoneurial fibroblast-like cells, with long cytoplasmic processes that wrapped the regenerating unmyelinated or thinly myelinated nerve fibres, in most of the specimens. There were areas of contact between these cytoplasmic processes and the nearby

endoneurial macrophages. Some of the endoneurial fibroblasts were flattened and fibroblast-like, whereas others appeared fusiform (Figs. 3B, C).

After two weeks after the crush, the endoneurial fibroblast-like cells were arranged in cellular layers in the subperineurial and around the regenerating nerve fibres, forming barrier-like cellular sheets (Figs. 4). Channel-like spaces appeared in the endoneurium. These spaces are lined by fibroblast-like cells and collagen bundles and contained degenerated myelin debris and accumulated endoneurial oedema. The channel-like spaces were continuous with the subperineurial space. The endoneurial macrophages had areas of contact with the endoneurial fibroblast-like cells.

The subperineurial barrier-like sheets were interrupted where the channel-like spaces communicated the subperineurial space and also where the endoneurial macrophages were located (Fig. 4). The endoneurium was divided into areas of regenerated nerve fibres surrounded by the cytoplasmic processes of the fibroblast-like cells (Fig. 4).

During the third week after the crush injury, the endoneurial fibroblast-like cells were apparently decreased in number, with the disappearance of most of the endoneurial channel-like spaces. The fibroblast-like cells wrapped the regenerating nerve fibres in most of the specimens and formed single subperineurial cellular sheet (Fig. 5).



Fig.3. A. Normal sural nerve with myelinated (m), unmyelinated (u) nerve fibres and collagen bundles (C) in the subperineurial (SUB) space. PER, perineurium. Scalebar 1 μ m. B. One week after crush injury, the endoneurial fibroblast (F) and the endoneurial fibroblast-like cells were increased in the subperineurial space among the regenerating nerve fibres, there is accumulation of endoneurial oedema (O). Scale bar, 5 μ m. C. Endoneurial fibroblasts with long cytoplasmic processes (pr), with cytoplasmic rough endoplasmic reticulum (rER) and mitochondria (M) that partially surrounded the regenerating nerve fibres (R) and have areas of contacts with the endoneurial macrophage (MG), one week after the crush. Scale bar, 2 μ m.

DISCUSSION

Traumatic nerve injury and various pathological conditions result in the accumulation of endoneurial oedema;

a salient feature in most types of neuropathies (Pedowitz *et al.*; Gabreëls-Festen *et al.*). Diabetes is one of the most

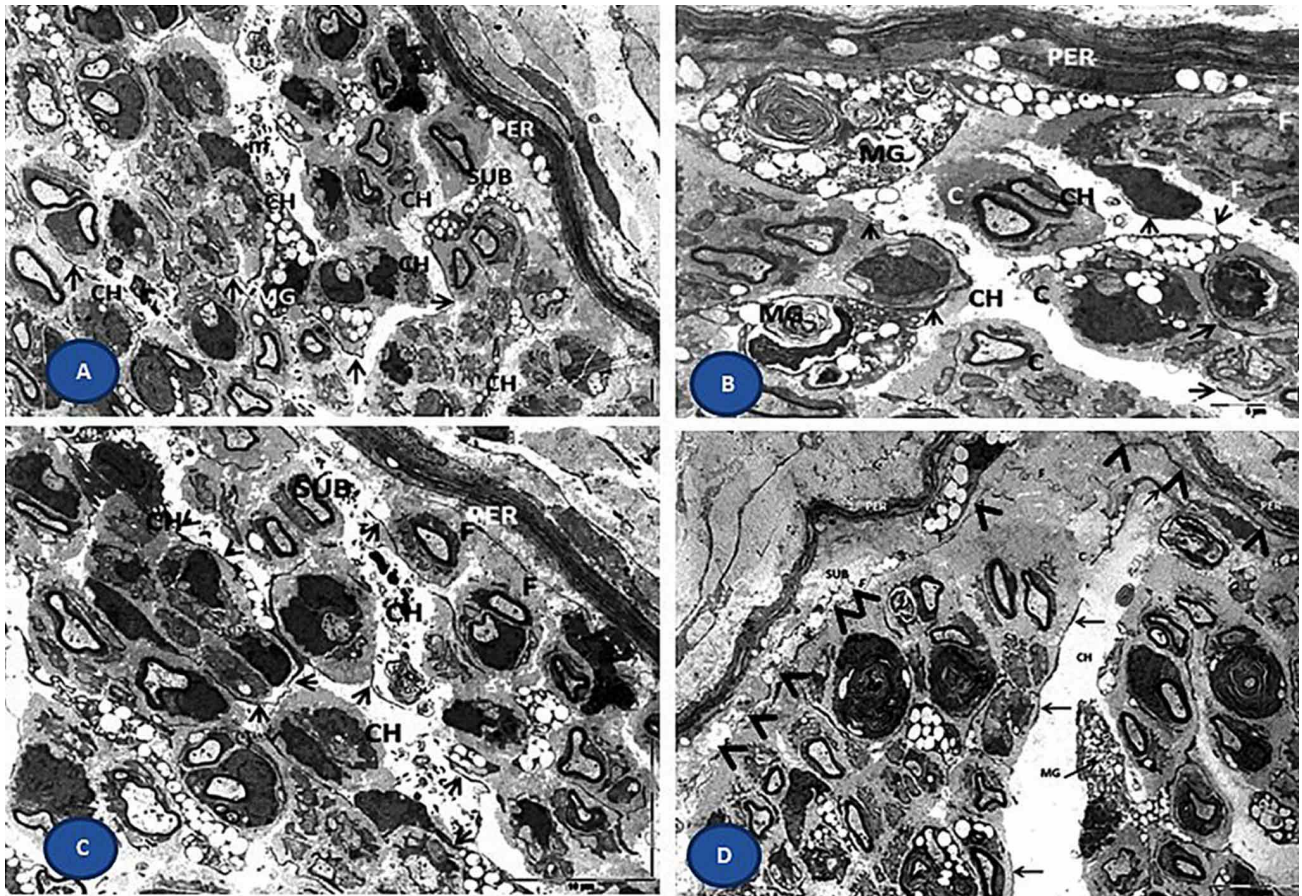


Fig. 4. The sural nerve after 2 weeks of the crush injury shows the endoneurial channel-like spaces (CH) lined by fibroblast-like cells (arrows) and collagen bundles (C). They contain degenerated myelin and endoneurial macrophages (MG), and some are continuous with the subperineurial (Figs. 5A-5D). Fig. 5D shows subperineurial cellular barrier-like sheets of fibroblast-like cells (arrow heads). PER, perineurium. Scale bars 10 μ m, 2 μ m, 10 μ m and 10 μ m, respectively.

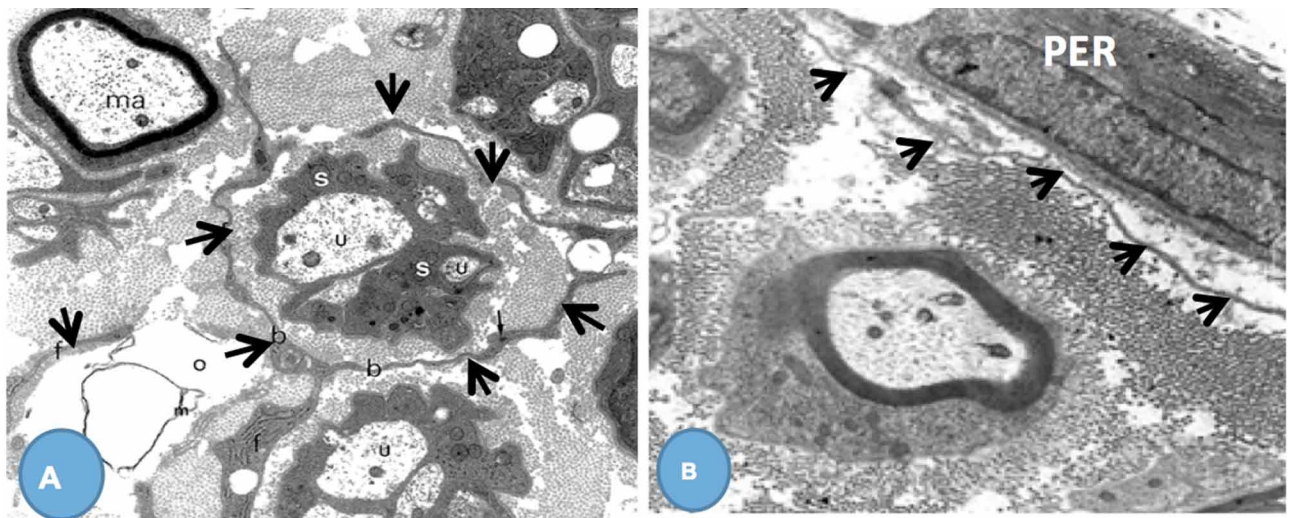


Fig. 5. The sural nerve during the third week after crush injury showing the endoneurial fibroblast-like cells (arrows) surrounding the regenerating nerve fibers in A. and form cellular sheet in the subperineurial space in B. PER, perineurium; ma, myelinated nerve fibers; s, Schwann cells, o, oedema; u, unmyelinated nerve fibers

common diseases that produce persistent peripheral neuritis as a result at least partially to the resulting endoneurial oedema secondary to effects on the vasa nervosa of the peripheral nerves (McManis *et al.*; Maxfield *et al.*).

Accumulation of endoneurial oedema is a result of damage to the blood-nerve barrier, which is consisted of the endoneurial blood vessels and the inner cellular layer of the perineurium. Consequently, the permeability of the endoneurial blood vessels increases and the accumulation of endoneurial oedema more in the subperineurial and perivascular spaces, although there is no clear explanation for such sites of accumulation (Pedowitz *et al.*). It results in an increase of intraneural pressure, which in turn reduces the blood flow in the endoneurium and endoneurial oxygen tension. The mechanical affection of the perineurial and epineurial blood vessels are observed to be resulted in degeneration of the nerve fibres (Low *et al.*; Gonda *et al.*, 2010).

Ultra-structural studies of the recovering crushed peripheral nerves showed marked progressive reduction of the endoneurial oedema until it resolves completely (Pedowitz *et al.*; Gabreëls-Festen *et al.*). Consequently, nerve recovery after traumatic or pathological injury depends mainly on the resolution of endoneurial oedema, thus decreasing the intraneural pressure and increasing the endoneurial blood flow. It was reported that the maximum accumulation of endoneurial oedema was during the second week following the traumatic injury to the peripheral nerve, which coincides with the maximum increased permeability of the blood-nerve barrier (Pedowitz *et al.*). The rate of resolution of such an oedema will match the rate of functional nerve recovery. The fate of the endoneurial oedema, together with the cellular events and mechanisms of its resolution, remain unclear.

The present study showed that differentiated endoneurial fibroblast-like cells, in the segments distal to the site of the crush injury of the sural nerve, were apparently increased. These cells were flattened with long branching cytoplasmic processes that contained, in many cases, pinocytotic vesicles with areas of contacts in between. During the second week after nerve crush injury, the flattened fibroblast-like cells formed cellular barrier-like layers in the subperineurial space. During the third week following crush injury, a barrier-like cellular layer was a complete sheet of cells interrupted at sites where the endoneurial oedema communicated with the subperineurial oedema. The cellular sheet made by the fibroblast-like cells were isolated from the inner cellular layer of the perineurium by the accumulated subperineurial oedema which could explain the subperineurial accumulation of the endoneurial oedema following nerve injury.

The current study also showed that the fibroblast-like cellular barrier-like sheets probably aimed at supporting the disturbed inner cellular layer of the perineurium; one site of the blood-nerve barrier. Such subperineurial accumulation of oedema could also increase the fluid pressure in the subperineurial, which may help in the absorption of the endoneurial oedema through the perineurium into the epineurial blood vessels. The scattered endoneurial fibroblasts and the absence of fibroblast-like cellular barrier-like sheets in the normal nerves may support this hypothesis.

During the current study, the endoneurial fibroblast-like cells together with the collagen bundles wrapped around groups of the regenerated nerve fibres, thus creating endoneurial channel-like spaces in-between. These spaces were bounded on both sides by fibroblast-like cells and collagen bundles and contained degenerated myelin and endoneurial oedema. In most of the specimens, endoneurial macrophages made part of the wall of these channel-like spaces. The subperineurial space was in the communication of these spaces in certain areas of the endoneurium. Therefore, endoneurial oedema can reach the subperineurial where its absorption and resolution can occur. It is suggested that movements of the long processes of the fibroblast-like cells may create a current for the direction of the endoneurial oedema in these spaces towards the subperineurial. Moreover, isolation of the regenerated nerve fibres by fibroblast-like cells can help the regenerative process of the nerve fibers.

The stroma of the tumours contains an increased number of cancer-associated fibroblasts (CAFs) which are pro tumorigenic. There is growing evidence that CAFs are genetically different from the normal fibroblasts and could be potential targets for anti-cancer therapy.

Evidence that is epigenetically and possibly also genetically distinct from normal fibroblasts is beginning to define these cells as potential targets for anti-cancer therapy (Kobashigawa *et al.*, 2011). On the other hand researchers found that the blood-borne fibroblast-like cells have the common surface markers of the hematopoietic stem cells CD34 (37).

Endoneurial Fibroblast-Like Cells might represent around 2 percent to 9 percent of the endoneurial cells. The spindle shaped cells on electron microscopy (EM) with rectangular or triangular bodies of cells when viewed in the transverse section. They have long processes of cytoplasmic that expands either laterally between nerve fibers or along the nerve trunk; these types of processes usually loosely interdigitate with the neighbouring endoneurial

fibroblast-like cells and also enclose one or various Schwann cells. In contrast with the Schwann cell nuclei, their nuclei seem paler and their cell membrane represents micropinocytotic vesicles in smooth invaginations. The cytoplasm of endoneurial fibroblast-like cells contains Golgi apparatus, prominent endoplasmic reticulum and scattered mitochondria which is frequently orientated and is dilated in places and more or less in parallel arrays. Granular material is present in the cisternae. These cells comprise of only a few lysosomes in normal nerves. It is very complex to distinguish between extremely convoluted cells and intracytoplasmic vacuolation observed in cross section. Intermittently, the cytoplasm of endoneurial fibroblast-like cells is invaginated by bundles of collagen that is present in the plasma membrane with direct contact (Richard *et al.*, 2012, 2014).

CONCLUSION

The results indicated that fibroblast-like cells might play an important role in localising the endoneurial oedema in the subperineurial space by forming barrier-like cellular sheets. These cells also lined channel-like endoneurial spaces that contained degenerated myelin and oedema and are continuous with the sub-perineurial space. Consequently, fibroblast-like cells may play an important role in the localization of endoneurial oedema following crush injury. Immunohistochemistry study of the fibroblast-like cells in normal and crushed nerves is recommended.

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RESUMEN: El edema endoneural es una característica destacada de todos los tipos de neuropatía. Su eliminación es importante durante las complicaciones de la recuperación nerviosa. El objetivo fue estudiar un posible papel de los fibroblastos endoneurales en la resolución del edema nervioso. En este estudio se utilizaron 42 ratas macho albinas con edades entre los 30 y 40 días (peso 200 a 250 g). Los nervios surales izquierdos de 36 ratas se sometieron a lesiones por aplastamiento en intervalos de una a tres semanas con seis animales por intervalo. Se

usaron los nervios surales derecho e izquierdo de las seis ratas restantes como controles. Al final de la segunda semana después de la lesión por aplastamiento, el endoneuro mostró espacios en forma de canal que estaban revestidos por células similares a fibroblastos y haces de colágeno que contenían mielina degenerada y se conectaron a los espacios subperineurales. Las células aplanadas de fibroblastos se dispusieron en varias capas en el subperineuro, formando láminas celulares de tipo barrera que se localizaban en el espacio del edema endoneural. Las células similares a fibroblastos también envolvían las fibras nerviosas regeneradoras con sus procesos citoplásmicos ramificados. Durante la tercera semana, las células aplanadas de fibroblastos formaron láminas celulares casi continuas en los espacios subperineurales. Los macrófagos se observaron con frecuencia entre estas láminas similares a barreras celulares y en el subperineuro. Las células de tipo fibroblasto endoneural formaban láminas celulares de tipo barrera que probablemente localizan el edema endoneural en el espacio subperineural. También parece que crea espacios en forma de canal endoneural que contienen mielina degenerada y edema endoneural, que pueden ser útiles para localizar y resolver este edema.

PALABRAS CLAVE: Nervio sural; Células similares a fibroblastos endoneurales; Edema endoneural; Barreras y Espacios semejantes a canales.

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