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REVIEW ARTICLE

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Elastin and collagen fibres in cutaneous wound healing

Leire Gardeazabal[1] | Ander Izeta[1,2]

[1]Biogipuzkoa Health Research Institute, Tissue Engineering Group, Donostia-San Sebastián, Spain

[2]Department of Biomedical Engineering and Sciences, Tecnun-University of Navarra, Donostia-San Sebastián, Spain

Correspondence
Ander Izeta, Biogipuzkoa Health Research Institute, Tissue Engineering Group, Paseo Dr Begiristain s/n, 20014, Donostia-San Sebastián, Spain.
Email: ANDER.IZETAPERMISAN@osakidetza.eus

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Abstract

Skin forms the outer barrier of the body. Upon injury, successful wound healing in normal skin restores tissue damage and counteracts the loss of extracellular matrix (ECM) proteins and cells. Collagens and elastin are the most abundant structural proteins of the ECM. In homeostasis, collagen type I is the prevalent form, but it is replaced by type III collagen upon wounding, and only later remodelled. In turn, unsuccessful healing results in scars, which tend to be inflexible and inelastic as compared to normal elastic dermis. Scar inelasticity may be due to the absence of mature elastin fibre formation and cross-linking. In this review, the available information on the process of formation of new collagen and elastic fibres during wound healing is analysed. The distinct roles of elastin and collagen proteins during healing are revisited and future research directions proposed which may help improve clinical management of open wounds and scars.

KEYWORDS
collagen, elastic fibres, extracellular matrix (ECM), skin, wound healing

1 | INTRODUCTION

The skin serves as the body's main protective barrier, regulates and maintains body temperature and forms part of the somatosensory system.[1] The highly cellularized epidermis is the outermost layer of the skin, and is separated from the underlying dermis (vascularized and relatively acellular) by the basement membrane.[2,3] Beneath the dermis lies the subcutaneous hypodermis (Figure 1). The dermis is subdivided into the upper papillary layer, which supports the epidermis, and lower reticular dermis and dermal white adipose tissue layers, which present dense frameworks of extracellular matrix (ECM) components.[4]

In the dermis, fibroblasts are the most abundant cell type responsible for the synthesis, secretion and remodelling of ECM components, and also to communicate with other cell types such as immune cells.[5] There are several molecules found in the ECM including collagens, elastin, fibrillins, fibronectin, vitronectin, proteoglycans, laminin, fibrin, tenascin, integrins and laminins.[6,7] The two most abundant proteins in the skin are collagen and elastin. Collagen accounts for approximately 50%–90% of the integument, and there are many types of collagens. For instance, in adults collagen type I is the most abundant form and during gestational development, collagen type III is the dominant one. In contrast, elastin comprises between 0.6% and 7.9% of the ECM.[7]

Upon skin injury there is a damage and loss of ECM proteins and cells, but a cascade of highly regulated and sophisticated reparative processes occurs that renews the integrity and structure of the skin, and maintains homeostasis on the integument.[8–10] However, the most usual result of the healing process is the formation of a scar, which is rich in collagen, fairly acellular and without skin appendages.[11] There are four overlapping but distinct phases during adult wound healing: clotting and coagulation (haemostasis), inflammation, proliferation and remodelling.[7]

After injury to the skin, platelets contact exposed collagen from the ECM and endothelial wall and the clotting and coagulation cascade starts.[7] During the inflammatory phase, fibronectin and other ECM protein fragments from the wound area act as chemoattractants

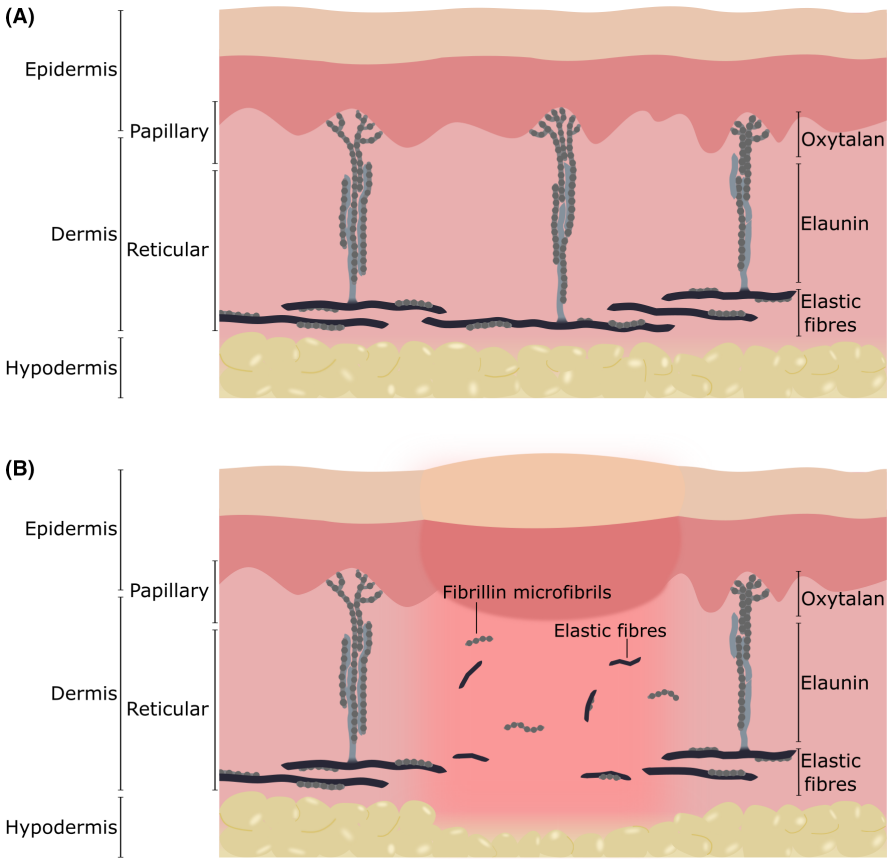

FIGURE 1 Schematic representation of elastic fibres in homeostasis and in full-thickness wound healing. (A) Typical elastic fibre structure in homeostasis. In the lower dermis, well-organized horizontal mesh-like layers of thick, discrete elastic fibres are found. In contrast, in the upper layer, thinner elastic fibres that merge into fibrillin-rich microfibrils at the dermo-epidermal junction are seen. (B) In remodelling wounded skin, newly synthesized (immature) elastic fibres are fragmented, thin and appear as a disorganized network in scar tissues.

for monocytes.[12] At the proliferation phase, granulation tissue is filled with fibroblasts, myofibroblasts, immune cells and endothelial cells. Fibroblasts are secretory cells that secrete large amounts of ECM components, most importantly, collagen type I and fibronectin.[13] Elastin is not present on the newly formed granulation tissue,[12] but is demonstrated to appear after initial wound phases have progressed.[7] The synthesis of collagen type I and III rises during the remodelling phase.[8]

This review aims to highlight the distinct roles of elastin and collagen fibres during wound healing, as they have been shown to be highly important for successful completion of the wound healing process.

2 | ELASTIN

Elastic fibres are a vital protein component of the ECM providing the elasticity and mobility to skin, lungs, vasculature, ligaments and external ear's cartilage.[14–17] In the skin, elastic fibres are involved in the core architecture of the dermis, taking part in the structural and functional integration of the skin that supports cell growth.[18] As a result, elastin is directly in contact with different cell types.[14] Elastin is implicated in controlling several cellular activities including cell migration, proliferation and differentiation as well as modulation of the coagulation cascade.[19] Elastin proteins have been shown to induce different pathways such as fibroblast migration and proliferation, smooth muscle proliferation, keratinocyte migration, calcium transport, ECM turnover and cell survival.[20] Elastic fibres in the dermis also regulate cell phenotypes, and matrix and cytokine production.[21]

In normal skin, elastic fibres in the dermis account for approximately 2%–4% of fat-free dry weight.[22–24] Elastic fibres have a half-life of more than 70 years, and can be stretched up to eight times their normal length and return to their original size and shape, defining the resilience, recoil and elasticity of the skin.[16,23] In the lower reticular dermis, elastic fibres are properly organized as thick horizontal, discrete fibres. In the papillary layer thin elastic fibres run perpendicular to the thicker ones localized in the reticular dermis and finally merge into fibrillin-rich microfibrils at the dermo-epidermal junction[25,26] (Figures 1 and 2).

2.1 | Elastogenesis and elastic fibre assembly

The processes of elastin synthesis and assembly involve many steps which are regulated at multiple levels. Elastogenesis, the process of elastin formation, is highly active during fetal and early neonatal periods, and it is virtually absent afterwards.[22,27] The tropoelastin molecule, a 60–70 kDa polypeptide encoded by a 3–5 kb mRNA,[28] is a precursor protein secreted by fibroblasts and smooth muscle cells,[25] that binds to the 67 kDa elastin-binding protein (EBP) on the cell membrane through protein kinase A (PKA)-mediated phosphorylation.[21,29] EBP acts as a molecular chaperone that protects the hydrophobic tropoelastin molecule from degradation and intracellular self-aggregation,[21,30] and in the ECM facilitates the correct

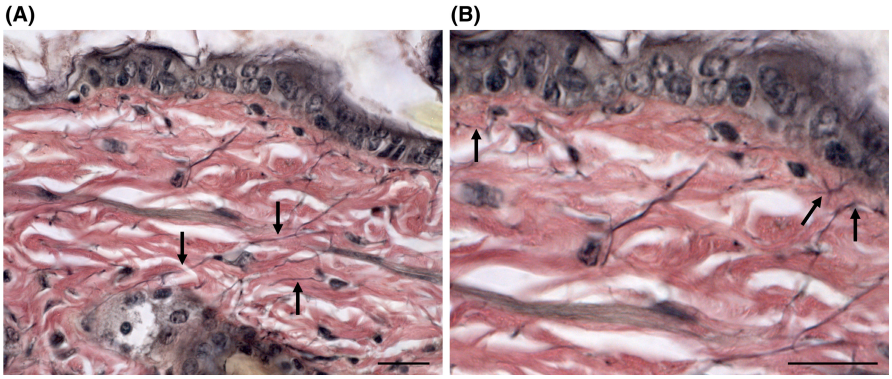

FIGURE 2 Elastic fibres in mouse skin. Verhoeff-Van Gieson stain in mouse skin sections allows the visualization of elastic fibres (arrows) as black filaments. (A) Arrows indicate horizontal elastic fibres parallel to the epidermis. (B) Magnification of the papillary dermis. Arrows indicate fibrillin-rich microfibrils at the dermo-epidermal junction. Scale bars represent 20 μm.

assembly on the microfibrillar scaffold by chondroitin sulfate moieties associated with microfibrillar glycoproteins.[30] Scaffold assembly enables the coacervation (a self-association process) of tropoelastin molecules on the microfibrils, which results in an organized filamentous structure that, when cross-linked by lysyl oxidase (LOX), forms mature elastic fibres.[25,28,31] Lysyl oxidases, primarily LOX and LOX1, catalyse the oxidative deamination of lysine residues. After elastin (ELN) is cross-linked with microfibrils, the formed fibres are resistant to tensile strength, stress and compression.[32]

2.2 | Microfibril components

Mature elastic fibres are composed of an internal core of cross-linked, amorphous elastin wrapped in a lower-abundance aligned sheath of microfibrils[33] with approximately 10–12 nm diameter.[34] Insoluble mature elastic fibres are metabolically inert, and the most durable element of the ECM that may last over the entire human lifespan in undisturbed tissues.[30] Fibrillin-1 and -2 (FBN1 and FBN2), two large glycoproteins assemble into microfibrils.[27,34] Microfibrils lacking elastin are also dispersed in the connective tissue and they connect elastic fibres, structural components of the ECM and cells.[34] In the skin, microfibrils and FBN1 colocalize with latent transforming growth factor β-binding proteins (LTBP-1, -2 and -4), members of the fibulin family (FBLN2, FBLN3, FBLN4 and FBLN5), and microfibril-associated protein-1, -3 and -4.[17,21] FBLNs are small glycoproteins of the ECM that seem to be important in wound healing and development.[35] In humans elastin is encoded by a single copy gene, the tropoelastin precursor, localized in human chromosome 7q11.1–21.1, and is highly conserved among mammals with a structure composed of 34–36 small exons spanning over 40 kb.[27,28,36]

Mutations in FBLN4 cause among other diseases cutis laxa in humans, with reduced elastic fibre production suggesting the essential role of FBLN4, also known as EFEMP2, in elastogenesis.[37] In addition to this, when both isoforms of LTBP-4 long (LTBP-4 L) and short (LTBP-4S) are inactivated, this leads to autosomal recessive cutis laxa type 1C (ARCL1C) in humans and to a similar phenotype in *Ltbp4*$^{-/-}$ mice, seriously affecting elastogenesis.[38] Indeed, it has been shown that Ltbp-4 L expression is necessary for FBLN4 to be incorporated into the elastic fibres.[38,39] Moreover, mutations in human LTBP-4 impair its deposition into the ECM, causing increased TGF-β activity and alterations in elastic fibres.[40] Similarly, LTBP-1 is essential for human skin ECM assembly as altered LTBP-1 hinders FBLN4 incorporation into the ECM leading to cutis laxa.[41] It has been described that FBLN4 and the LOX propeptide interact, enabling the assembly between LOX and tropoelastin. Therefore, FBLN4 is necessary for the correct maturation of elastic fibres.[42]

Elastin microfibril interface-located proteins (EMILINs) 1 and 2 are extracellular glycoproteins which structurally are very similar, but with independent network formation. In skin, both EMILINs are targeted to fibrillin microfibrils. The formation of the EMILIN-1 and -2 network is dependent on the presence of fibronectin and fibrillin microfibrils.[43] EMILIN1 is a structural component of elastic fibres and is located between the fibrillin microfibril scaffold and the elastin core. It connects elastic fibre network with the formation of collagen fibrils.[44] EMILIN1 interacts directly with fibulin-4 and is required for proper ECM deposition of FBLN4.[45] EMILIN1 deposition is upstream of FBLN4 in elastogenesis[44] and, therefore, FBLN4 is required for LOX targeting and function.[46] Lack of EMILIN1 impairs FBLN4 ECM deposition and LOX function leading to impaired elastogenesis, decreased collagen cross-linking and abnormal growth factor signalling, indicating that both EMILIN1 and FBLN4 are necessary for proper LOX activity.[44] In addition, homozygous *EMILIN1* loss-of-function variants lead to defective elastin and collagen fibre formation, and mutations in EMILIN1 lead to cutis laxa syndrome.[44]

2.3 | Elastic fibre types

In the skin, depending on the elastin quantity associated with microfibrils there are three types of fibres: oxytalan, elaunin (eulanin) and mature elastic fibres.[47] Oxytalan fibres are composed of fibrillin-rich microfibril bundles without obvious amorphous elastin, normally present at the dermo-epidermal junction with a candelabra-like pattern (Figure 1). Elaunin fibres are formed by fibrillin-rich microfibrils mixed with amorphous elastin, and interconnect oxytalan fibres in the papillary dermis with elastic fibres present in the reticular dermis.[48] Elastic fibres in the reticular dermis are mainly composed of elastin.[49]

In some metabolic disorders, and after menopause and structural damage or enzymatic degradation of elastic fibres, there is a continual deprivation of elasticity. In photo-damaged patient's skin where chondroitin sulfate moieties accumulate, and also in

heritable disorders or Costello syndrome the release of tropoelastin molecules impedes the assembly of tropoelastin with elastic fibres, and this results in the formation of amorphous tropoelastin coacervates.[30] Inherited elastic fibre disorders include Marfan syndrome caused by mutations in FBN1, and autosomal dominant cutis laxa caused by mutations in the elastin gene.[50] It is suggested that in *cutis laxa acquisita* degradation of elastic fibres and therefore, inefficient remodelling may be due to a dysfunction in Golgi apparatus, most probably caused by medical treatment.[51] Additionally, elastin and elastic fibres have a very low and slow rate of turnover, and therefore, are susceptible to damage over time from many factors.[22] Elastin degradation by elastases which come from inflammation, sun exposure, disease and free radical damage forms elastin fragments, called elastokines, which represent a strong tissue repair signal.[22,28]

3 | ELASTIN IN WOUND HEALING

Since tropoelastin expression stops after late embryonic period, there is no production of elastin in adults. However, its synthesis is induced by injury or disease, and the expression of elastic fibre proteins is influenced by tumour necrosis factor-α, transforming growth factor β (TGF-β), interleukin-1β, vitamin D and insulin-like growth factor-1.[25,52] Elastin and its derivatives can change cell activity, thereby significantly impacting adult wound healing. Tropoelastin binds to dermal fibroblasts and interacts with elastin peptides, having an effect on cell behaviour.[25] Tropoelastin is placed in unimpaired elastic fibre nucleation sites for correct fibre growth. Chronic overexpression of proteolytic enzymes can cause the degradation of elastic fibres, ultimately affecting the matrix assembly.[21]

The rise in tropoelastin synthesis at the beginning of skin damage suggests a multifunctional role during wound healing. Apart from elastin's mechanical and signalling properties, it owns cell-signalling properties that can cause biological responses in cells such as proliferation and migration.[29] Elastin peptides with certain sequences can promote cell spreading, attachment and signalling in skin wound healing and homeostasis. Moreover, cell behaviour can be altered by elastin peptides from the alternating hydrophobic domains.[53] Tropoelastin production is also affected by a variety of exogenous factors.[36] Furthermore, elastin lessens wound contraction and enhances dermal regeneration.[54] The rebuilding of a working elastic fibre network is essential to restore entire skin function after wounding.[25]

3.1 | Elastokines and signalling

In wound healing, solubilized elastin seems to be involved in the signalling of human dermal fibroblasts. FBN1 has been shown to be involved in the transdifferentiation of fibroblasts into myofibroblast via TGF-β, which help close the open wound by contraction.[55] It has been shown that elastin can play a key role in this differentiation changing the cell function and phenotype, although the specific region of elastin and the exact mechanism are underexplored.[14,54] On the contrary, tropoelastin is involved in the maintenance and induction of myofibrillar organization in vascular smooth muscle cells via the hexameric peptide VGVAPG.[56] More specifically, elastin causes the terminal differentiation and migration of human epidermal keratinocytes via VGVAPG, which is needed for the completion of a stratified epidermis and subsequently, to restore the skin barrier function.[14]

Preclinical data show that exogenous tropoelastin administration allows for proper organization of elastic fibres upon wounding and angiogenesis.[22] In the more regenerative species elastin is synthesized during skin wound healing, conferring certain flexibility to the wound microenvironment.[57] After injury, tropoelastin expression starts rapidly.[58] However, the fact that elastic fibres are detected progressively and do not reach normal skin levels led some authors to believe that they do not have a prominent role in wound healing.[49,59]

Elastin peptides qualify as matrikines which are peptides formed by the fragmentation of proteins from the ECM and have biological functions.[60] Elastin fragments produced by the degradation of the normal matrix, elastokines, can act as signalling molecules in wound healing.[10]

3.2 | Elastic fibre maturation in wound healing

In adult wound healing, newly synthesized elastic fibres appear, although they are not mature. Instead they are large, fragmented, thin, and appear as a disorganized network in scar tissues[20,25,48,49,53,61] (Figure 1). Aberrant elastin production persists several months after injury.[48,62] Specifically, 12 months after injury elastin appears to reach maximum levels both in fibre number and size.[49] In contrast, in pig skin elastin bundle regeneration occurs in a matter of months,[63] and is detectable by day 21 post-wounding.[64] Of note, in human scars older than 10 years elastic fibres never reach the size and maturity of fibres of the normal tissue.[49,53] This limitation in elastogenesis might be one of the reasons why hypertrophic scars present reduced elasticity.[53] In response to wounding or to UV radiation exposure,[65] tropoelastin synthesis restarts but normal elastic fibre formation is not reached.

Newly synthesized elastin fibres upon wounding appear disordered functionally and spatially,[21] with a provisional arrangement.[66] As elastin regeneration is insufficient and collagen synthesis and accumulation increases, scar tissue tends to be inflexible and inelastic in comparison with normal elastic dermis.[21,48] One of the crucial problems in the restoration of the new elastic matrix seems to be the absence of mature elastin fibre formation and cross-linking, instead of the recruitment and production of tropoelastin precursors.[21] It has been proposed that during human skin regeneration microfibrils are generated at the dermo-epidermal junction, develop downward crossing the papillary dermis and unite with an independently formed horizontal microfibrillar net in the reticular dermis.[62]

3.3 | Role of lysyl oxidases and other protein components

What is the role of LOX and LOXL1 in wound healing? Direct interaction among tropoelastin and LOX, and between ELN and FBN1 have been reported.[67] However, interactions between LOX and FBN2 have not been described, which leads to additional molecular mechanisms for LOX activity.[32] FBN1 and FBN2 are the main proteins forming microfibrils.[68] During acute wound phase, FBN2 expression occurs at the edge of the wounds similar to TGF-β.[69] Thus the regulation of TGF-β and integrin-mediated cell spreading and adhesion is driven by elastic fibres taking part in wound healing.[70] Integrins have been identified to interact with both FBN1 and latency-associated peptide (LAP) of TGF-β1, also known as the TGF-β1 prodomain, and to be upregulated in the wound healing process.[17]

LTBP-1 forms a complex covalently linked with latent TGF-β and targets it to the extracellular matrix. It is proposed that FBN1 and LTBP-1 stabilize and regulate latent TGF-β complexes in the ECM.[70,71] Further, Isogai et al. proposed that FBN1 deprivation may end this stabilization and cause the activation of TGF-β. Nevertheless, several studies support the role of fibrillin-1 in the sequestration of TGF-β, although the mechanisms are still to be clarified.[70] The fibrillin microfibril network and LTBPs, form a scaffold where TGF-β-related growth factors are targeted, and bone morphogenetic proteins (BMPs) form complexes with their growth factors. It has been determined that prodomains of BMPs (BMP-2, -4, -5, -7 and -10 and GDF-5 (growth and differentiation factor-5) interact with FBN1 and FBN2.[72,73] It is suggested that fibrillin microfibrils work as sequestration scaffolds during wound healing, as they are deposited early into the wound bed. In burn wounds, fibrillin microfibrils colocalize with large latent complex and LTBP-1 during the early phase of regeneration.[17]

After full-thickness excisional wounds, EMILIN-1 and -2 were found to be upregulated in the wound bed. Both EMILINs were overlapping with fibronectin and fibrillin, indicating that EMILINs are laid down and coregulated with fibronectin and fibrillin fibres.[43] *Emilin1*$^{-/-}$ mice presented epidermal and dermal hyperproliferation and accelerated wound closure. EMILIN1 seems to interact with α4β1 and α9β1 integrins to provide an external signal important for preserving skin homeostasis.[74]

3.4 | Healing versus scarring

In a periodontal disease model in Marfan syndrome mice, wound healing is delayed. FBN1 expression showed increased levels at the beginning of wound healing stage, but diminished during healing.[75] Staining for FBN1 in hypertrophic scars and keloids appeared diminished; in keloids, there was a rise in elastin at the deep dermis but a reduction in FBN1 showing changes in the composition of microfibrils.[48] One study reported that FBN2 is highly expressed in the dermis during wound healing and also in keloids, and that FBN2 and tenascin-C colocalize.[69] Yoshiba et al. suggest that in vitro, the expression of alpha smooth muscle actin (α-SMA) is TGF-β1 dependent, and that in the differentiation of fibroblasts into myofibroblasts FBN1 is implicated in dental pulp wound healing.[55] In the event of mechanical injury, FBLN5 is stimulated in smooth muscle cells and vascular endothelial cells, proposing that FBLN5 regulates endothelial cell function and vasculogenesis.[76]

Fibulin-5, also known as DANCE [developmental arteries and neural crest epidermal growth factor (EGF)-like] or EVEC (embryonic vascular epidermal growth factor-like repeat-containing protein), is a calcium-dependent integrin ligand necessary for elastic fibre organization and assembly.[77] FBLN5 is an important multifunctional ECM protein linking cells to elastic fibres that regulates tissue and cell development, repair, remodelling and cell adhesion.[78] FBLN5 is found to be associated with microfibrils, and microfibrils surround the amorphous elastin core of elastic fibres.[79] Fibulin-5 deficient mice display a disorganized elastic fibre network throughout the body.[77] These mice survive to adulthood but exhibit loose skin (*cutis laxa*), emphysematous lungs and abnormalities in the vasculature.[77,80] This phenotype looks like *cutis laxa* syndrome in humans, where abnormalities in FBLN5 are responsible for its recessive form,[79] revealing a crucial role for FBLN5 as a scaffold protein which binds elastic fibres to cells.[80] This might be mediated by the FBLN5 arginine-glycine-glutamate (RGD) motif that binds the calcium-binding EGF repeats and the cell surface integrins, which in turn bind elastin.[80]

In an in vivo rabbit ear full-thickness dermal ulcer wound model, wounds treated with FBLN5 showed accelerated wound closure rates, an increase in granulation tissue volume, and the stimulation of collagen type I synthesis. FBLN5 may also stimulate wound healing by promoting elastic fibre assembly and incorporation into microfibrils.[78] Interestingly, microfibril-associated glycoprotein 4 (MFAP4) belongs to the fibrinogen-related protein superfamily and plays a critical role in the assembly process of elastic fibres via interactions with fibrillin.[81] A study showed that aloe vera flower and processed Aloe gel demonstrated synergistic wound healing effects targeting MFAP4 and its signalling pathways.[82]

In diabetic wounds, there is a constant inflammatory environment resulting in decreased elastin and collagen deposition and impaired function of fibroblasts and myofibroblasts.[83] Atrophic scars appear to have increased irregular and thin elastic fibres, while in acne-mediated inflammation scars lack elastic fibres.[84] After severe burn injuries, elastin is inadequately regenerated in the scar tissue and is disorganized.[33] Atrophic, hypertrophic and keloid scars are formed in part due to the lack of organization and degradation of components of the elastic fibres.[22] In different tissues, biomolecules such as growth factors, exogenous enzymes, matrix glycosaminoglycans, vitamins, nucleotides and steroids influence elastic matrix synthesis and assembly. In contrast, versican for instance can inhibit elastic ECM synthesis.[21]

Interestingly, one study examined scar tissue that had been present for 4 months–30 years in 14 patients (15–45 years old males and females). In atrophic scars, increased fine fibres (up to 0.1 μm) and decreased numbers of thick elastic fibres (1–3 μm) were found in younger scars in comparison to older scars. In hypertrophic scars,

incomplete elastic fibres, very fine elastic fibres and few thick fibres with very fine elastic fibres were observed as scars became older. Therefore, the authors proposed that there is a difference in the synthetic activity of fibroblasts between atrophic and hypertrophic scar tissues, concomitantly to increasing age of the scars.[59] In another study, scars with less than 3 months were devoid of elastic fibres, while scars older than 3 months showed very thin, fragmented fibres, at the beginning growing focally and afterwards throughout the scar.[49]

3.5 | Other elastic fibre alterations

The absence of collagen and elastin fibres is considered to have relevant effects in mast cell degranulation. Alterations in the organization and quality of elastin and collagen are reported in *striae distensae*.[15] Treatment in *striae distensae* (also referred to as *striae*, *striae atrophicans*, *striae rubra*, *striae alba*, *striae gravidarum* and/or stretch marks) with tropoelastin has been proposed to enhance the elastic fibre network and skin ECM structure. Scar skin tissue due to cuts, damaged skin from severe acne or sun, burns, *striae distensae* or ageing can lead to a disorganized elastic fibre network throughout the skin repair phase.[22] This emphasizes the key role of elastin fibres in scar improvement.[15]

An actinic damage in the form of fragmentation of elastic fibres and microfibrils, and deprivation of elastin is seen in sites of the skin exposed to the sun.[49] In different animal models, the use of elastin as well as elastin peptides improve wound healing.[85] Dermal equivalents with elastin-derived peptides and fibroblasts might improve the wound healing process.[86] In vitro, dermal fibroblasts of older donors synthesize less elastin as the age of the donor rises.[21]

In an in vivo model, excisional wounds were generated in hyperglycemic mice and topically treated with glycerol-plasticized chitosan-alginate membranes. At day 7 post-wounding, small concentrations of thin elastic fibres were detected. By day 14 post-wounding, elastic fibres appeared all over the dermis with improved reorganization and with eulanin microfibrils, which are thicker and contemplated as necessary for skin elastogenesis. Wounds gained elasticity and retraction due to elastic fibres, having a key role in the biochemical responses and the mechanical forces.[47]

A proteolytic digest of bovine elastin increased the production of new elastic fibres in cultured dermal fibroblasts as well as in human skin explants mediated by stimulation of cellular elastin receptor. When human fibroblasts treated with the proteolytic digest were injected into the skin of nude mice, they increased the expression of elastic fibres.[30] Another study reported that in stretched skin and scars there is a parallel alignment of collagen fibres compared to unstretched skin and scars, similar to elastic fibre arrangement after stretching.[18]

Apparently, elastin deposition is hampered by the accumulation of matrix components such as proteoglycans, and inflammatory cells and cytokines. In adult tissues and diseased microenvironments, accumulation of proteoglycans can hinder the nucleation of elastin precursors on the EBP, like versican and biglycan.[21] Moreover, in diseased tissues inflammatory cytokines can lead to chronic overexpression of elastolytic enzymes such as matrix metalloproteinases (MMP)-2, MMP-9, MMP-12 and neutrophil elastase.[21]

4 | COLLAGEN

Collagen constitutes around 30% of total protein mass in mammals,[87] as a key structural component of skin, blood vessels, heart, tendons, ligaments, lung, liver, kidney, teeth, bones and cartilage.[88] Fibrillar collagen is abundant in the dermis[89] where it contributes to elasticity and mechanical strength and serves as a substrate for cellular proliferation, attachment and differentiation.[90–92] Collagen is involved in many functions such as cell migration, tissue scaffolding, tissue morphogenesis, tissue repair, tissue organization and regulation of resident and inflammatory cell function.[89,93] Moreover, some collagens play crucial roles in the peripheral nervous system, affecting the behaviour of Schwann cells and preserving the physiological function of peripheral nerves.[87] Both collagen type I and III aggregate into fibrils; collagen type III has key roles in homeostasis, embryogenesis and wound healing. Collagen type III fibrils are part of the vasculature, but when copolymerized with collagen type I and V, they form a heterotypic fibril found in skin, tendons and bones.[94]

4.1 | Collagen types

There are 40 collagen genes that encode 29 different homo- and/or heterotrimeric molecules, from collagen types I to XXIX.[87,95] The Roman numerals are used to point out the type and the Greek letters to identify chains, bands and higher molecular weight components.[95] Collagens can be divided into fibril-forming collagens (types I, III and V), fibril-associated collagens (types XII, XIV, XVI and VI), network-forming collagens, anchoring fibrils, transmembrane collagens, basement membrane collagens and others.[87,91] In normal skin, collagen I comprises 80%–85% of the dermal ECM, whereas collagen III constitutes 8%–11%.[96] Collagen type I has thicker fibre bundles compared to type III.[97] Collagen has a low turnover, with a half-life of 15 years in skin.[98]

4.2 | Collagen synthesis

Molecularly, collagens are typically composed of repeated proline rich amino acid sequences, with a glycine molecule every third position, according to the formula Gly-X-Y. The next most prevalent amino acids are proline and 4-hydroxyproline, that normally occupy the X and Y positions. These polypeptides form α-chains, which assemble into a triple helix. Therefore, collagens are composed of three procollagen chains. Collagen type I is a heterotrimeric protein while type III is formed from homotrimers.[96,99] Collagen synthesis

needs the hydroxylation of proline, lysine, ferrous iron and vitamin C. Deficiency in some of these cofactors leads to impaired wound healing.[100]

Collagen is synthesized by adventitial cells of the vessel wall, endothelial and smooth muscle cells.[101] The procollagen alpha chain is synthesized and afterwards, it transcribes the information needed to encode the collagen gene. Then, it translates the collagen polypeptide chain corresponding amino acid sequence. The procollagen α-chain is composed of five regions: an N-terminal propeptide, an N-terminal peptide, a triple helix region, a C-terminal peptide and a C-terminal front. The procollagen α-chain is hydroxylated and glycosylated by the action of hydroxylase, and galactose and glucose invertase, resulting in a large amount of hydroxyproline of the α-chain. The α-chains of procollagen create disulfide bonds to form a three-helix core. Lastly, the procollagen molecules are secreted outside the cells and converted into tropocollagen molecules, where they assemble and aggregate into supramolecular collagen aggregates. Consequently, there are five hierarchical structures: primary structure (amino acid triplet), secondary structure (α-helix), tertiary structure (triple helix) and quaternary structure (fibrils) and supramolecular aggregation structure.[102]

5 | COLLAGEN IN WOUND HEALING

The type, quantity and organization of collagen changes during wound healing and defines the tensile strength of the scar.[91] Apart from being the principal protein component of the healing wound, collagen plays a vital role in the inflammatory phase of wound healing, influencing cellular differentiation, mitogenesis and migration, and promoting synthesis of inflammatory cytokines and growth factors by surrounding cells.[103] It has been suggested that upon injury, collagen fibril is in a closed conformation that with the exposure to blood shows cell- and ligand-binding sites that may promote the process of healing, and serve as a scaffold for cell attachment.[91] Moreover, during the inflammatory response, fragments of collagen types I and IV are able to act as mediators and serve as chemoattractants for neutrophils, improving phagocytosis, the immune response and modulating gene expression. Collagen has also a key role in angiogenesis, promoting or inhibiting it depending on the collagen type. For instance, the C-propeptide fragment of collagen type I stimulates angiogenesis by engaging specific integrin receptors and recruiting endothelial cells. On the contrary, proteolytic collagen fragments of collagen type IV and XVIII have angiogenesis-inhibiting effects.[91] Aside from providing tissue integrity and strength, collagen is key in skin homeostasis and in epithelialization at later stages of the healing process.[104] The scar tissue recovers approximately 50%–80% of skin's original tensile strength. One of the main differences between wounded and unwounded skin seems to be the fibre size, orientation and density of the collagen fibrils.[91] Collagen also synthesizes proteins in the ECM, and interacts with enzymes such as MMPs and their tissue inhibitors (TIMPs).[103]

During the early stages of granulation tissue formation, TGF-β and platelet-derived growth factor (PDGF) set off phenotypic changes converting fibroblasts into myofibroblasts, which create contraction forces that enable wound closure.[96] Myofibroblasts deposit type III collagen at the wound site,[89,98,103,105] giving tensile strength to the ECM,[105] and determining the fibril diameter of collagen type I.[89] Later on, granulation tissue is resorbed and myofibroblasts undergo apoptosis,[98] and the matrix is replaced by collagen type I.[98,105] Myofibroblasts secrete many other ECM proteins during wound repair, including collagens type IV, V and VI, laminin, tenascin, fibronectin and glycoproteins. Furthermore, apart from myofibroblasts endothelial, epithelial and inflammatory cells also produce these proteins.[98] Several tissues including skin, blood vessels, lung and intestine have a collagen III/I ratio of 1 to 2–3.[105] Collagen ratios impact the tensile strength of the wound, increasing from 20% to a maximum ≈70% of normal skin 3 weeks after the injury.[103] Therefore, collagen is able to interact with different regenerative pathways in skin wound healing.[96] In contrast, fibrotic tissues appear to have increased content of collagen III, and thus, the normal collagen ratio III/I is altered.[105] Collagen type V is also increased in desmoplastic human breast carcinomas and in small airway fibrosis of *bronchiolitis obliterans*.[98]

5.1 | Collagen fibril formation

The biosynthesis activities of fibril-forming collagens entail numerous complex steps. After transcription, the pre-pro-collagen is post-transcriptionally modified into procollagen, taking out the signal peptide on the N-terminus. The triple-helical structure is formed after hydroxylation and glycosylation of amino acid residues. The procollagen triple-helical structure is stabilized with the help of chaperons, and assembled into secretory vesicles that eject into the ECM space. Here, the procollagen is enzymatically modified into tropocollagen. The final collagen fibril assembly occurs by covalent cross-linking, and the elasticity and deformation of fibrillar collagens depends on this cross-linking process.[91]

5.2 | Collagen degradation

Degradation of collagen is regulated by extracellular pathways involving both membrane-bound and secreted proteolytic enzymes. It can also be regulated by intracellular pathways where the internalization of intact collagen fibrils and fragmented collagen proceeds by enzymatic breakdown. Faults in these regulations leads to pathological conditions such as fibrosis. Treatment with exogenous collagenases that degrade the ECM have been used in combating excessive fibrosis.[88] Collagens type I and III are preferentially cleaved by MMP-8 and MMP-1, respectively. MMP-1, 2, 8, 13 and 14 are all capable of hydrolyzing collagen types I, II and III, while MMP-3 and MMP-9 are unable to degrade tropocollagen,[95] but MMP-9 can degrade collagen type IV.[91]

After synthesis of the peptide chain some of the proline is hydroxylated, a process nearly exclusive to collagen. Protocollagen proline hydroxylase (PPH) is the enzyme in charge of this function, and is an indicator of one early critical step in the rate of collagen synthesis in a variety of tissues and conditions, giving the wound its tensile strength.[106] At day 5 upon skin wounding in rats, PPH-activity seems to reach its maximum. Similarly, in humans, day 5 skin wounds showed a similar magnitude of increase of PPH-activity, while in human unwounded skin there was a low level of PPH-activity.[106] Patients which have prolidase deficiency have low proline levels and deficits in wound healing.[107] Interestingly, arginine supplementation in dosages of 17–24.8 g/d enhance collagen deposition in healthy human adults and elderly volunteers. However, arginine supplementation had no effect on the rate of epithelialization of superficial skin defects, showing that the main effect of arginine is on wound collagen deposition. One possible mechanism for the positive effects of arginine on wound healing might be that as arginine comprises a tiny proportion of the collagen molecule (<5%), supplemental arginine provides substrate for the Arginine → Ornithine (ORN) → glutamine semialdehyde → proline pathway. In an inducible nitric oxide-synthase knockout mice model, ORN rises wound breaking strength and collagen accumulation, to a similar degree as in normal mice.[107] Supplementation with arginine and ORN seem to support wound collagen biosynthesis, but if this is reached by conversion to proline still remains to be clarified.

Proline and hydroxyproline are crucial for collagen structure, biosynthesis and strength. Proline has a key role in wound healing, immune responses and antioxidative reactions, and acts with arginine, leucine and glutamine to enhance synthesis of proteins in cells and tissues.[104] Chitin and chitosan seem to induce collagen fibres, and chitin has been found to enhance the synthesis of collagen types I, III and IV.[108]

TGF-β regulates α2(I) procollagen gene (COL1A2) promoter via the Smad transduction pathway. In contrast, interferon-γ negatively regulates COL1A2 transcription.[109] A cysteine-rich domain within the N-propeptide of collagen type III is able to bind and decrease TGF-β signalling, but not to completely abolish it, both in vitro and in vivo.[110] Connective tissue growth factor (CTGF) is selectively induced by TGF-β, and both are coordinately expressed at wound sites and fibrosis. Fibroblast proliferation, differentiation and collagen synthesis are regulated by TGF-β via CTGF-dependent pathways, and these functions can be blocked by anti-CTGF antibodies or by inhibition of CTGF synthesis.[111] Wnt signalling is also implicated in the progress of fibrotic disease in several organs, and canonical Wnt signalling results in the stabilization and cytoplasmic accumulation of β-catenin. Wnt signalling is active during wound healing and constitutively active β-catenin supports wound hyperplasia with excessive collagen synthesis. Moreover, canonical Wnt signalling is required for the TGFβ1 pathway to promote fibrosis.[112] Early growth response gene-1 (egr-1) has been identified as the inducer of the transcription of other genes during the wound healing process such as collagen type II (α1) and PDGF.[109]

5.3 | Collagen structure deregulation and wound contraction

In human normal skin, collagen fibres form a three-dimensional basketweave-like network,[89,91,113] while in rodents normal skin has a reticular collagen pattern (Figure 3A).[89] In human scars, including normotrophic, hypertrophic and keloid scars, collagen forms cross-links to align in a single direction parallel to the epithelial surface,[89,91,113] opposite to the rat. In rodents scars, large parallel collagen bundles at about right angles to the basement membrane are formed (Figure 3B). Moreover, human scars appear to have extensive collagen density and larger fibre size compared to normal skin.[89] Keloid scars seem to have abnormally thicker collagen bundles that are poorly organized with fewer cross-links than normal skin, normotrophic scar and hypertrophic scar.[91,113] Hypertrophic scars have thinner collagen bundles compared to keloid or normotrophic scars.[91]

Tissue contraction and collagen deposition have been considered to happen simultaneously, although not as interdependent processes during wound healing. Contraction is attributed to cell tractional forces. Collagen deposition is considered to provide load-bearing and stress-shielding functions following tissue contraction.[114] Cell locomotion forces need dynamic microfilaments to contract and relax. Wound contraction requires the uniform packing of collagen fibrils into thicker and longer collagen fibres through rapid myosin ATPase activity, and while packing closer together they eliminate water. Collagen fibrils connected to microfilaments are dragged over the fibroblast's cell membrane surface without changing the cell's

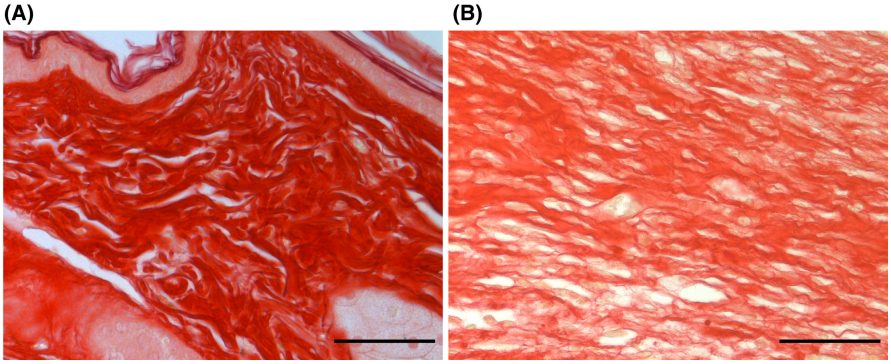

FIGURE 3 Collagen architecture in mouse skin. Aspect of collagen fibres in normal skin (A) and in normotrophic scar (B) is shown by picrosirius red staining. Scale bar represents 50 μm.

shape and by collagen fibrils incorporation into growing collagen fibres, they become part of the granulation tissue. Tension is formed between the granulation tissue and the surrounding dermis, which takes around 7 days.[115] Furthermore, collagen synthesis comes to a maximum at around 6 months post-injury and starts to reduce to a normal turnover rate 2–3 years later.[116]

In an open wound repair model in rat skin, collagen synthesis at the wound centre was observed as early as 24 h after wounding.[117] In contrast, tenascin-X knockout mice have reduced collagen deposition in the skin, similar to what happens in the human Ehlers–Danlos syndrome, and have higher skin extensibility and decreased strength.[98] Lack of CD44 appears to impact fibrogenesis, matrix remodelling and inflammation during skin wound healing. CD44-null mice display decreased collagen degradation, and thus, have increased fibrillar collagen accumulation. This results in decreased tensile strength, suggesting a key role of CD44 in fibrillar collagen accumulation during wound healing.[90] In addition, cutaneous wounds in collagen III-deficient (*Col3*$^{+/-}$) mice were observed to heal with increased scar tissue compared to wild-type (*Col3*$^{+/+}$) mice. *Col3*$^{+/-}$ aged mice seemed to have accelerated wound closure, probably due to increased wound contraction. Cutaneous healing in *Col3*-deficient mice is possibly happening via a decreased regenerative response.[118] Another study showed that, 90 days after transplantation of a human reconstructed skin model for the treatment of full-thickness skin wounds on nude mice, the collagen fibril network in the reconstructed skin was remodelled in a basketweave-like pattern, similar to the ECM organization in nude mice.[119]

5.4 | Healing versus scarring

In fibrotic lesions myofibroblasts remain and are thought to be responsible for the immoderate collagen production that results in altered tissue architecture,[111] compromising the skin function and anatomical structures.[120] Diabetic wounds have increased collagen type III content compared to normal wounds.[97] On the contrary, chronic nonhealing ulcers lack collagen deposition, have altered progression of the wound healing phases, and wounds are weak.[120] Key factors of chronic wounds are high levels of destruction of ECM (because of increased MMPs), continuous inflammation and incorrect activation of soluble mediators during wound healing.[91] Under pathological conditions, collagen fibrils have abnormal assembly and architectural arrangement.[114] Under disease conditions, collagen-binding integrins play a role, and α11β1 integrins have been found to mediate collagen remodelling during wound healing.[121]

Between wounded skin scars and unwounded skin several differences remain, including thickness of collagen fibres, collagen density and fibre orientation, as well as absence of adnexal structures and changes in elastin and other ECM proteins.[122] Human dermal collagen fibrils in the papillary dermis appear to be thinner than those in the reticular dermis. In normal scars, collagen fibrils diameter was smaller at superficial levels and thicker at deeper levels of the wound. In contrast, collagen fibrils tended to be small in diameter in hypertrophic scars at all levels.[123] Hypertrophic scars have been characterized by increased deposition of type III collagen in the deep dermal layer as compared to normal scars, while no differences in type I collagen have been observed.[116,124] Fibroblasts isolated from keloid scars have been shown to have increased collagen synthesis rate compared to any other control group, which might explain to some extent why keloids present increased collagen deposition.[125]

Collagen biomaterials are extensively used for biomedical applications due to excellent biocompatibility, biodegradability, weak immunogenicity, hydrophilicity, abundant source, easy processing and absorbability in the body.[92,102,126] However, collagen has also its drawbacks as it has poor physical and chemical properties.[102] Collagen-based dressings have been used in effective treatment of chronic wounds.[126] Biomaterials have to meet the assessment of biocompatibility and toxicity both in vitro and in vivo.[92] An excisional and ischemic wound porcine model treated with modified collagen gel (bovine collagen-based) was effective to solve inflammation and to improve angiogenesis.[126]

6 | MAJOR OPEN QUESTIONS

Wound healing is a complex and coordinated process involving different cellular and molecular processes. Elastic fibres play a crucial role in directing growth factor signalling. Growth factors are well known to be necessary for proper matrix deposition and remodelling during wound healing, since deficiencies in growth factors lead to chronic wounds.[127] Elastic fibres through their association with fibrillin microfibrils regulate the activity of TGF-β. TGF-β1 has been shown to accelerate wound healing, and a variety of other growth factors and cytokines have been found to have some effectiveness in promoting wound healing.[78] Other growth factors from the TGF-β superfamily, such as BMPs and activins, have also been implicated in wound healing, contributing to various stages of the healing process. MMPs primarily mediate the degradation of the ECM during wound remodelling. In fact, mutations in MMPs lead to aberrant wound healing.[128] Proteolytic prodomain cleavage involves MMPs, which allows for the release of BMP growth factors for fibrillin microfibrils in the ECM.[129] The use of exogenous growth factors in medical settings has reduced efficacy owing to limited absorption through the skin and in vivo stability, among other things.[127] The exact mechanisms by which elastic fibres regulate these growth factors during wound healing are complex and not fully understood. Further research is needed to fully understand the intricate interactions between elastic fibres and growth factors during wound healing to develop effective therapeutic outcomes.

Although there have been relevant advances in the field of elastic and collagen fibre biology, undoubtedly some functions and mechanisms involving these ECM components have yet to be discovered. To this end, ongoing research in regenerative animal models such as *Acomys* may help illuminate our understanding of the composition of proregenerative ECM as compared to the more fibrosis-prone ECM components.[130,131] While the main aspects of ECM composition and

response upon wounding have been elucidated, a major unresolved issue is how best to approach the generated knowledge from a clinical perspective. More studies are needed to elucidate the potential of ECM modulatory drugs in promoting successful wound healing on human skin.

7 | CONCLUSIONS AND PERSPECTIVES

Elastin is responsible for defining skin elasticity and resilience, and has many functions both in homeostasis and during wound healing. Elastin and its derivatives can change cell activity having consequences in adult wound healing, and tropoelastin can rapidly start again its expression, showing its importance in wound healing. Chronic overexpression of proteolytic enzymes can cause the degradation of elastic fibres, ultimately affecting the matrix assembly and the regenerating tissue.

On the contrary, collagen is the structural component of many tissues and organs such as skin, blood vessels, heart and liver. Fibrillar collagen in the dermis contributes to the elasticity and mechanical strength of the skin and plays a role as a natural substrate for cellular proliferation, attachment and differentiation, as well as in angiogenesis, epithelialization at later stages of the healing process, and provides tissue integrity and strength.

It has been described that fibroblast proliferation, differentiation and collagen synthesis are regulated by TGF-β via CTGF-dependent pathways. In addition, the regulation of TGF-β and integrin-mediated cell spreading and adhesion is driven by elastic fibres taking part in wound healing. Integrins appear to be important for proper collagen and elastic fibre remodelling during wound healing. Furthermore, lysyl oxidase is both important for proper elastic fibre and collagen deposition in the formation of the granulation tissue. Thus, elastin and collagen fibres during the phases of wound healing are necessary not only for tissue remodelling, but also for tissue integrity and function.

AUTHOR CONTRIBUTIONS

LG drafted the original manuscript. AI revised it and contributed corrections and discussion. Both authors approved the final version before submission.

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CONFLICT OF INTEREST STATEMENT

The authors state no conflict of interest.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Leire Gardeazabal https://orcid.org/0009-0008-7016-404X
Ander Izeta https://orcid.org/0000-0003-1879-7401

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