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The performance of an orthosilicic acid-releasing silica gel fiber fleece in wound healing

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ABSTRACT

In the present work, we have examined the impact of an inorganic orthosilicic acid-releasing spun fiber fleece (SIFIB) on wound closure in a porcine wound model *in vivo* as well as on wound healing-relevant parameters *in vitro*. *In vivo* SIFIB was completely bio-degradable and had no negative effects on wound closure or the wound healing process. In the *in vitro* experiments, SIFIB had no negative effects on proliferation of human skin fibroblast (FB) and endothelial cell (EC) cultures but strongly retarded the growth of the human monocyte cell line THP-1, and effectively inhibited human skin keratinocyte (KC) proliferation, which based on significantly enhanced KC differentiation. Furthermore, SIFIB exhibited strong anti-inflammatory properties, which based on SIFIB-dependent inhibition of expression and activity of NF-κB and/or concomitant enhanced expression of IκB, a NF-κB-inhibiting protein. Additionally, SIFIB significantly inhibited TGFβ-induced fibroblast differentiation and collagen synthesis as well as effectively reduced TGF-β synthesis of activated fibroblasts. We have demonstrated wound healing-relevant biological activities of a silica-based bio-degradable inorganic material, which might represent a new therapeutic tool in the treatment of chronic wounds.

1. Introduction

Healing of cutaneous wounds is a complex and well-orchestrated physiological event designed to restore skin integrity. Cutaneous wound repair can be divided into a series of dynamic phases including formation of fibrin clot and inflammatory response, granulation tissue formation, re-epithelialization, angiogenesis, and extracellular matrix formation and remodeling [1,2]. The initial inflammatory phase following cutaneous injury is dominated by reactions mediated by cytokines, chemokines, growth factors and their actions on cellular receptors [3]. An imbalance in wound healing processes, initiated or supported by persistent infections, unregulated prolonged inflammatory response, ischemia and repeated trauma [4] or diseases such as diabetes, respectively, are thought to promote the development of chronic wounds [5]. In the last few years, chronic wound, i.e. in the form of ulcers, has gained importance due to the demographic state of obsolescence and increasing appearance of chronic metabolic disorders like diabetes.

Chronic wounds due to a deregulated inflammation and/or infection are characterized by an increased production of inflammatory mediators such as Interleukin-1β (IL-1β), Interleukin-6 (IL-6), Interleukin-8 (IL-8) and/or Tumor Necrosis Factor-α (TNFα) [6–11]. Additionally, in chronic and not healing wounds elevated expression of pro-inflammatory cytokines correlates with elevated levels of interstitial collagenases, gelatinases, and stromelysins [12]. However, TNFα and Il-1β synergistically increase the expression of Matrix Metallo Proteases (MMPs) and also reduce synthesis of Tissue Inhibitors of Proteases (TIMPs) [10,13,14]. MMPs disintegrate extra cellular matrix, inhibit cell migration and collagen deposition, and break down growth factors and their target cell receptors [7]. As a consequence, an imbalance in proteolytic activity reflects a deregulated prolonged inflammation phase and is assumed to contribute to impaired healing in chronic wounds cytokines, i.e. TNFα [8,15] or IL-1β [16], respectively.

Wound contraction and scar formation are still unavoidable components of the healing process of normal wounds. In chronic wounds, the imbalance between synthesis and degradation of extracellular matrix is one of the key factors leading to impaired

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healing [17,18]. Derailment of this system results in prolonged wound healing and can result in (hypertrophic) scar formation. The characteristics of hypertrophic scars are excessive collagen deposits, altered collagen remodeling and contraction. Transforming growth factor-β1 (TGF-β1) plays an important role in these processes as it mediates in the transition of fibroblasts into myofibroblasts. This fibroblast subtype is characterized by α-smooth muscle actin (α-SMA) expression and is involved in wound contraction. TGF-β1 induces collagen deposition by up-regulation of transcription and mRNA stability, and reduces collagen degradation by decreasing the expression of matrix metalloproteinases (MMPs) and inducing the expression of tissue inhibitors of metalloproteinases (TIMPs) [19,20].

Till recently, application of modern wound dressings in chronic wound therapy, predominantly tended towards the regulation of moisture [21,22] and pH homeostasis [23]. But now, anti-inflammatory interventions in the therapy of chronic wounds are based on pharmacological derivation of the respective dressing material, e.g. using antiseptic agents like chlorhexidine, polyhexanide or silver [24–26]. To our knowledge, there are no effective or sustainable concepts and approaches to chronic wound healing, which are solely based on the therapeutic properties of the dressing material. Therefore, there is a constant need for pharmaceutical strategies as well as and smarter materials with improved wound healing characteristics. In the present *in vitro* study, we have examined the properties of an inorganic and degradable orthosilicic acid-releasing silica gel fiber fleece on wound healing and relevant parameters in human skin cells.

Table 1
ICP-MS operating conditions and parameters.

ICP-MS	Elan-DRCII (Perkin–Elmer)
Nebulizer	Meinhard Type A quartz (Part No.: WE02-4372
Spray chamber	Quartz Cyclonic Part No.: WE02-5222
RF power	1100 W
Plasma Ar flow	15 L/min
Nebulizer Ar flow	0.93 L/min
Aux. Ar flow	1.1 L/min
Injector	2.0 mm i.d. Quartz (Part No.: WE02-3916)
Monitored ion *m*/*z*	63 (63Cu) and 65 (65Cu)
CeO+/Ce+	<3%
Sample preparation (without microwave assisted digestion)	
Acetify-reagent and volume	20 μL HNO_3 (65%) suprapur
Internal standard (IS) and volume	100 μL Rhodium (1 μg/mL)

2. Materials and methods

2.1. Materials

If not otherwise mentioned, all chemicals were purchased from Sigma (Deisenhofen, Germany). Cell culture materials were obtained from Greiner (Erlangen, Germany).

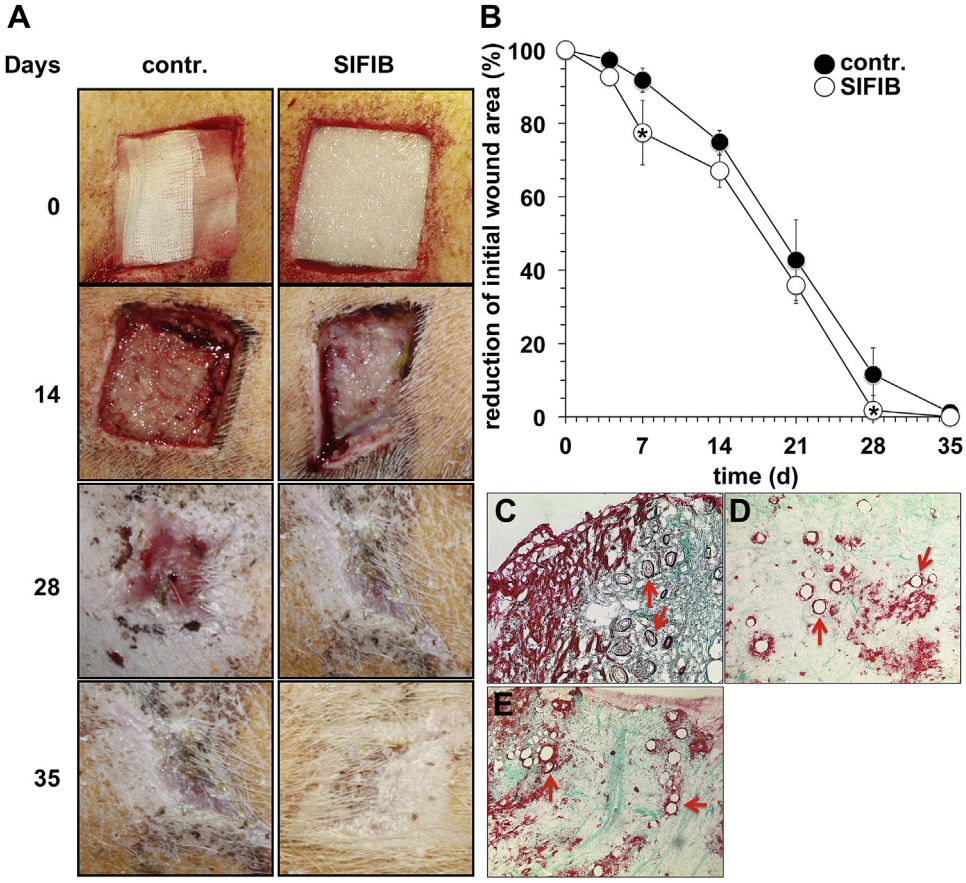

Fig. 1. Macroscopic evaluation of wound healing time and residual wound surface. In an animal model of Göttingen minipigs, full-thickness wounds (4 × 4 cm) were excised to the subcutaneous fat tissue on the back of the animals. The depth of the wounds was approximately 3.5 mm. In the control group, the wounds were sterilely covered by a gauze bandage and a dressing plaster. The gauge bandage was changed every two days. In the second group, SIFIB was inserted into the wounds, which were then sterilely covered by a dressing plaster. Here the silica fiber fleece remained in the wound although the dressing plaster was changed every two days. Wound contraction was measured by planimetry for 8 weeks after wound induction. A, Representative macroscopic pictures of important wound healing phases. B, Time course of wound healing (reduction of initial wound area). Values represent the mean ± S.D. of 6–8 wounds. *, $p < 0.005$. C, Skin section of a biopsy taken on day 7 and stained with Masson's Trichrom stain. D, E, Skin section of biopsies taken on day 14 and stained with Masson's Trichrom stain. Cyan, collagen; red, cytoplasm, and keratin; gray, nuclei.