



## Localized controlled release of stratifin reduces implantation-induced dermal fibrosis

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### ABSTRACT

Localized controlled release of anti-fibrogenic factors can potentially prevent tissue fibrosis surrounding biomedical prostheses, such as vascular stents and breast implants. We have previously demonstrated that therapeutic intervention with topically applied stratifin in a rabbit ear fibrotic model not only prevents dermal fibrosis but also promotes more normal tissue repair by regulating extracellular matrix deposition. In this work, the anti-fibrogenic effect of a controlled release form of stratifin was investigated in the prevention of fibrosis induced by dermal poly(lactic-co-glycolic acid) (PLGA) microsphere/poly(vinyl alcohol) (PVA) hydrogel implants. Pharmacodynamic effects were evaluated by histopathological examination of subcutaneous tissue surrounding implanted composites. Controlled release of stratifin from PLGA microsphere/PVA hydrogel implants significantly moderated dermal fibrosis and inflammation by reducing collagen deposition (30%), total tissue cellularity (48%) and infiltrated CD3<sup>+</sup> immune cells (81%) in the surrounding tissue compared with the stratifin-free implants. The controlled release of stratifin from implants markedly increased the level of matrix metalloproteinase-1 expression in the surrounding tissue, which resulted in less collagen deposition. These stratifin-eluting PLGA/PVA composites show promise as coatings to decrease the typical fibrosis exhibited around implanted biomedical prostheses, such as breast implants and vascular stents.

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## 1. Introduction

Local fibrosis is one of the main factors that reduce the efficacy of implanted biomedical prostheses. Fibrous capsular contracture, appearing after implantation of breast implants, remains the greatest risk of this procedure. Various factors have been proposed to elicit capsular contracture, such as foreign body reaction, hematoma, subclinical infections and the physical–geometrical characteristics of the implant [1]. Nevertheless, the specific pathophysiology of this process remains unknown.

Localized elution of anti-fibrogenic factors and corticosteroids has been used to suppress inflammation and fibrosis associated with implantation and continuous *in vivo* residence of biomedical devices [2,3]. Anti-proliferative-eluting coronary stents (either sirolimus- or paclitaxel-eluting stents) in current clinical use have shown lower rates of myocardial infarction and restenosis by preventing fibrosis compared with bare-metal stents [4,5]. The advent of a locally controlled release of an anti-fibrogenic factor to prevent excessive scar formation would be an ideal strategy for the

prevention of implant-induced fibrosis. The advantages of this local delivery system would be the need for only a low therapeutic dose and the avoidance of systemic application.

Stratifin (14-3-3σ protein; SFN) is a potent anti-fibrogenic factor that is involved in keratinocyte–fibroblast communication [6]. SFN is specifically expressed in stratified epithelial cells and increases the expression of matrix metalloproteinases (MMPs) in dermal fibroblasts [6,7]. It has been demonstrated that SFN enhances the expression of MMPs through the activation of a c-Fos and mitogen-activated protein kinase pathway [8]. MMPs are a group of diverse proteolytic enzymes that function to facilitate cell migration by breaking down collagen and other extracellular matrix components [9–11]. Collagen is the primary component of the extracellular matrix and is essential for tissue repair and regeneration; however, when expressed in excess, it can lead to fibrosis. The endogenous release of SFN from keratinocytes during normal wound healing appears to inhibit the net accumulation of collagen, thereby reducing scar formation. Although other agents, such as the cytotoxic drug suramin or the cytokine interferon alpha, can influence wound healing, these effects appear to be less precise and are associated with a number of potential systemic side effects even with local application, such as anticoagulation, immunosuppression [12], flu-like symptoms, headache, fever and muscle ache

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