Extended Abstract Polymer Sciences 2020
Vol.6 No.2

Biopolymers 2019: Development of a Novel Polymer-Based mRNA Coating for Surgical Suture to Enhance Wound Healing - Antonia Link-University Hospital Tuebingen

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Introduction:

In industrialized nations, the incidence of obesity and type II diabetes continues to increase as society simultaneously grows older. In Germany alone, 2.5% of the population suffers from chronic wounds with rising tendencies. Furthermore, chronic wounds are, on the one hand, a major burden for the person concerned and, on the other hand, they pose a socio-economic challenge: About 2% of the health budget must be raised each year to treat poorly healing wounds. Therefore, in order to cope with the enormous financial burden, new strategies must be developed for achieving rapid and complete wound healing. Moreover, wound healing is a complex three-stage process mediated by a large number of molecules such as different enzymes, cytokines, and growth factors. Since the process of wound healing is determined by the nature of the wound, the healing prospects are best with smooth and closely adjacent wound edges. Therefore, surgical sutures are used for wound closure to achieve this state whenever tissue separation occurs due to an incision, puncture, abrasion, or other injuries.

Additionally, sutures can involve of natural or synthetic textile biomaterials and they can be either monofilament with a smooth surface or braided to a multifilament structure. The sutures' physical and mechanical properties, handling properties, biocompatibility, and antimicrobial characteristic are of utmost importance. Moreover, various types of research have provided good anesthetic and antineoplastic properties to the surgical threads. Consequently, several groups have incorporated different antimicrobial agents into sutures to impart microbe resistance characteristics and prevent infections at the surgical site. A suture modification that promotes wound healing by triggering cell differentiation and proliferation in the wound area had not been introduced until now. The growth factor KGF plays an important role in wound healing because it stimulates the differentiation and proliferation of epithelial cells and conveys an anti-apoptotic effect.

Methods:

A therapeutic strategy to improve wound healing has become an increasingly important medical task due to the rising incidence of adiposity and type II diabetes as well as the proceeding population aging. In order to cope with the resulting burdens, new strategies to achieve rapid and complete wound healing must now be developed. Accordingly, the development of a bioactive wound dressing in the form of a messengerRNA (mRNA)-bearing poly(lactide-co-glycolide acid) (PLGA) coating on surgical suture is being pushed further with this study. Furthermore, the evaluation of the polymer-based transfection reagent Viromer RED has shown that it can be used for the transfection of eukaryotic cells: The mRNA gets properly complexed and translated into a functional protein. In addition, the mRNA-PLGA coating triggered the expression of the keratinocyte growth factor (KGF) in HaCat cells although KGF is not expressed under physiological conditions. Moreover, transfection via surgical sutures coated with mRNA does not affect the cell viability and a proinflammatory reaction in the transfected cells is not induced. These properties make the mRNA-PLGA coating very attractive for the in vivo application. For the future, this could mean that through the use of mRNA-coated sutures in surgical wound closure, cells in the wound area can be transfected directly, thus accelerating and improving wound healing.

Results:

Evaluation of a suitable Transfection Agent for the Construction of a mRNA Coating for Seam Material : During previous studies, it could be shown that mRNA can be delivered to cells with a variety of different transfections agents, all leading to the expression of a functional protein. For the present study, it was important to check whether the complexed mRNA could be incorporated into a coating made up of PLGA (Figure 1a). The resulting coating is extensively spread on the surface of the suture (Figure 1b,c) and ought to work as a carrier system that transfects epithelial cells with growth factor-encoding mRNA and, thus, improves wound healing.

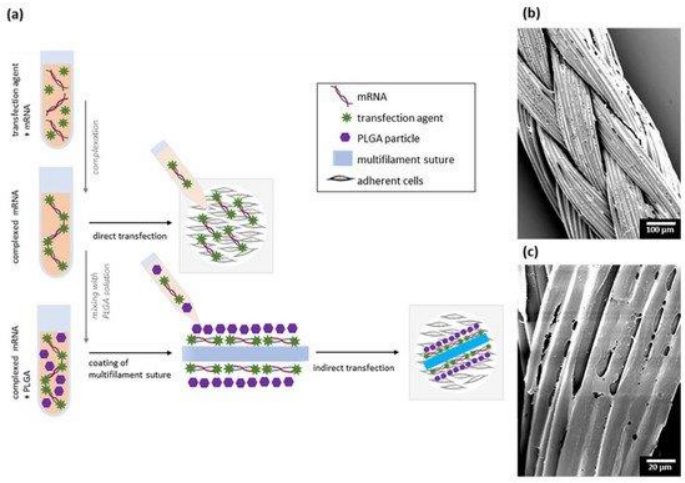

Figure 1. Schematic overview of the coating process and microscopic view of the coating. After complexation of a

specific mRNA, cells can either be transfected in a direct manner or the complexed mRNA can be mixed with a PLGA solution followed by coating of multifilament sutures and subsequent indirect transfection (a). Scanning electron microscope visualization of the surface of the mRNA-PLGA coated multifilament suture in 100-fold (b) and 500-fold (c) magnification.

Discussion

This study aimed to present a novel approach in the development of bioactive suture material using a polymer-based, mRNA-containing coating, which supports wound regeneration by specific transfection of cells in the wound area. Consequently, through the induced expression of the growth factor KGF, wound healing should be stimulated by the differentiation and proliferation of epithelial cells and the additional mediated anti-apoptotic effect. The results show that polymer-based reagents are more effective in the transfection of cells with mRNA than lipid-based reagents.

Conclusion:

In conclusion, our work describes a novel approach to support the process of wound healing by mRNA-coated suture materials. For the development of a bioactive suture coating, modified mRNA was complexed with Viromer RED and incorporated into a solution of the biodegradable polymer PLGA. The coating enabled the transfection of different cell lines as well as primary cells: The mRNA coating led to both the expression of a functional fluorescent protein as well as of the growth factor KGF. The transfection of cells via the mRNA-PLGA coating was not accompanied by cytotoxic or immunogenic effects in vitro and the results of this study suggest that the performance of the mRNA-PLGA coating can be improved even further by using other solvents for the coating solution. The excellent cytocompatibility of the coated seam material indicates that even higher amounts of mRNA could be incorporated.

To our knowledge, the present study describes, for the first time, the development of an mRNA-based suture coating aiming to transfect cells in the wound area and thus improve wound healing, which would also be of particular interest in other fields of wound management.

This work is partly presented at 9th World Congress on Biopolymers & Bioplastics, August 26-27, 2019, London, UK