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Collagen for Cell Delivery

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Advances in regenerative medicine have opened doors to new possibilities in patient treatment with the potential to repair or replace damaged tissue using cell delivery. A critical aspect of cell delivery is the delivery vehicle.

The delivery material must be biocompatible, be able to support cell growth, and degrade after treatment is completed without leaving behind any foreign matter. Many natural polymers have been studied as cell carriers, however concerns have arisen regarding their biocompatibility, immunogenicity and the ability to extract suitable amounts of material (Temenoff, et al., 2004). Collagen is an abundant natural polymer that is easily extracted and is therefore readily available. As a large component of the extracellular matrix (ECM) of humans and animals, collagen interacts closely with cells and influences their ability to migrate, proliferate, differentiate, and survive (Yang, et al., 2004). Collagen is also widely accepted to be safe, biodegradable and biocompatible.

Attachment of a cell to their carrier is crucial for cell survival and the regulation of cellular activity. Collagen has long been used as a substrate for cell culture due to its ability to enhance cell adhesion. As early as 1972, three-dimensional collagen gels were found to guide fibroblast cells towards mimicking their physiological behavior in an in vitro environment (Cukierman, Pankov, & Yamada, 2002). Since then, collagen has been proven to be an exceptional substrate for multiple cell types (Zhang, et al., 2008). In addition, collagen is one of the major components of Matrigel, a commonly used cell culture substrate in research.

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An interesting characteristic of collagen is that it has the ability to flow when cold, then gel at physiological temperatures and neutral pH. This has made collagen useful as an injectable cell delivery vehicle that will gel and protect cells once in the body. This has been particularly useful in cardiology, where collagen-encapsulated cells have been used to selectively target and promote the repair and revascularization of infarcted myocardium (Suuronen, et al., 2006). Another study has shown that collagen combined with poly(N-isopropylacrylamide) (PNIPAAm) can potentially be an injectable carrier for delivering retinal pigment epithelial cells into the subretinal space for treating retinal degeneration (Fitzpatrick, Mazumder, Lasowski, Fitzpatrick, & Sheardown, 2010).

Non-viral gene therapy has been heavily investigated as a potential treatment for a variety of diseases such as immunodeficiency, sickle cell anemia, and cancer, and has additionally been applied to tissue regeneration. Cells obtained from patients' blood or bone marrow are transfected with a particular gene then injected into the desired area of the body. Capito et al. showed that collagen-glycosaminoglycan scaffolds seeded with chondrocytes carrying IGF-1 genes were successful in facilitating cartilage regeneration (Capito & Spector, 2007), while work by Bolliet discovered the possibility of brain-tissue formation with transfected mesenchymal stem cells seeded on freeze-dried collagen scaffolds (Bolliet, 2007).

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Mesenchymal stem cells (MSCs) are of great interest in tissue regeneration because of their ability to differentiate into several tissue-specific cell types such as osteoblasts, adipocytes, and hepatocytes. Collagen has been found to be an excellent material to encapsulate MSCs as it not only acts as a protective carrier, but also acts as a three-dimensional matrix that supports their growth and allows them to function as they do in vivo (Hui, Cheung, Cheung, Chan, & Chan, 2008). A study by Perez et al. was carried out to encapsulate MSCs in collagen-alginate and implant them in injured rat skulls (Perez, et al., 2013). The group observed that the capsules did not induce any adverse reactions and supported MSC differentiation towards an osteogenic cell line, inducing bone remodeling.

Collagen is also an ideal material for wound healing, not only for its natural ability to interact with cells and the ECM, but also for its ability to absorb wound fluid (Ramshaw, Werkmesiter, & Glattauer, 1996). The market for wound dressings is so large that a number of cell-carrying collagen dressings are already available for clinical use. For example, Apligraf, a product for diabetic foot and venous leg ulcers, is a bilayer living skin graft containing a base layer of collagen mixed with fibroblasts below a layer of epidermis. In addition to wound care dressings and sponges, a variety of wound care creams, gels, pastes, and sprays are commercially available. Further, product development and research is continually being carried out to optimize therapies for cell delivery and treatment of advanced wounds and burns (Figure 1).

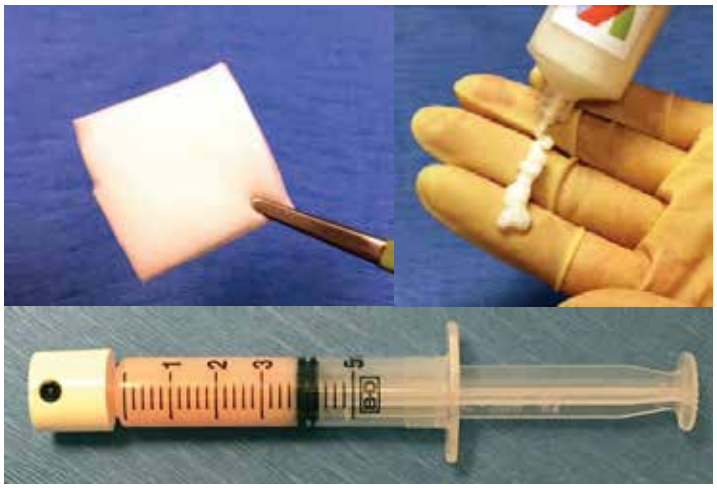

Figure 1. Collagen-based wound care products. Clockwise from top left: wound care sponge (7 mg/ml), flowable fibrillar collagen (65 mg/ml), and sprayable wound sealant (20 mg/ml).

In addition to cardiovascular, orthopedic, and wound care applications, collagen has been utilized in the development of neurological therapies. Peripheral nerve damage can be a painful experience for a patient, and is therefore a focus of many studies. A common treatment is to use autologous nerve grafts for neural regeneration. However, due to the limited availability of donor nerves, a need for fabricated nerve guides has arose. Several studies have been carried out to investigate the use of collagen as a nerve guide material in the delivery of Schwann cells for neural lesion repair. Such studies have indicated that collagen-based therapies may be superior to autologous nerve grafts (Parenteau-Bareil, Gauvin, & Berthod, 2010).

Collagen, a naturally occurring biopolymer in the ECM, has many advantages as a cell delivery vehicle for tissue regeneration. Numerous studies have exploited the unique molecular architecture of collagen to direct cell adhesion, migration, proliferation, and differentiation in tissue regeneration applications. These numerous successful examples, as well as the vast amount of ongoing research focused on regenerative medicine, indicate that collagen will be a material of choice for cell and drug delivery vehicles as new findings in the area of cell therapy are made.

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