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Editorial

Fibrin-Based Matrices for Tissue Engineering

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Editorial

Fibrin is uniquely suited to serve as a matrix for tissue engineering applications. The tissue engineering paradigm combines cells, biomaterials and signaling molecules to replace lost or damaged tissue that doesn't heal normally. As a natural component of the wound healing process, fibrin acts as a provisional matrix for cells involved in the repair of damaged tissue as well as a reservoir for cytokines and growth factors that are released during the wound healing cascade. As new vasculature is established and cells begin to migrate and produce new extracellular matrix, collagenase and plasmin get activated to degrade the fibrin clot [1]. Not only is fibrin biodegradable but the degradation products are safe as well.

These qualities have made fibrin attractive for clinical applications and the Food and Drug Administration (FDA) has approved fibrin as a sealant, hemostat and adhesive. Fibrin based products have been developed that mimic the final stage of the coagulation cascade where fibrinogen, the precursor to fibrin, is activated by thrombin to make a fibrin clot. In a peripheral vascular study, fibrin sealant achieved hemostasis within 4 minutes in 63% of patients with bleeding from suture holes for polytetrafluoroethylene grafts with no serious adverse events [2]. As a hemostat, fibrin has also been utilized in a variety of clinical procedures, such as: abdominal, cardiac, liver resection, and pediatric extracorporeal oxygenation cannulation [3]. Additionally, fibrin sealant has also used to prevent leakage from colonic anastomoses. Finally, fibrin has had success as an adhesive for skin grafts. A phase 3 clinical study showed that after 28 days 70% of patients with skin grafts affixed with fibrin sealant had complete wound closure compared to staples at 65%. Furthermore, hematoma/seroma occurrence was significantly less with fibrin sealant and had improved humanistic outcomes including ease of use for physicians and patient preference over staples [4].

The clinical success of fibrin has motivated the focus of this lab which is advancing the clinical applications of fibrin based technologies. First, understanding how the formulation of the fibrin matrix affects the porosity, permeability, and stiffness and the subsequent effect on the cells grown in fibrin is important if fibrin is to be used for tissue engineering applications. Results have shown that by changing the concentrations of fibrinogen and thrombin used to make the three-dimensional (3D) fibrin matrix, it is possible to control the stiffness and porosity. Specifically, increased fibrinogen concentration increased the stiffness of 3D fibrin matrices [5-7] and decreased the porosity [5], with thrombin concentrations having a parallel, albeit weaker, effect. These findings are significant as porosity is important for nutrition uptake, gas exchange and waste removal. Additionally, these results can be used in fibrin-based drug delivery devices as changes in porosity can alter the release profile of biologically active molecules. Finally, fibrin stiffness effects cell morphology, protein expression and migration via mechano transduction [6]. Ultimately, these findings demonstrates that it is possible to tailor fibrin matrices to suit the application.

One such application is skin tissue engineering. Current options for replacing lost skin tissue due to burns, chronic wounds, and skin diseases are limited by both quantity and quality. Fibrin's ability to sequester growth factors as well as its biocompatibility and biodegradability make it an attractive scaffold material for cells involved in skin wound healing, including immune cells, fibroblasts and keratinocytes [7]. Fibroblasts grown in 3D fibrin matrices prepared with varying concentrations of thrombin and fibrinogen were shown to increase the matrix stiffness over time, however the growth of fibroblasts was limited in constructs prepared with fibrinogen concentrations >5 mg/mL [6]. The increase in stiffness is a result of fibrin promoting extracellular matrix deposition by fibroblasts, while increased proliferation in fibrin matrices prepared with lower concentrations of fibrinogen is from the increased porosity, which facilitates cell infiltration and nutrient diffusion. Keratinocytes, however, degrade fibrin matrices specifically fibrin matrices that contain plasminogen – a precursor to plasmin – but when keratinocytes are grown in plasminogen-deficient (PD) fibrin matrices, they degrade more slowly [7]. These findings indicate that by altering the physical and biochemical composition it is possible to design fibrin matrices optimized for the proliferation of multiple cell types and for structural properties. In this way, the skin wound healing environment can be mimicked for skin tissue engineering applications.

Another application is bone tissue engineering. Every year in the United States there are 600,000 bone-grafting procedures performed to treat bone defects [8]. Current treatments are limited by donor site morbidity, availability and risk of pathogenic transmission, inflammation, and host immune rejection. Grafts that utilize fibrin, an endogenous material to the bone wound healing environment, could alleviate these limitations and make an ideal bone scaffold. Work from this lab has demonstrated that fibrin can not only serve as delivery vehicles for growth factors but also help direct the osteogenic differentiation and promote proliferation of human mesenchymal stem cells (hMSCs). For instance, hMSCs grown in fibrin matrices prepared with 5mg/mL fibrinogen had increased proliferation [9] but with fibrinogen concentrations ≥25 mg/mL hMSCs exhibited increased alkaline phosphatase expression, increased bone sialoprotein gene expression and mineralization was also observed [10]. However, osteocalcin expression, a late marker for

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osteogenic differentiation, was not increased indicating hMSCs had not fully differentiated into mature osteoblasts. In a study of hMSCs response to two-dimensional substrates of various ECM proteins, fibrinogen (10 mg/mL) showed light calcium deposition after 30 days of culture but collagen type I (1 mg/mL) had the greatest osteogenic differentiation [11]. Calcium deposition was further increased when cultured in osteogenic differentiation medium. It is likely that collagen type I production is upregulated in fibrin matrices thereby inducing osteogenic differentiation.

Fibrin's ability to control the presentation of growth factors and recapitulate an environment present during the native wound healing process highlights its strength for tissue engineering applications. In addition to aiding in the fabrication of new tissue engineering based products, findings from these projects have a significant impact from a basic science perspective. The successful fabrication of 3D fibrin-based matrices creates an in vitro model where the biochemical, cellular, and mechanical cues between progenitors cells, soluble factors, and the extracellular matrix can be studied as well as their influence on the cellular proliferation and differentiation. This equips scientists with a new tool to further their understanding of the complex biochemical and molecular events involved in the wound healing process and the maintenance of healthy tissue.

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