The Summer Undergraduate Research Fellowship (SURF) Symposium
24 July 2015
Purdue University, West Lafayette, Indiana, USA

Harnessing Notch Signaling for Biomaterial Scaffold-based Bone Regeneration

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ABSTRACT

Bone fracture has recently become prevalent, especially with an increasingly aging population. Current bone grafts procedures, including autografts and allografts, are hindered by multiple factors, such as limited supplies and inconsistent bone healing. Scaffold-based bone tissue engineering emerges as a prospective strategy to aid in bone regeneration through delivery of growth factors such as bone morphogenic proteins (BMPs). However, the use of BMPs suffers from several drawbacks such as protein instability and immunogenicity. Therefore, there exists a great need for the development of novel therapies to promote bone healing. Notch signaling, a pathway critical for cell-fate determination has been shown to regulate osteogenesis, which suggests the potential of targeting Notch to enhance bone repair. The long-term goal of this work is to develop biomaterial-based regenerative technologies to induce bone regeneration by fine-tuning Notch signaling. In this study, a three-dimensional (3D) porous scaffold system was fabricated from biodegradable poly(lactide-*co*-glycolide) (PLGA) to mimic structural and mechanical properties of native bone using a microsphere sintering technology. *In vitro* studies were conducted to evaluate the effects of notch inhibition via a γ-secretase inhibitor DAPT on osteoblast responses. When the DAPT was added during the 2D culture on tissue culture polystyrene (TCPS), the osteoblast mineral deposition was significantly enhanced. Intriguingly, the enhancement was more pronounced on the 3D PLGA scaffolds, which may be attributed to the increased cell-cell contact in the 3D culture environment. Current efforts are focused on scaffold-based modulation of Notch signaling with both quantitative and temporal precision for enhanced osteogenesis.

KEYWORDS

Notch signaling, osteogenesis, biomaterials, regenerative engineering, scaffolds