Phospholipid delivery for cell-based approaches to treat critical-sized craniofacial bone defects
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Bone defects resulting from tumor resection, disease, and trauma pose a significant health problem, and current therapies for bone regeneration and replacement are limited. Adipose stem cells (ASCs) can form mineralized tissues *in vitro* and *in vivo* and are of great interest for cell-based therapies. The efficacy of cell-based tissue repair is impaired by the significant number of cells lost upon implantation, due to the absence of a provisional matrix to retain the cells and the harsh defect microenvironment that induces apoptosis. Emerging evidence suggests that cells from older donors are more vulnerable to apoptosis compared to cells from younger donors, potentially compromising the effectiveness of autologous cell-based approaches to bone repair in the growing aging population. Therefore, agents that enhance the vitality of stem cells could be valuable additions to tissue engineering-based therapies. Lysophosphatidic acid (LPA) is a platelet-derived lipid growth factor present within the initial hematoma following fracture and is required for angiogenesis *in vivo*. LPA fosters the proliferation and survival of bone-forming osteoblasts *in vitro* and promotes the survival and viability of osteoprogenitor cells within hypoxic microenvironments characteristic of new bone fractures and large defects. Our central hypothesis is that localized presentation of LPA will be an effective osteostimulative agent by inhibiting apoptosis in implanted cells, promoting ASC survival, and enhancing neovascularization through ASC secretion of trophic factors. **Aim 1:** Fabricate fibrin hydrogels for ASC entrapment and sustained presentation of LPA at bioactive levels. LPA will be released from fibrin gels over 3-5 days by controlling fiber cross linking. **Aim 2:** Determine the anti-apoptotic and osteogenic effect of sustained LPA release from fibrin hydrogels on entrapped human ASCs from aged donors. The ability of localized LPA release to inhibit apoptosis in hypoxic and serum-reduced conditions will be assessed, and the resulting osteogenic response to these stimuli will be quantified. **Aim 3:** Determine the capacity of ASCs from aged donors to resist apoptosis, enhance vascularization through trophic factor secretion, and promote bone formation when implanted in LPA-eluting hydrogels in a rodent critical-sized calvarial defect model. Collectively, the results of these studies will provide a novel approach for enhancing the efficacy of cell-based approaches toward bone repair.