Universität Basel

Research Project

Bone prefabrication for osteonecrosis

Third-party funded project

Project title Bone prefabrication for osteonecrosis
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Background

Avascular necrosis (AVN), also known as osteonecrosis, leads to sclerosis and collapse of bone. The surgical standard uses vascularized, autologous bone grafts but is highly limited by donor site morbidity and availability. Alternative approaches are thus highly required to meet this strong clinical need. Regenerative approaches based on cell therapy with bone marrow-derived cells are not easily standardized and have so far shown variable clinical outcome. We have recently described the generation of an axially-vascularized bone graft substitute, based on freshly isolated, human adipose-derived cells, compatible with an intraoperative approach for bone repair, and demonstrated its potential to revitalize dead bone in a rat model of AVN. Beyond the proof-of-concept, the current limitation of this approach is the yet too limited amount of bone formation inside the axially-vascularized grafts.

Working hypothesis

The development and use of osteo-inductive, engineered biomaterials, based on an endochondral ossification (ECO) paradigm, combined to an axially-vascularized graft, can generate strong and reproducible bone formation in preclinical animal models of AVN.

Specific aims

In this project, 3 aims are defined: 1) Aim 1 will compare different approaches to engineer hypertrophic cartilage tissues (HCT) and evaluate their respective ectopic bone formation capacity through an ECO process. The role of integrin receptors and extracellular matrix proteins in this process will be elucidated. 2) Aim 2 will investigate how these HCT could be devitalized while maintaining their matrix properties, in order to generate devitalized osteo-inductive matrices. The performance of such matrices in bone formation and in bone repair will be assessed. 3) Finally, aim 3 will investigate the implementation of such devitalized HCT inside the axiallyvascularized grafts we recently developed and will assess if HCT can induce a more massive, reproducible and homogenous bone formation inside the grafts and in the necrotic bone around it.

Experimental design

HCT will be generated either by seeding human bone marrow- and adipose-derived mesenchymal stromal cells (MSC) onto collagen sponges, or by fractionating native, human adipose tissue followed by 3 weeks of culture on agarose-plated petri dishes. All constructs types will then be differentiated into HCT, analyzed or implanted ectopically to assess osteogenicity. The role of integrins will be studied by overexpression/silencing with lentiviral transduction/CRISPR-Cas9-mediated knockout. The performance of HCT, devitalized by various techniques (e.g. freeze drying or hydrostatic pressure) will be analyzed in

ectopic and orthotopic (calvaria) in
vivo models in rodents. Axially-vascularized grafts will be generated as previously described, containing either ceramic granules (current composition) or devitalized, osteo-inductive HCT, and will be tested in the rat model of AVN for revitalization, vascularization and bone formation potential.

Expected value of the proposed project
The present project is essential to introduce a routine clinical use of axially vascularized osteogenic grafts as prefabricated bone. The knowledge gained in this study will be useful not only to define formulations for AVN applications but also for other surgical bone regeneration strategies. In addition, more fundamental and molecular knowledge will be acquired on ECO by human bone marrow- and adipose-derived MSC, allowing for a better control of MSC differentiation into HCT and thereby a more efficient and reproducible bone formation in vivo. Finally, this project will directly contribute to the definition of a second-generation of osteogenic grafts
to be tested clinically, in the form of a clinical trial.

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