Extracellular Matrix Biphasic Scaffold Synergizing Metformin and Kartogenin for Osteochondral Tissue Engineering
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INTRODUCTION: Osteoarthritis (OA) is a musculoskeletal disorder that is common in older adults and associated with high rates of morbidity. With limited durable treatments, mesenchymal stem cell (MSC)-based tissue engineering emerges as a potential regenerative strategy. Moreover, affordable and selective, small molecules drug can modify stem cell behavior during differentiation, holding promise for clinical use.

METHODS: This research introduced a biphasic scaffold (BPS) integrating a bone layer (gelatin/hydroxyapatite/metformin [GHSM]) and a cartilage layer (gelatin nano-fiber/kartogenin [NGFK]). The BPS, built on the extracellular matrix (ECM), was embedded with two small-molecule drugs, kartogenin (KGN) and metformin (MET), to drive osteochondral regeneration. Leveraging ECM-based biomaterials mirroring native tissues, the scaffold facilitated cell recruitment, infiltration, and differentiation without supplementary growth factors.

RESULTS SECTION: The BPS exhibited favorable in vitro biocompatibility. Mesenchymal stem cells (MSCs) displayed adherence, proliferation, and differentiation capabilities on both the GHSM and NGFK layers.

DISCUSSION: Co-culturing with NGFK and GHSM layers led to upregulation of double-stranded DNA (dsDNA), sulfated glycosaminoglycan (sGAG), as well as osteo- and chondrogenic biomarkers, alongside increased relative mRNA levels. Notably, histological staining indicated successful rat osteochondral defect regeneration in vivo.

SIGNIFICANCE/CLINICAL RELEVANCE: Anticipated to bolster subchondral bone healing and cartilage rejuvenation, this innovative biphasic scaffold demonstrates impressive abilities in fostering cell attraction and the enlistment of native cell populations.

IMAGES AND TABLES:

![Figure 1. Relative osteogenic and chondrogenic gene expression in hMSCs cultured with the GHSM and NGFK, compared with the control group.](image1)

![Figure 2. Immunofluorescence staining of osteo- and chondro-specific biomarkers. Osteocalcin and aggrecan were stained in red, and the different types of collagens were stained in green.](image2)

![Figure 3. Histological staining. (A) H&E staining of subchondral bone. (B) AB/PAS staining of cartilage regeneration. The positive reaction between AB and PAS makes neutral and acidic mucocutaneous appear purple.](image3)