The Chinese University of Hong Kong
Department of Biomedical Engineering

Graduate Seminar – PhD Oral Defence

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Date : 2 June 2022 (Thursday)
Time : 10:00 am
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Meeting ID : 425 463 1137
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Title: Development-inspired Biofunctionalization of Hydrogels for Tissue Regeneration and Regulating Cellular Function

Developing cell-laden tissue engineering scaffolds to mimic the biochemical complexity of the cellular microenvironment is pivotal to promoting the desired cellular events and tissue regeneration. This thesis focuses on the biomimetic biofunctionalization of hydrogels with development-relevant cues to regulate cell behaviors. Modifying hydrogels with development-inspired ligands activates the specific signaling events during stem cell differentiation or T cell activation to mediate targeted therapeutic responses. In contrast to adding these bioactive ligands directly to culture media, where they are diluted and may lose their bioactivity after internalization by cells, these functionalized ligands are believed to enhance local concentration and prolong ligand bioactivity ligated to membrane receptors. Therefore, we demonstrate several synthetic presentation approaches for biomimetic ligands within biomaterial scaffolds to guide cell lineage commitment and skeletal tissue regeneration. Also, we developed a biomaterial-based presentation platform for T cell antigens to enhance ex vivo stimulation and activation of T cells.

Firstly, we investigated the effect of a synthetic Wnt5a mimetic ligand (Foxy5 peptide)-functionalized hyaluronic acid hydrogel on chondrogenesis of hMSCs and the potential molecular mechanisms involved. According to our findings, the conjugation of Foxy5 peptide in the hydrogels activates non-canonical Wnt and the IKK/NF-κB signaling of encapsulated hMSCs via the upregulation expression of PLCE1, CaMKII-β, and downstream NFATc1, The activated signaling pathway further leads to enhanced expression of chondrogenic markers (SOX9), promotes chondrogenesis of hMSCs and the cartilage matrix formation and inhibits the chondrocytes hypertrophy. The Foxy5 peptide-functionalized hydrogels effectively boost glucose metabolism and ATP expression level. In the second study, we conjugated the porous hyaluronic acid hydrogels with a Jagged-1 mimetic peptide ligand (Jagged-1) and investigated the effect of promoting the mechanotransduction and osteogenesis of human mesenchymal stem cells by activating Notch signaling pathway. Our findings indicate that the immobilized Jagged-1 mimetic ligand activates Notch signaling via enhancing the formation of focal adhesions (elevated pFAK and Vinculin expression), ROCK2 expression, and YAP nuclear localization which promotes the expression of osteogenic markers including Runx2, ColI, ALP, and SPP1. Furthermore, the formation of CSL-NICD-MAM complex in the nucleus leads to the up-regulation of NICD, downstream of MSX2, enhanced mechanotransduction, and osteogenesis of stem cells. We further demonstrate that the functionalization of Jagged-1 ligands in the porous scaffold promotes angiogenesis, regulates macrophage recruitment and polarization, and enhances in situ regeneration of rat calvarial defects. In the third study, we decorated HA with the anti-CD3 (stimulation signal 1) and anti-CD28 (co-stimulation signal 2) antibodies via the CD – ADA host-guest complexation to investigate the effect on T cell activation and the cell-based therapeutic application. Furthermore, the

dynamic host-guest substrate promotes the TCR activation marker genes (IFN-γ, TNF-α, and NFATc1). It, therefore, enhances the maturation and immune functionality of the naïve CD8+ T cells, the memory cell induction, and functional T cell generation. Furthermore, the in vivo cytotoxic killing assay results show that CD8+ T cells harvested from the dynamic substrate effectively eliminate the antigen-expressing cancer cells, suppress the tumor growth, and promote the survival rate of tumor-bearing mice.

In summary, this thesis highlights the importance of the biofunctionalization of biomaterial scaffolds with development-relevant cues in directing the cell fate and enhancing the regenerative outcome of regenerative cell-based treatments and the anti-cancer efficacy of immune cells. These findings provide valuable guidance to the development-inspired rational and biomimetic design of biomaterials for a wide array of therapeutic applications.

***** ALL ARE WELCOME *****

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