The Chinese University of Hong Kong
Department of Biomedical Engineering

Graduate Seminar – PhD Oral Defence

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Date	***:***	18 May, 2021 (Tuesday)
Time	***:***	2:30 pm
Zoom Link	***:***	https://cuhk.zoom.us/j/4934442203?pwd=NWpYOStkTXlzN3BDeUs3dVppYU1MZz09
Meeting ID	***:***	493 444 2203
Password	***:***	569046

Title: Development of Stimuli-Responsive Single-Chain Nanogels with Tunable Ligand Presentations for Regulating Cellular Behaviors

Design of biomaterials to regulate cell behaviors require precise control over the architecture and the function of synthetic materials. Among various preparation methods of polymeric biomaterials, the bottom-up approach is one of the powerful techniques that utilize molecular level design to fine tune the properties and function of biomaterials at different scales. The single chain polymeric nanoparticles or nanogels (SCNPs or SCNGs) is a class of single chain polymeric nano-objects that are suitable for such molecular design. The SCNPs are prepared by intramolecular collapse of linear polymers in a manner analogous to protein folding, the obtained SCNPs possess the folded protein-like structure and can be used in a wide array of applications. In addition, the SCNPs can be unfolded chemically or mechanically, and this is advantageous to achieve dynamic control of cellular behaviors. In this dissertation, we present a SCNP-based platform with conformational dynamics to achieve tunable ligand presentations, thereby regulating cell behaviors.

In the natural cell microenvironment, many biomacromolecules can present multiple ligands in a single molecule and synergize their effect on regulating cellular functions. On the other hand, biomacromolecules can also undergo conformational changes in response to environmental stimuli, such as protein unfolding due to cellular forces, thereby exposing cryptic receptor-binding sites, and such dynamic presentations of hidden ligands enable the spatiotemporal regulation of the ligand−receptor ligations and associated signaling events. Inspired by these properties of biomacromolecules, we developed a reduction-responsive single-chain macromolecular nanoregulator by using our recently developed scaled-up reversible addition fragmentation chain transfer (RAFT) polymerization. The SCNGs contain a terminal master ligand (Foxy5 peptide, Wnt5a mimetic peptide) and a cryptic ligand (RGD peptide) concealed in core domain. Such SCNGs are capable of mediating a triggered co-presentation of the dual ligands to elicit the synergistic crosstalk between two intracellular signaling pathways: Non-canonical Wnt signaling pathway and integrin-mediated mechanotransduction. Our finding demonstrated that the SCNGs with non-unfoldable crosslinker can effectively hide the cryptic RGD ligand in the core domain and hamper cell adhesion and spreading. In contrast, SCNGs with unfoldable crosslinker can present RGD ligand upon unfolding and promote cell adhesion and mechanosensing. Moreover, our results also showed that SCNG-based dual ligand co-presentation platform possesses better efficacy to induce osteogenic differentiation than that of the SCNGs containing only the master ligand and non-unfoldable SCNGs. More importantly, our finding showed that the co-presentation of dual ligands in separate SCNGs cannot achieve the same effect in osteogenic differentiation as that of the co-presentation of dual ligands in the same SCNG, and this indicates that dual ligand presentation in the same SCNG can promote the physical proximity of the corresponding receptors, thereby synergistically activating the Non-canonical Wnt signaling pathway and integrin-mediated mechanotransduction. We envision our biomimetic SCNG-based macromolecular regulator can be a potential platform to investigate the impact of nanoscale ligand presentations on the functions and behaviors of different cell types.

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

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