Programmable Hydrogels for Drug Delivery and Regenerative Medicine

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Statement of Purpose: The development of materials with multiple functions that can be regulated on demand in response to different requirements is an essential topic in the field of biomaterial sciences and engineering. While this speculation has existed for decades, the realization of such a concept is still a challenge. Great efforts have been made in developing materials that can respond to a variety of physical stimuli such as pH, temperature, magnetism, ultrasound, etc. Recent studies have shown that biomolecules can be used to develop multifunctional materials whose properties can be controlled at the molecular level. This presentation will introduce how nucleic acid aptamers and hydrogels are used to develop programmable materials for biomedical applications such as drug delivery and regenerative medicine.

Methods: Programmable hydrogels were synthesized with two different methods including free radical polymerization and physical entrapment. In the method of free radical polymerization, monomers and Acrydite-functionalized aptamers were mixed with initiator and catalyst. In the method of physical entrapment, aptamers were first tethered onto the surface of particles and the particles were subsequently suspended in pregel solution to form a hydrogel. The hydrogels were characterized with numerous assays such as rheology and fluorescence imaging. The hydrogels were also characterized to demonstrate their capability of controlling the on-demand release of multiple protein drugs. The molecular recognition and drug release were characterized with surface plasmon resonance, ELISA and in vitro cell proliferation assays. The hydrogels were also examined by evaluating their interactions with target cells including cancer cell lines and cells harvested from human patients. The cells were examined with diverse assays to characterize their attachment, morphology, and viability.

Results: Our experimental results show that aptamers could be effectively incorporated into hydrogels. Moreover, the incorporation of aptamers into hydrogels did not compromise their molecular recognition capabilities. Resultantly, the incorporated aptamers were able to hold protein drugs with high binding strength and specificity. By using aptamers with different binding affinities and concentrations, different release kinetics could be achieved. More importantly, when the sequences complementary to aptamers were applied to treat hydrogels, the hydrogels were able to respond to the complementary sequences and release the loaded protein drugs on demand. When multiple protein drugs and aptamers were incorporated into the same hydrogel, the treatment of hydrogels with different complementary sequences led to the sequential release of the loaded drugs at predetermined time points with the right amount. In addition to the examination of the programmable hydrogels for controlled protein release, the outcomes of the controlled release were also evaluated using intervertebral disc cells harvested from human patients. The results show that the released protein drugs (e.g., PDGF-BB) were able to stimulate the growth of human IVD cells. The programmable release of multiple protein drugs is currently evaluated in animal models.

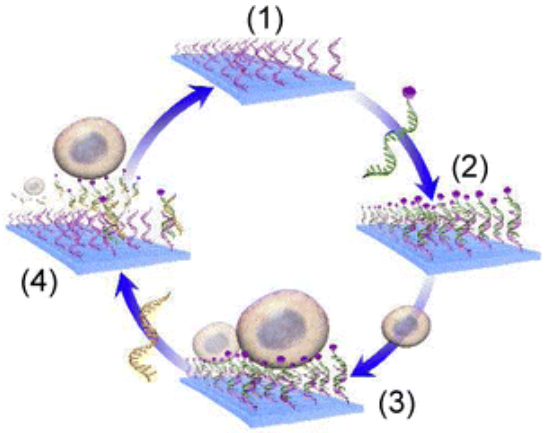

Figure 1. Schematic illustration of a programmable hydrogel for controlling cell-hydrogel interaction. (1) Hydrogel regeneration. (2) Display of nucleic acid aptamers on the hydrogel. (3) Aptamer-mediated cell catch. (4) Complementary sequence-programmed cell release for hydrogel regeneration.

In addition to the examination of programmable drug release, hydrogels were also evaluated by investigating their interactions with target cells (**Figure 1**). The results successfully demonstrate that the interactions between cells and hydrogels could be programmed by using aptamers and their triggering complementary sequences. In the absence of the triggering sequences, the aptamers allowed for strong cell attachment. In the presence of the triggering sequences, the aptamers were transformed into a new hybridized state that weakened the binding of cells to hydrogels. Resultantly, cells could be released from the attached hydrogels. Importantly, the entire procedure of cell attachment and dissociation could be repeated.

Conclusions: Nucleic acid aptamers and hydrogels can be applied to the development of programmable materials for not only on-demand drug delivery but also the regulation of cell-material interactions. While hydrogels have been studied as a model, the same concept can be extended to any other biomaterial by using the aptamer-based molecular recognition principle.

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