Preparation of MMP-sensitive Hyaluronic Acid Hydrogels and Their Impact on Cell Migration

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Mimicking the structures and functions of extracellular matrix (ECM) is an important guidance for biomaterials design. ECM takes a key role in signal transduction. For example, enzymes are secreted or locally activated by migrating cells to degrade, and then to remodel the ECM. Therefore, a 3D matrix simulating the structure and function of ECM provides a better model system of physiological environment for cell migration study. Hyaluronic acid (HA) derivatives are widely used in biomedical field. The present study mainly focuses on the fabrication of an active and cell-responsive HA-based hydrogel. The migration of vascular smooth muscle cells (SMCs) is studied in the 3D matrix.

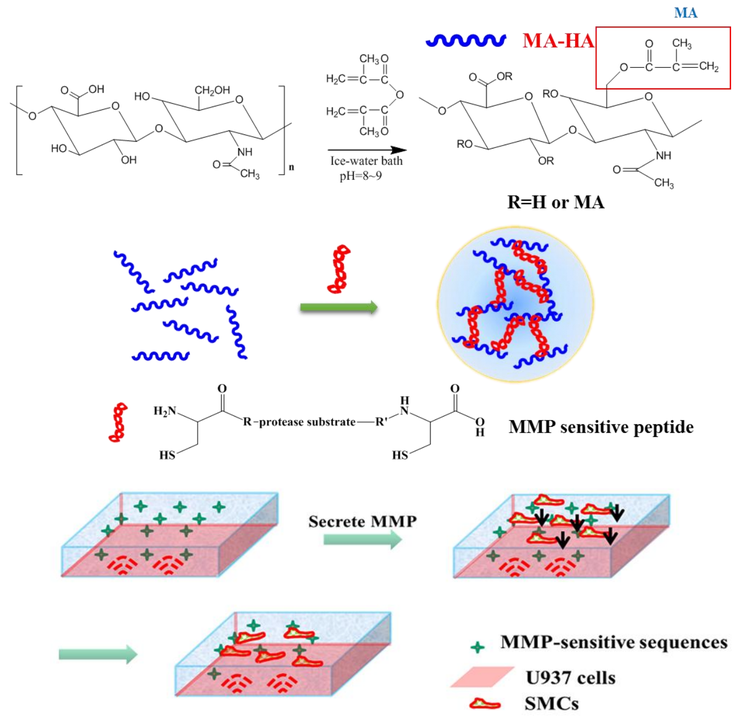

Figure 1 Schematic illustration of fabrication of HA derivatives, formation of hydrogel, and the invasion of SMCs in a 3D matrix. The peptide (Ac-GCRD-GPQG-IWGQ-DRCG-NH_2, MMP SP) with two -SH groups and sensitive to matrix metalloproteinases (MMPs), a protease family extensively involved in tissue development and remodelling. U937 cells (a model macrophage cell) were used to be a signal source and MMP producer to induce the SMCs invasion to mimic the sequential tissue regeneration process in vivo. DTT crosslinked hydrogel was treated as a non-degradable hydrogel.

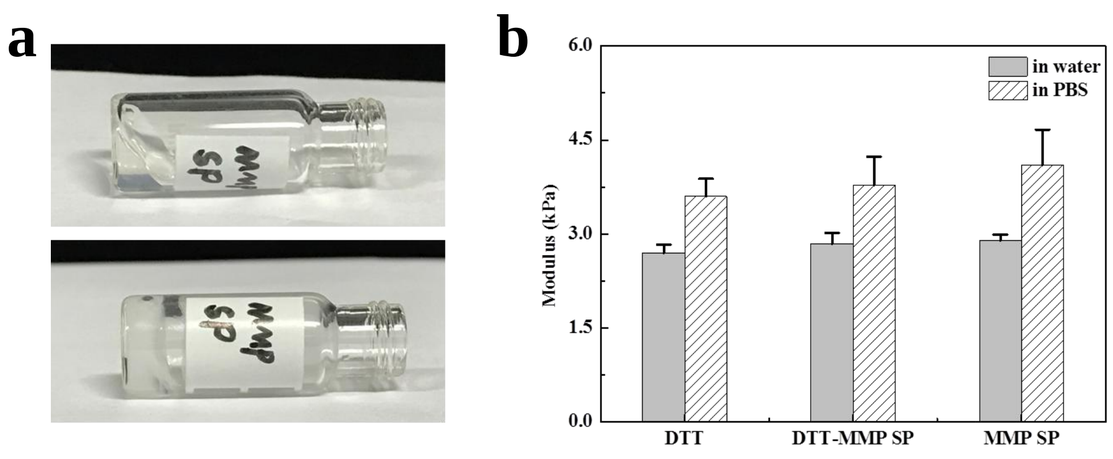

Figure 2 (a) Formation of MMP sensitive peptide (MMP SP) crosslinked hydrogel; (b) Mechanical properties of hydrogels in water and PBS.

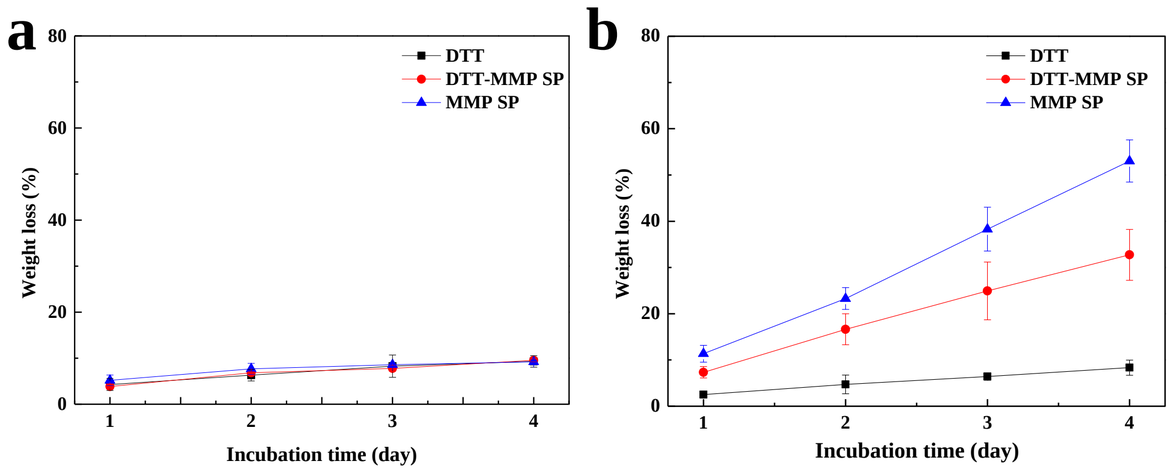

Figure 3 (a) Weight loss of hydrogels in PBS; (b) Weight loss of hydrogels in PBS containing 0.2 μg/ml MMP.

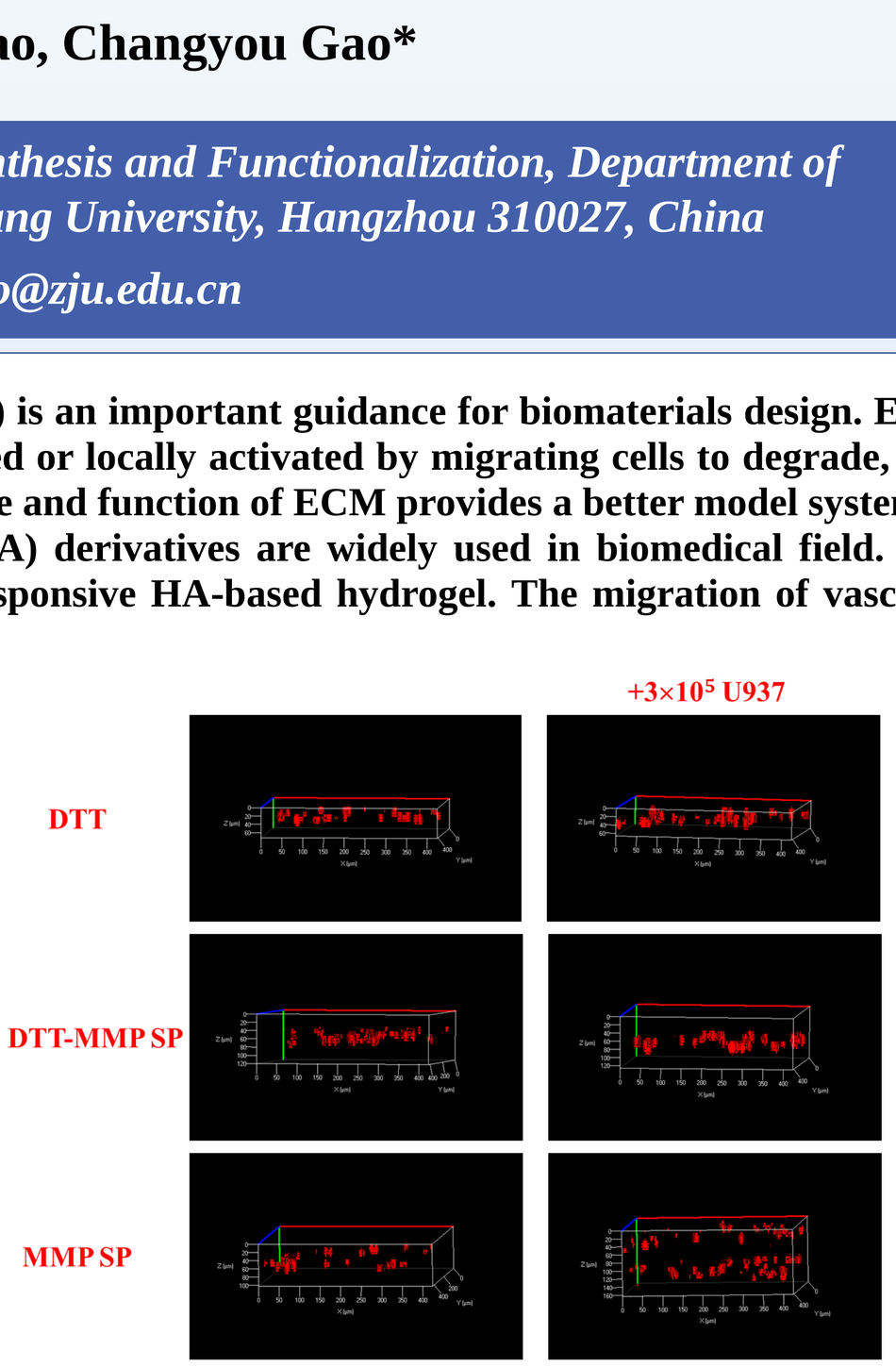

Figure 4 3D constitution confocal images of SMCs invasion distance at 3 days in different hydrogels with or without U937 cells.

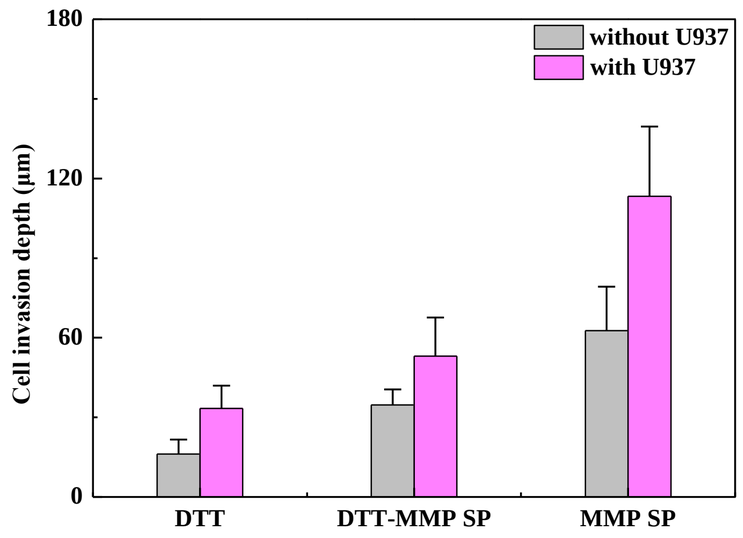

Figure 5 SMCs invasion distance at 3 days in different hydrogels with or without U937 cells.

Conclusion

Through MMP SP crosslinking, a cell-responsive hydrogel was fabricated. In the non-degradable hydrogels, SMCs only invaded a distance of 50 μm into the hydrogels after 3 days, even with the attracting signal from U937 cells. In contrast, the SMCs invaded much deeper (over 150 μm) into the MMP-sensitive hydrogels toward the direction of U937 cells. The study provides a versatile model to study multiple important physiological processes, such as tissue regeneration and tumor metastasis.

Acknowledgement

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