Development of a peptide forming a hydrogel with higher-order structural transition and application to tissue regeneration

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The extracellular matrices (ECMs) provide a biological niche for regulating cellular responses by regulating not only cell adhesion but also the binding and release of secreted proteins. In regenerative medicine, as artificial ECMs, self-assembling peptide hydrogels can be widely used because of their cell-adhesive properties and degradability into chemically-defined molecules. However, incorporating and releasing secreted proteins are generally incompatible, and development of peptidic materials capable of incorporating and releasing secreted proteins remains mostly unexplored.

Here, we developed a novel cell-adhesive fiber-forming peptide allowing efficient incorporation and sustained release of vascular endothelial growth factor (VEGF), and the peptide gel showed cell transplantation-free regenerative therapeutic effects on a subacute-chronic phase mouse stroke model.[1] We focused on dynamic higher-order structural transition as a new approach to achieving efficient protein binding and sustained release functions. The AxxxA and GxxxG motif, amino acid sequences in which two alanines or glycines are present across three residues, found in membrane proteins that transform the structure from α-helix[2] to *β*-strand in response to the external environment to form nanofibers.[3] Inspired by this dynamic property, we have developed the alternating amphiphilic peptide JigSAP (Ac-RIDARMRADIR-NH_2) with the AxxxA motif. JigSAP formed supramolecular nanofibers and a hydrogel (Fig. 1a) through a helix-to-strand transition (Fig. 1b) under physiological conditions. The fibers were dispersed homogeneously in the hydrogel. The supramolecular properties of JigSAP hydrogel allowed efficient incorporation and sustained release of VEGF-JigSAP (Fig. 1c). JigSAP incorporating VEGF-JigSAP showed enhanced angiogenesis *in vitro* (Fig. 1d) and demonstrated regenerative therapeutic effects in a subacute-chronic phase mouse stroke model.

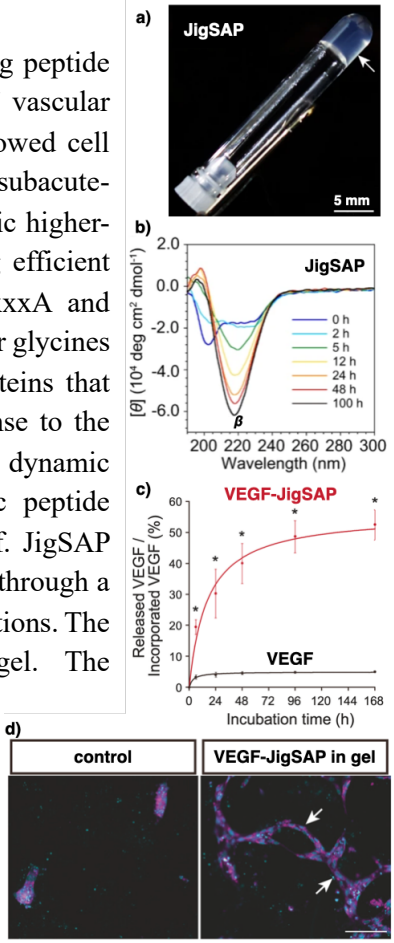

Fig. 1 a) Photograph of JigSAP hydrogel. b) Time-course CD spectral change of JigSAP after dissolved in a buffer. c) Time-course releasing profile of VEGF from JigSAP hydrogel. d) LEL (magenta) and DAPI (cyan) fluorescence images of HUVECs.

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