Smart Supramolecular Hydrogels for Long-term Bioengineered Stem Cell Therapy

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Statement of Purpose: Synthetic hydrogels have been extensively investigated as an artificial extracellular matrix (ECM) for tissue engineering *in vitro* and *in vivo* [1]. Crucial challenges for such hydrogels are the long-term encapsulation and spatio-temporal control of cells with proper cues for cell proliferation and differentiation at the right place and time [2]. Here, we report *in situ* supramolecularly assembled and modularly modified hydrogels using cucurbit[6]uril conjugated hyaluronic acid (CB[6]-HA), diaminohexane conjugated HA (DAH-HA), and tag-CB[6] for the treatment of intractable diseases with long-term bioengineered mesenchymal stem cell (MSC) therapy.

Methods: All-*trans*-retinoic acid (ATRA) was conjugated to HA in DMSO. Diaminohexane (DAH) was grafted to HA. Dexamethasone (Dexa)-CB[6] was prepared by the conjugation between dexamethasone-21-hemiesters and amineCB[6] using DCC/NHS chemistry in DMSO. The ATRA-HA and Dexa-CB[6] were characterized by ^{1}H NMR analysis. Each 3 wt% solution of CB[6]-HA and DAH-HA (with or without ATRA and Dexa-CB[6]) was prepared and mixed in the presence of engineered MSCs (eMSCs) [3] for the preparation of *in situ* forming hydrogels by host-guest interaction between CB[6] and DAH [4]. The HA-CB[6]/DAH hydrogel was modularly modified by simple mixing with Dexa-CB[6]. The disease models of cancer and ischemia were prepared and treated with CB[6]/DAH-HA hydrogels with Dexa-CB[6] and ATRA encapsulating eMSCs for IL-12M or hHGF.

Results: Figure 1 shows a schematic illustration for the supramolecular hydrogel of CB[6]/DAH-HA hydrogels to encapsulate eMSCs. Dexa-CB[6]/RA-DAH-HA hydrogel was prepared to treat intractable disease by simple mixing of CB[6]-HA solution and RA-DAH-HA solution in the presence of MSCs engineered for IL-12M (eMSCs/IL-12M) with modular modification of Dexa-CB[6].

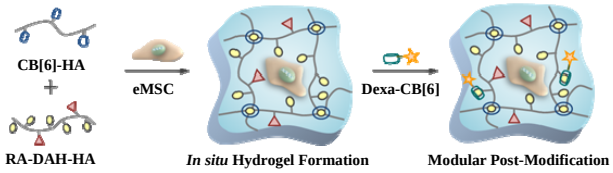

Figure 1. A schematic illustration for engineered mesenchymal stem cell (eMSC) therapy using supramolecular hyaluronic acid (HA) hydrogels.

Figure 2a shows the anti-tumor effect of long-term repeated eMSC cancer therapy using supramolecular HA hydrogels. The repeated injection of eMSC/IL-12M in the hydrogel precursor solutions resulted in significantly reduced tumor growth for up to 40 days. Remarkably, the post-injection survival period of eMSCs/IL-12M in the Dexa-CB[6]/RA-DAH-HA hydrogel was extended to approximately 85 days.

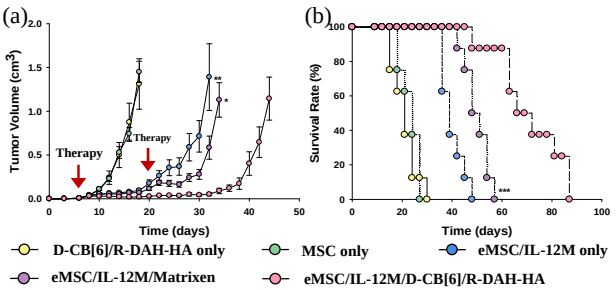

Figure 2. Long-term repeated engineered mesenchymal stem cell (eMSC) cancer therapy using supramolecular hyaluronic acid (HA) hydrogels: (a) tumor growth and (b) survival rate.

Figure 3 shows the effect of eMSC therapy on limb ischemia according to the laser Doppler flowmetry. The intramuscularly injected CB[6]/DAH-HA hydrogels with Dexa-CB[6] and ATRA encapsulating MSCs engineered for hHGF significantly increased the blood vessel regeneration with a drastically enhanced blood perfusion.

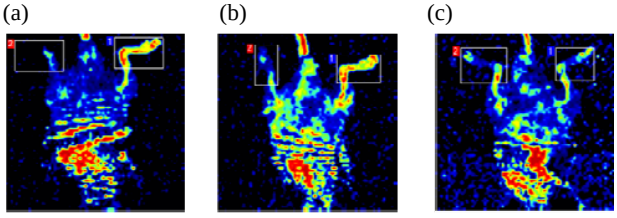

Figure 3. The effect of engineered MSC ischemia therapy using CB[6]/DAH-HA hydrogels with Dexa-CB[6] and ATRA: (a) media only, (b) eMSC/hHGF only, and (c) eMSC/hHGF/D-CB[6]/R-DAH-HA hydrogel.

Conclusions: The long-term release of therapeutic proteins by bioengineered MSCs in the supramolecular hydrogels resulted in the effective treatment of intractable diseases such as cancer and limb ischemia. Taken together, we could confirm the feasibility of Dexa-CB[6]/RA-DAH-HA hydrogels for various cell therapies and tissue engineering applications.

References:

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