Smart Supramolecular Hydrogels for Long-term Bioengineered Stem Cell Cancer 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 tags-CB[6] for long-term bioengineered mesenchymal stem cell (MSC) cancer 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 bioengineered MSCs [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]. C57BL/6 mice were injected with B16F10 murine melanoma cells to prepare cancer animal models for 6 days and treated with CB[6]/DAH-HA hydrogels with Dexa-CB[6] and ATRA encapsulating MSCs engineered for IL-12m.

Results: Figure 1 shows a schematic illustration for the supramolecular hydrogel of CB[6]/DAH-HA hydrogels encapsulating MSCs. ATRA was directly conjugated to HA backbone and Dexa-CB[6] was modularly modified to the hydrogel. ATRA is known to enhance transgene expression of recombinant adenoviral (rAd) vector which includes cytomegalovirus (CMV) promoter [2]. Dexa has a positive effect on the proliferation of MSCs.

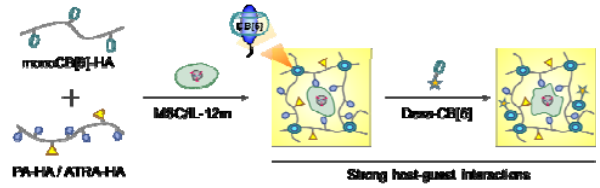

Figure 1. Schematic representation of supramolecularly assembled and modularly modified CB[6]/polyamine (PA) - HA hydrogel with Dexa-CB[6] and ATRA encapsulating MSCs engineered for IL-12 expression.

Figure 2a shows *in vitro* release of Dexa by the hydrolysis of ester linkage between Dexa and CB[6] in the hydrogels. According to IL-12 ELISA, CB[6]/DAH-HA hydrogel with both Dexa-CB[6] (D) and ATRA (R) revealed the highest IL-12 expression for 10 days, followed by CB[6]/DAH-HA hydrogel with Dexa-CB[6], that with ATRA, that without Dexa-CB[6] and ATRA, Matrigel, and Matrixen (Figure 2b).

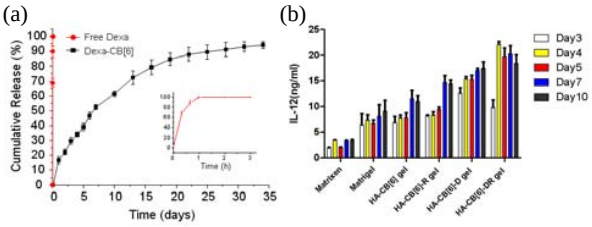

Figure 2. (a) *In vitro* release of Dexa from CB[6]/DAH-HA hydrogel modularly modified with Dexa-CB[6]. (b) *In vitro* release of IL-12 from various hydrogels.

Figure 3 shows the effect of MSC cancer therapy on (a) the tumor growth and (b) the survival rate. The intratumorally injected CB[6]/DAH-HA hydrogels with Dexa-CB[6] and ATRA encapsulating MSCs engineered for IL-12 significantly reduced the tumor growth rate with a drastically enhanced survival rate.

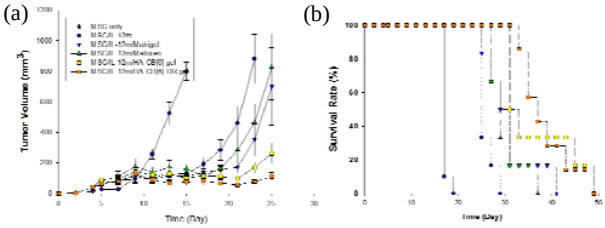

Figure 3. The effect of engineered MSC cancer therapy using CB[6]/DAH-HA hydrogels with Dexa-CB[6] and ATRA on (a) the tumor growth and (b) the survival rate.

Conclusions: The long-term release of IL-12 by bioengineered MSCs in the supramolecular hydrogels resulted in the effective inhibition of tumor growth with a significantly enhanced survival rate. These results confirmed the feasibility of CB[6]/PA-HA hydrogels for various tissue engineering applications.

References:

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