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Development of Tissue Adhesive Organic/Inorganic Hybrid Particles for Local Hyperthermia after Removal of Early-Stage Gastrointestinal Cancer

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Abstract

Incomplete removal of early-stage gastrointestinal cancers by endoscopic treatments often leads to recurrence induced by residual cancer cells. However, few biomaterials can be applied as endoscopic devices to locally kill cancer tissues and cells. We previously reported that decyl group-modified Alaska pollock gelatin-based microparticles (C10MPs) can adhere to gastrointestinal tissues by forming a colloidal gel driven by hydrophobic interactions. In this study, we combined C10MPs with superparamagnetic iron oxide nanoparticles (SPIONs; SP) to develop a heat-generating material (SP/C10MP colloidal gel) for localized thermal cancer treatment. The tissue adhesion strength of SP/C10MP colloidal gel was improved by the modification of decyl group and the addition of SPIONs. Moreover, SP/C10MP colloidal gel locally generated heat in response to an alternating magnetic field and successfully killed cancer cells in colon cancer-bearing mouse models.

1. Introduction

Endoscopic technique has been known as a minimally invasive treatment to remove early-stage cancer in the gastrointestinal tract. However, the recurrence of cancer after the endoscopic surgery occurs with a certain ratio when cancer tissue is not completely removed. Therefore, a biomaterial that can locally kill the residual cancer cells and tissue is required. In this study, we designed organic /inorganic hybrid biomaterial that combined with the tissue adhesive C10MPs[1-4] and the SPIONs as a heat-generating nanomaterial to achieve a stable wound covering and thermal cancer treatment (**Fig. 1**)[5].

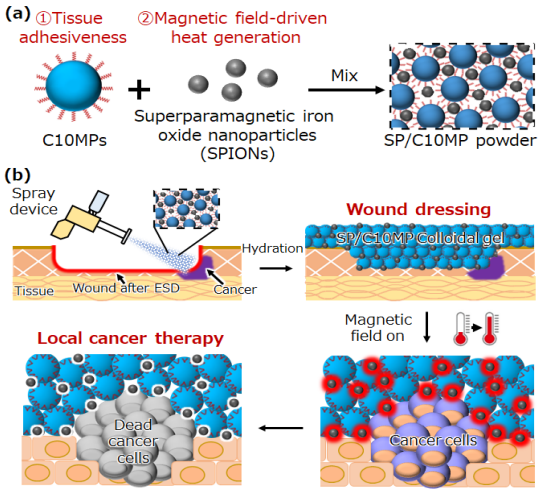

Fig. 1 (a) Mixing C10MPs and SPIONs to prepare SP/C10MP powder. (b) Application of SP/C10MP colloidal gel for local thermal cancer therapy.

2. Experiment

C10MPs were prepared from decyl group-modified Alaska pollock gelatin by coacervate formation, freeze-drying, and thermal crosslinking. SPIONs were prepared by the co-precipitation of Fe^{2+} and Fe^{3+}. C10/SPMP colloidal gel was prepared by physically mixing the C10MPs and SPIONs, followed by hydration. The tissue adhesion strength of SP/C10MP colloidal gel was measured by ASTM F2258-05 using a porcine stomach. SP/C10MP colloidal gel was implanted in a colon cancer-bearing mouse, and an alternating magnetic field (130 G, 373 kHz) was applied to generate heat and observe the thermal treatment effect.

3. Results and discussion

OrgMPs (non-modified ApGltn microparticle), C10MPs, and SPIONs with a particle size of 3.5 ± 1.8 μm, 2.3 ± 1.0 μm, and 11 ± 2.4 nm were prepared (**Fig. 2**). SP/C10MP powder was prepared by physically mixing the obtained C10MPs and SPIONs and colloidal gel was prepared by hydration of mixed powder (**Fig. 3**). The mixing ratios of SPIONs were varied (SP/C10 = 0/50, 20/50, 40/50, and 60/50 mg/mg) to evaluate the effect of SPION addition. The tissue adhesion strength of SP/C10MP colloidal gel was higher than SP/OrgMP colloidal gel due to the hydrophobic interactions between C10MP-C10MP and tissue-C10MPs. Interestingly, the maximum adhesion strength was obtained at SP/C10MP = 40/50 mg/mg (**Fig. 4**). This result is because SPIONs formed coordination bonds with the carboxy groups of ApGltn molecules to improve the storage modulus of the colloidal gel. However, the high content of SPION (SP/C10MP = 60/50 mg/mg) resulted in a decrease in adhesion strength due to the less hydrophobicity of colloidal gel. On the other hand, when SP/C10MP colloidal gel (SP/C10MP = 40/50 mg/mg) was implanted in a colon cancer-bearing mouse and a magnetic field (130 G, 373.35 MHz) was applied, the local temperature increased to 43.5°C. After the thermal treatment for 12 days, the tumor volume in the thermally treated group significantly reduced compared to that in the untreated group (**Fig. 5**). These results suggest that SP/C10MP colloidal gel can be applied to local thermal cancer treatment.

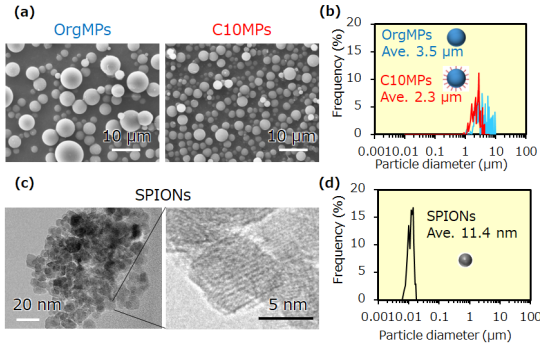

Fig. 2 (a) SEM images of OrgMPs and C10MPs. (b) Particle size distribution of OrgMPs and C10MPs. (c) TEM image of SPIONs. (d) Particle size distribution of SPIONs.

Fig. 3 (a) Preparation of SP/C10MP colloidal gel.

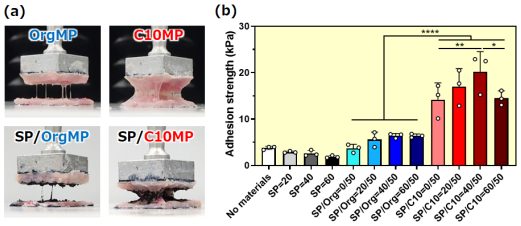

Fig. 4 (a) Images of tissue adhesion test using porcine stomach submucosal tissue. (b) Maximum adhesion strength of SP/OrgMP and SP/C10MP colloidal gel. *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$.

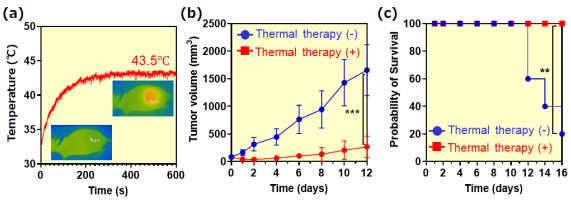

Fig. 5 (a) Temperature change under the magnetic field where SP/C10MP colloidal gel was implanted in a mouse. (b, c) Comparison of (b) tumor volume change and (c) probability of survival between thermally treated and untreated groups.

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