Biodegradable and biocompatible 3D-printed scaffolds loaded with chemotherapy drugs: A new horizon for treatment of colon cancer with diffuse intraperitoneal metastasis

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1. Introduction:
Diffuse intraperitoneal metastasis is a big challenge in colorectal cancer patients. In this study, we used 3D printers to prepare biodegradable and biocompatible scaffolds loaded with doxorubicin. We believe sustained degradation of these completely degradable scaffolds in the peritoneal cavity can cause the sustained release of the drug in this cavity and decrease the drug’s systemic side effects while increasing therapeutic efficacy.

2. Method:
Gelatin (10%, 20%, 40%), polyurethane, and hydroxyapatite were dissolved in acetic acid to form the scaffold dough and then doxorubicin was added. At last, this mixture was 3D printed in mesh-like cubic scaffolds with 100 μm filament diameters. The scaffolds were sutured to the internal side of the peritoneal cavity of balb/c mice suffering from diffuse intraperitoneal metastasis of CT-26 colorectal cancer.

3. Results:
At first, three different scaffolds with different concentrations (10%, 20%, 40%) of gelatin were printed. The implantation procedure of the scaffolds in the peritoneal cavity is illustrated in Figure 1.

Then, their degradation was monitored by CT-scan imaging. The scaffold consisted of 40% gelatin were completely biodegradable, while the others exhibited lower levels of degradation as the overall structure of scaffolds remained stable after 14 post-implantation.

Figure 1: Steps of the scaffolds implantation procedure in the peritoneal cavity of mice (from left to right).

Therefore, 40% gelatin scaffolds were selected for further steps. The balb/c mice were intraperitoneally injected with CT-26 murine cancer cells to establish a syngeneic diffuse intraperitoneal metastasis model. Subsequently, the mice were divided into three groups including, Control, Doxorubicin (2.5 mg/kg intravenously for 5 days), and Doxorubicin-loaded degradable scaffolds.

4. Discussion and conclusion:
This preclinical study introduces a novel treatment for colorectal diffuse intraperitoneal metastasis with higher therapeutic efficacy in comparison with current intravenous chemotherapy. Local and sustained release of chemotherapy drugs into the peritoneal cavity due to controlled degradation of the 3D-printed scaffolds not only significantly increased the therapeutic effects of the chemotherapy drug in comparison with i.v administration method, but also decreased its systemic side effects. Taking together, further investigations are needed to improve and expand this novel method for increasing the efficacy of chemotherapy drugs for intraperitoneal metastasis of colon and other cancers.

Figure 2: CT-scan images of the scaffold-bearing mice 7 and 14 days after implantations. (Gel-Gelatin)

On the other side, undegradable scaffolds caused significant side effects which are illustrated in Figure 3 which were absent at the biodegradable scaffolds implanted animals. Although the 10% and 20% gelatin-containing scaffolds exhibited limited rate of degradation, 40% gelatin scaffolds completely degraded after 14 days (Figure 4) and this maybe the main cause of not causing any sides effects.

Figure 3: Biocompatibility of 40% gelatin-containing scaffolds in comparison with side effects of undegradable scaffolds (Bowel obstruction, connective tissue over reaction, and scaffold infection).

Figure 4: Despite limited degradation of the 10% and 20% gelatin-containing scaffolds, 40% gelatin-containing scaffolds were completely degradable.

Figure 5: The peritoneum and diaphragms of colorectal diffuse intraperitoneal metastasis models in different groups.

As Figure 5 illustrates, The Dox-loaded scaffolds exhibited significant inhibition in the formation and growth of the intraperitoneal metastatic colonies in comparison with control and systemic doxorubicin treated mice. In addition, the survival time of the scaffold group was considerably higher than the other groups. As the scaffold was completely biodegradable and compatible no side effects were observed during follow-up.