Heterocellular 3D scaffolds as biomimetic of peritoneal metastases

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INTRODUCTION

Peritoneal carcinomatosis is a major source of morbidity and mortality in patients with advanced abdominal neoplasms. Intraperitoneal chemotherapy (IPC) is an area of intense interest given its efficacy in ovarian cancer. However, large peritoneal metastases with adequate blood flow have a high interstitial fluid pressure, which inhibits intratumoral drug distribution (1). To study drug penetration and its influencing factors, reliable in vivo models that mimic peritoneal metastases are crucial.

EXPERIMENTAL METHODS

Poly-lactic acid scaffolds of 0.1cm^3 were coated with gelatin and were seeded with combinations of ovarian cancer cells (SK-OV-3-Luc-eGFP, 2x10^6) and cancer-associated fibroblasts (CAF, 8x10^6). Viability of these tumor scaffolds was longitudinally monitored by bioluminescent imaging (BLI) and assessed by end-point Live/Dead staining. Cancer cell-CAF organization in the scaffolds were visualized by histology, scanning electronic microscopy (SEM, fig 1A)) and confocal microscopy (fig 1B). After 3 weeks of in vitro culture, the tumor scaffolds were intraperitoneally implanted onto the peritoneal wall. Cancer cell viability was monitored by BLI, blood vessel infiltration by µCT and tissue formation and organization by histology (fig 1C-E).

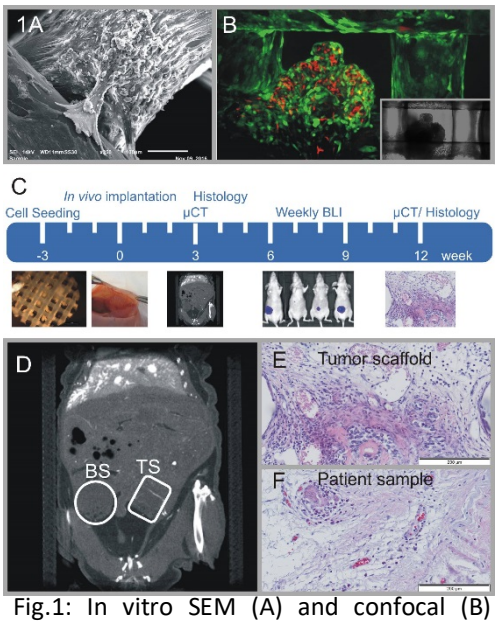

Fig.1: In vitro SEM (A) and confocal (B) images of tumor scaffolds (green: cancer cells; red: CAFs). C) a timeline of the in vivo experiments. D) Contrast-enhanced µCT 3 weeks after implantation: TS (tumor scaffold), BS (blanc scaffold, no cells) The two scaffolds are differently oriented. H&E staining of a tumor scaffold 4 weeks after implantation (E) and a patient-derived ovarian cancer peritoneal metastasis (F). Scale bar 200µm.

RESULTS AND DISCUSSION

CAFs (fig 1B red) are organized into spheroids between the pores, whereas cancer cells (fig 1B green) grow both on the scaffold struts and also in the aforementioned spheroids. Cancer cells adhered to the 3D scaffolds follow the print direction of the struts. After in vivo implantation, tumor scaffolds become vascularized (fig 1D) and show exponential growth of cancer cells. Histological analysis reveals infiltration of host fibroblasts, inflammatory cells and both small and large pericyte-covered blood vessels. All these histological aspects show remarkable similarities to size-comparable peritoneal metastases of ovarian cancer patients (fig.1E-F).

CONCLUSION

In vitro cultured heterocellular 3D scaffolds become functionalized in vivo by the host. The newly formed tissue remarkably biomimics a peritoneal metastasis of an ovarian cancer patient. This model opens new opportunities for therapeutic evaluation of drugs against peritoneal metastases (and their microenvironment).

REFERENCE: 1) Koppe M. et al., J. Surg. Oncol. 10:6, 2014
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