EVENT ABSTRACT

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NewTumor-environment biomimetics delay peritoneal metastasis formation by deceiving and redirecting disseminated cancer cells abstract created on Monday June 29, 2015

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Introduction: Biomimetics of the tumor-environment, an ecosystem, can be applied to create an ecological trap. An ecological trap is an environment of low quality for survival that is preferred by an organism over a better available environment. Carcinoma associated cancer cells (CAFs) produce an extracellular matrix (ECM) that exerts a high attraction to disseminated cancer cells, and is the perfect bait for an ecological trap. Microparticle encapsulated CAFs (MP[CAF]) can redirect adhesion of disseminated cancer cells from the peritoneal wall to the MP[CAF] surface to prevent peritoneal metastasis formation.
Materials and Methods: Encapsulation: CAFs cells are encapsulated into microparticles (MP[CAF] 500-700µm) by dripping a mixture of alginate (1.5%), gelatin (0.5%) and CAFs (2.106/ml) in to a CaCl2 bath (1.3%) though a needle (260µm inner diameter) surrounded by an airflow. MP[CAF] where layer-by-layer coated with poly-styrene sulfonate and poly-allyamine (PSS/PAH), with or without the incorporation of iron-oxide nanoparticles between the layers.
In vitro confrontation assay: MP[CAF] and MPs without CAFs where confronted with luciferase positive cancer cells (1.105) while shaking. After 48h adhesion the two types of MPs are magnetically separated and the adhesion of SK-OV-3 Luc on the MPs is measured through bioluminescence.
In vivo: MP[CAF] (200) are inserted through a small incision in to the abdominal cavity of nude mice. 1.105 ovarian cancer cells (SK-OV-3 Luc IP1) are injected. 24h later MPs with captured cancer cells are removed with a magnet. Sham threated mice underwent the same procedure but now MPs where inserted.
Results and Discussion: MP[CAF] are stable and encapsulated CAFs are viable and metabolic active for over 4 weeks.
CAF-derived ECM proteins are retained by the PSS/PAH coating. In vitro confrontation show that cancer cells have a higher affinity for MP[CAF] compared to empty MP (fig 1A-B). Small animal MRI imaging shows distribution of MP throughout the abdominal cavity without attachment to intestinal organs and without signs of inflammatory reaction. MP[CAF] trap cancer cells and redirect adhesion away from the wound site. Removal of the MP[CAF] results in a delay peritoneal metastasis formation and a prolonged survival in mice (fig 2A-D).

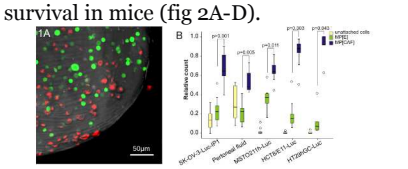

Figure 1: Tumor environment bio-mimetics trap cancer cells in suspension
A) Merged confocal image of captured cancer cells (DiI labeled SK-OV-3 in red) on MP[CAF]; CAF: carcinoma associated fibroblast (green). (PAH/PSS)2 (white). B) Confrontation assay: floating cancer cells show a higher affinity for MP[CAF] (SK-OV-3-Luc-IP1: 62%; SK-OV-3-Luc-IP1 in ascites: 47%; MSTO-211H-Luc: 62%; HCT8/E11-Luc: 85%; HT29hGC-Luc: 89%) compared to MP[E] (SK-OV-3-Luc IP1: 22% p<0.001; SK-OV-3-Luc-IP1 in ascites: 22% p=0.005; MSTO-211H-Luc: 36% p=0.011; HCT8/E11-Luc: 15% p=0.003; HT29hGC-luc:7% p=0.043) and compared to cells in suspension ((SK-OV-3-Luc-IP1: 13% p<0.001; SK-OV-3-Luc-IP1 in ascites:0.26% p=0.037; MSTO-211H-Luc: 1% p<0.008; HCT8/E11-Luc: 0% p=0.002; HT29hGC-Luc:0% p=0.043).

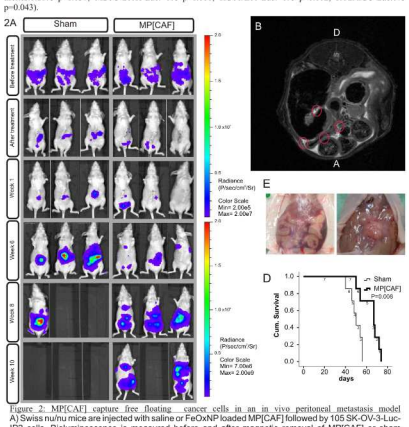

Figure 2: MP[CAF] capture free floating cancer cells in an in vivo peritoneal metastasis model
A) Swiss nu/nu mice are injected with saline or FeOxNP loaded MP[CAF] followed by 105 SK-OV-3-Luc-IP2 cells. Bioluminescence is measured before and after magnetic removal of MP[CAF] or sham treatment. Bioluminescence is further weekly monitored until week 10. Groups are 7 mice from which 3 are shown. B) T2-weighed MR images (D: dorsal, A: abdominal). Green: blood vessels, appear in sequential pictures. Red: MP[CAF], small black spots with a halo, due to their small diameter they do not appear in sequential images. C) Tumor growth at the surgical wound at endpoint. Sham treated mice show a large tumor at the wound site which infiltrates the peritoneal wall (H&E staining, representative image of 6/7 mice). MP[CAF], treated mice show a minimal tumor at the wound site in all treated mice (7/7). D) Kaplan-Meier survival curve; MP[CAF] treated mice have a significant longer survival time (67 days) compared to sham treated mice (50 days, p= 0.008). In the graph, animals at risk are indicated.

Conclusion: Biomimetics of the tumor-environment by encapsulating CAFs creates an ecological trap for disseminated cancer cells. The present results demonstrate the potential of ecological traps to prevent cancer metastasis.

Vlaamse Liga tegen Kanker; Stichting tegen Kanker; IWT

References:

[1] De Vlieghere et al. Biomaterials 2015, 54:148-157

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