The use of Cellular MRI to study the role of Cancer Stem Cells in metastasis development in vivo

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Introduction

The survival of cancer patients developing a localized melanoma is 98% over 5 years. However, when melanoma has metastasized, this rate decreases to 15.9% (SEER, 2006). Cancer Stem Cells are thought to be involved in the development of metastasis in distant organs. To study their role in this phenomenon, Cellular MRI can be used, since cancer cells can be tracked over time using iron-based magnetic cell labels. Here, we use cellular MRI to monitor the fate of iron-labeled melanoma cells in the liver and brain. This study will allow a better understanding of the mechanism underlying the metastasis growth *in vivo* and the influence of the cancer cell environment on their proliferation and/or dormancy states.

Materials and Methods

Mouse melanoma cells (B16F10) were labeled with micron-sized superparamagnetic iron particles (FlashRed-MPIO) and administered into black mice by either intracardiac injection into the left ventricle of the heart for delivery to the brain or via the mesenteric vein to target the liver. Mice were imaged on the day of injection and at days 5 or 7 and 14 post injection. MRI was performed on a clinical 3T scanner using custom-built high performance gradient insert coil. The balanced steady state free precession (bSSFP) imaging sequence was used with the following parameters: TR/TE=14/7ms; flip angle=25°; rBW=±21kHz; FOV=3cm; resolution=200x200x200µm; 8 phase cycles; NEX=2; Acq time=36min38s. At the end time point, tissues were extracted for fluorescence microscopy.

Results

In images acquired on the day of injection distinct regions of signal void were easily detected in the brain and in the liver. In the brain, the number of signal voids declined with time due to cell death. At the endpoint of the study few voids remained, but there was no evidence of the development of brain tumors. In the liver, the formation of tumors was observed by day 7 post injection. Tumors appear with high signal intensity in bSSFP images, which have contrast related to T2/T1. Some signal voids were still detectable in both tissues at endpoint, suggesting that some cells remain in a non-proliferative state.

Conclusion

This study highlighted the "seed and soil" hypothesis *in vivo*, demonstrating the importance of the cell environment in metastasis growth. Indeed, depending on the seeded organ, cancer cells can stay dormant or divide to induce the formation of tumors. Furthermore, dormant melanoma cells can be tracked during time, allowing to study their involvement in late-developing metastasis. Further immuno-histochemistry experiments will be performed on the extracted livers and brains to determine if these dormant cancer cells are Cancer Stem Cells.

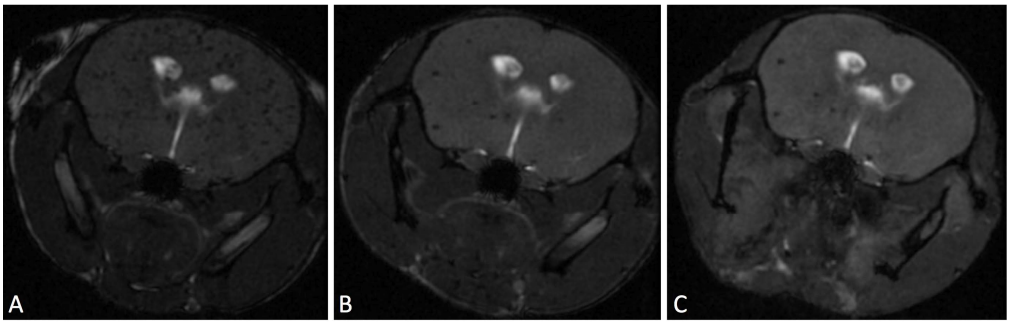

Figure 1: Iron labeled melanoma cells can be followed in the mouse brain. Mice were scanned at day 0 (A), 5 (B) and 14 (C) after intracardiac injection.

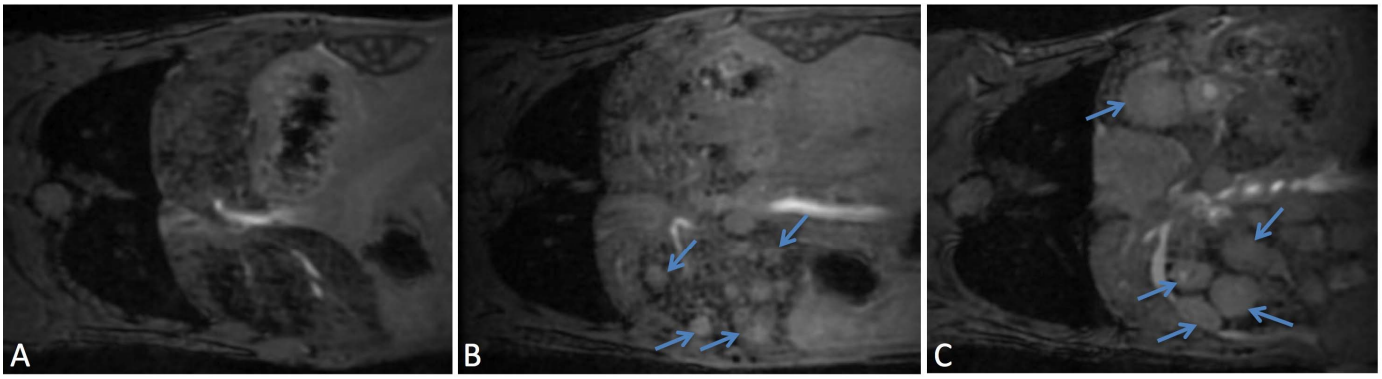

Figure 2: After injection in the mesenteric vein, some melanoma cells stayed dormant throughout the experiment (represented by voids), whereas some developed into metastasis (arrows). Mice were scanned at day 1 (A), 7 (B) and 14 (C) after injection into the mesenteric vein.