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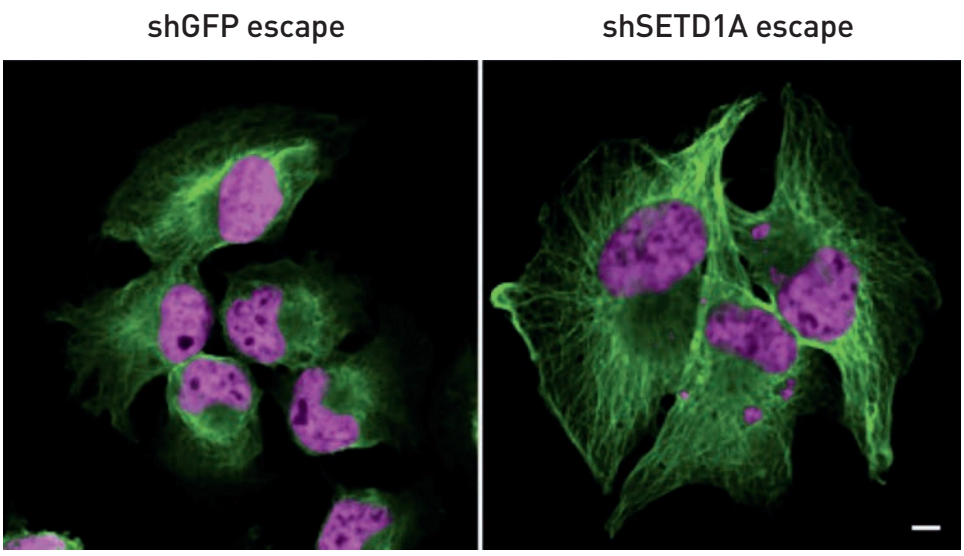
Metastasis, the leading cause of cancer-related deaths, is governed by multiple steps, which are not well understood. Using cell culture and mouse models, as well as patient-derived tumor tissues and tumor cells circulating in the blood (Circulating Tumor Cells/CTCs), **the Maheswaran laboratory** has uncovered novel tumor cell characteristics that promote metastasis in breast cancer patients. Our findings show that cancer cells exist in multiple cellular states, each state exhibiting different characteristics. As such, each breast cancer patient harbors a mixture of tumor cells with different functional properties. We intend to define the functional and molecular properties of different subclasses of tumor cells and their contribution to metastasis, tumor evolution and drug sensitivity using appropriate experimental models and patient-derived samples. These findings will provide insight into the contribution of heterogeneous cancer cell populations to metastasis and their significance as biomarkers and therapeutic targets.

Mechanisms of Breast Cancer Metastasis

The research in my laboratory is focused on defining the molecular mechanisms that drive breast cancer progression and metastasis. Cancer, initially confined to the primary site, eventually spreads to distal sites, including lung, liver, bone and brain, by invading into the bloodstream. Upon reaching these distal sites, the tumor cells continue to grow and evolve well after removal of the primary tumor resulting in overt metastasis and disease recurrence, the leading causes of cancer-related deaths. Using cell culture and mouse models, patient derived tissues, and circulating tumor cells (CTCs) enriched from the blood of women with breast cancer, we characterize the contribution of oncogenic-and tumor-microenvironment-derived signals to cellular states including: epithelial to mesenchymal plasticity, senescence, and how these aspects of tumor heterogeneity influence cancer progression and therapeutic responses.

Metastasis through the Prism of Circulating Tumor Cells

I am also collaborating with Drs. Daniel Haber and Mehmet Toner to define cancer biology across several tumor types including breast, prostate, liver, and lung cancers as well as melanoma using CTCs isolated from the blood of cancer patients. CTCs represent an extremely rare population of cells in the blood and their isolation presents a tremendous technical challenge. The CTC-iChip developed in Dr. Toner's laboratory enables enrichment of live CTCs through selective removal of blood components; red and white blood cells as well as platelets. Characterizing CTCs has far-reaching implications for both clinical care and defining cancer biology. They enable real time monitoring of tumor cells during disease progression and therapeutic responses, and could possibly be used for early detection of disease. Viable CTCs cultured from patients provide tremendous insight into the molecular heterogeneity



Confocal images of cells stained with tubulin (green) and DAPI (magenta) show that SETD1A-KD cells escaping senescence harbor chromosome segregation defects visualized as micronuclei (circled). The scale bar represents 50 µm.

and cellular plasticity of tumors that govern differential biological characteristics and responses to therapy. Characterization of CTCs ties in well with the overall goal of the lab to study cancer metastasis.

Selected Publications:

Tajima K, Matsuda S, Yae T, Drapkin B, Morris R, Boukhali M, Niederhoffer K, Comaills V, Dubash T, Nieman L, Guo H, Magnus NKC, Dyson N, Shioda T, Haas W, Haber DA, **Maheswaran S**. SETD1A protects from senescence through regulation of the mitotic gene expression program. *Nature Comm.* 2019 Jun 28;10(1):2854.

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