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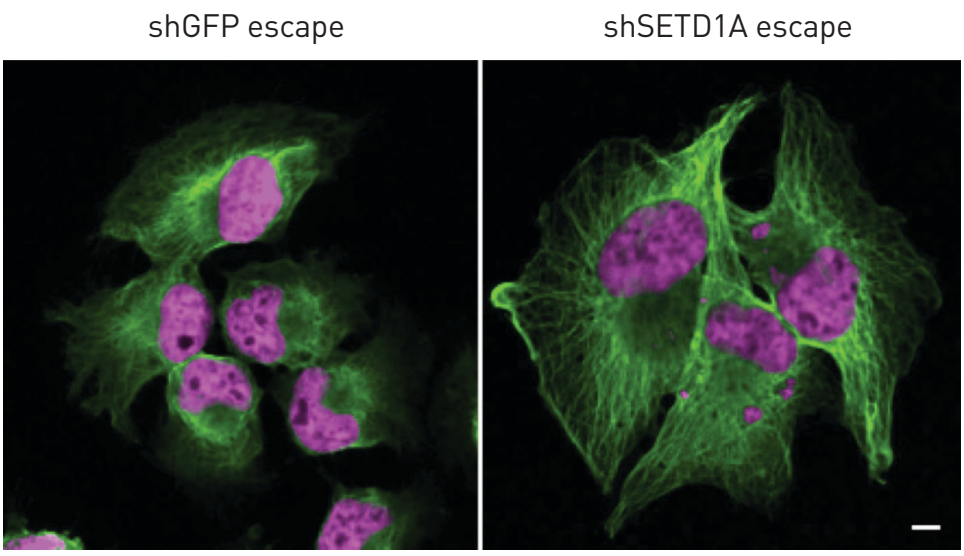
Metastasis, the leading cause of cancer-related deaths, is governed by multiple steps, which are not well understood. Using cell culture and mouse models, as well as patient-derived tumor tissues and tumor cells circulating in the blood (Circulating Tumor Cells/CTCs), **the Maheswaran laboratory** has 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.

Oncogenic and Epigenetic Cues in Senescence

Senescence, a state of prolonged growth arrest induced by stress, contributes to aging and age-related degenerative diseases. It is an important tumor suppressor mechanism in premalignant tumors, which override this safeguard machinery through the loss of the tumor suppressors RB and p53 and progress to become malignant tumors. Senescence is also an alternative cellular response to chemo- and radiation therapies, from which a few rare cells escape and exhibit highly drug resistant phenotypes. Taken together, there is a critical need to identify mechanisms that induce and maintain senescence independent of the RB and p53 signaling axes, which are often inactivated in cancers. Identification of druggable targets that can induce and maintain senescence as future therapies complementing current therapeutic interventions is an unmet need that is gaining significant attention from a clinical perspective. Based on our published



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.

work on SETD1A, we are investigating (a) the functional and mechanistic roles of SETD1A in cells, the deregulation of which induces senescence. (b) the role of SETD1A in maintaining the cellular equilibrium between proliferation, senescence and escape from senescence and (c) how SETD1A-KD-induced senescent cells remodel the microenvironment and its impact on tumor progression and drug responses. The long-term goal of this work is to ultimately exploit SETD1A, a druggable enzyme, to unleash the tumor suppressor effects of senescence and curtail cancer progression, drug resistance and possibly age-related diseases.

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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