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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.

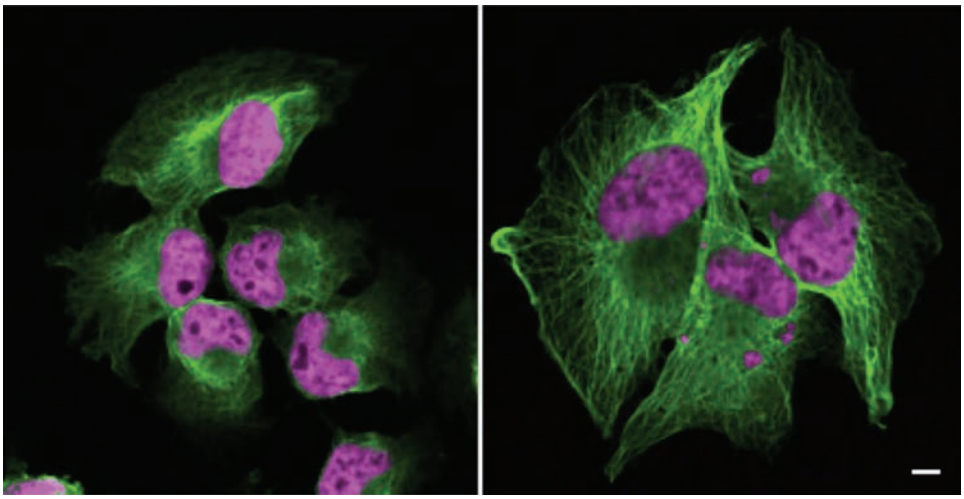
Mechanisms of Breast Cancer Metastasis

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.

Naturally occurring senescence induced by microenvironmental factors

Senescence is associated with the secretion of bioactive molecules - the senescence-associated secretory phenotype (SASP). SASP, which is context dependent, remodels the cellular microenvironment and contributes to many age-related diseases. Senolytic compounds, that eliminate senescent cells, alleviate these age-related conditions in preclinical models and in clinical trials; thus, senescence is a druggable cell state. TGFß, prevalent in the hypoxic tumor microenvironment, induces senescence in cancers, rendering it a physiological tumor cell state. In an immune-competent mouse lung cancer model, suppressing TGFß signaling, specifically in the tumor cells, ablated senescent cells in tumors and mitigated immune suppressive immune infiltration. In a therapeutic setting, non-small cell lung cancers with high TGFß/hypoxia-signaling and increased senescence - exhibit poor progression-free survival upon receiving immune checkpoint inhibitors

shGFP escape shSETD1A escape



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.

(ICI). We are now exploring whether microenvironmental hypoxia-TGFß-induced physiological senescence and SASP are exploited by tumors to mount an innate resistance to ICIs, and how we can exploit this phenotype to improve ICI responses.

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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Comaills V, Kabeche L, Morris R, Buisson R, Yu M, Madden MW, LiCausi JA, Boukhali M, Tajima K, Pan S, Aceto N, Sil S, Zheng Y, Sundaresan T, Yae T, Jordan NV, Miyamoto DT, Ting DT, Ramaswamy S, Haas W, Zou L, Haber DA, **Maheswaran S**. Genomic Instability Induced by Persistent Proliferation of Cells Undergoing Epithelial-to-Mesenchymal Transition. *Cell Reports* 2016. Dec 6;17(10): 2632-2647.

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Aceto N, Bardia A, Miyamoto DT, Donaldson MC, Wittner BS, Spencer JA, Yu M, Pely A, Engstrom A, Zhu H, Brannigan BW, Kapur R, Stott SL, Shioda T, Ramaswamy S, Ting DT, Lin CP, Toner M, Haber DA*, **Maheswaran S***. Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis. *Cell*. 2014; 158(5):1110-22.

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