The Ramaswamy laboratory is working to understand how solid tumor metastasis, dormancy, and drug resistance interrelate. Our major goal is to use insight from our studies to devise new strategies for the combination targeting of advanced cancers. Our multidisciplinary approach integrates clinical studies in solid tumor patients with experimental approaches in cancer, computational, & systems biology.

Asymmetric Cancer Cell Division

We have a special interest in the molecular basis of asymmetric cancer cell division. We have found that rapidly proliferating cancer cells occasionally divide asymmetrically to produce slowly proliferating “G0-like” progeny that are highly treatment resistant both in vitro and in cancer patients. We have developed reliable methods for the identification, isolation, tracking and experimental study of these G0-like cells. Our molecular and cellular studies have revealed that partial suppression of the AKT/PKB signaling pathway during mitosis induces a signal transduction and epigenomic network that regulates asymmetric cancer cell division and the production of G0-like cells. We have also discovered that these G0-like cancer cells broadly activate endo-vesiculo-membrane trafficking to secrete a broad array of inflammatory factors. Since virtually all tumors depend on AKT signaling for their growth and survival, we believe that understanding the mechanisms underlying this type of asymmetric cancer cell division in fine detail might enable us to develop entirely new strategies to diagnose and therapeutically target a wide variety of different cancer types where slowly proliferating and dormant cancer cells are difficult to eradicate. Current projects include 1) identifying upstream pathways that asymmetrically suppress AKT signaling in dividing cancer cells; 2) defining the signaling and epigenomic postures of G0-like progeny using next-generation sequencing, proteomic, and metabolomic approaches; 3) dynamically visualizing asymmetrically dividing cancer cells using live-cell imaging approaches in vitro and in vivo; and 4) determining how asymmetric cancer cell division may contribute to human tumor metastasis, dormancy and treatment resistance in vivo.

Cancer Cell Metastasis

We are working to understand how human cancer genomes regulate solid tumor progression. We are particularly interested in defining transcriptional networks that regulate metastasis, dormancy and drug response. Several years ago, we found that multigene transcriptional signatures are expressed by a majority of malignant cells within tumors that are destined to metastasize. These studies spurred the development and deployment of widely used gene-signature-based clinical diagnostics for the diagnosis and risk stratification of cancer patients with different tumor types. We subsequently found that virtually all of these poor prognosis signatures indirectly reflect the activity within tumors of the MYC transcription factor. Moreover, we found that in certain contexts MYC may specifically regulate cancer cell invasion and metastasis apart from its well-studied roles in proliferation and survival. Since MYC is
arguably the most commonly altered human oncogene, understanding how quantitative increases in MYC activity contributes to metastasis might suggest new strategies for therapeutically targeting advanced cancers. Current projects include 1) DNA-seq, RNA-seq and ChIP-seq profiling to comprehensively define the metastasis-related MYC transcriptional state; and 2) functional studies probing the MYC transcriptional network in vivo.

Center for Cancer Systems Discovery

A major challenge in modern cancer research is the generation, storage, analysis and interpretation of complex experimental data. Individual experiments using cutting-edge technologies can generate terabytes of data that must be quantitatively mined to identify important cancer genes, pathways and drug associations to drive the discovery of new biomarkers and drug targets. Scientists in Massachusetts General Hospital’s Center for Cancer Systems Discovery (CCD) have significant expertise in the analysis of high-throughput biological data from across the current technological spectrum including next-generation sequencing (i.e., DNA, RNA, ChIP-seq), microarrays (e.g., SNP, CGH, Expression, Tiling, ChIP-Chip), proteomics (array-based), genome-scale RNAi and chemical screens, and high-throughput microscopy. CCD scientists are developing new methods for the analysis, display and storage of large data sets generated with these cutting-edge technologies. CCD scientists also work closely with a wide spectrum of investigators throughout the Mass General Cancer Center on a variety of translational and fundamental research projects at any given time, both as collaborators and as consultants. In approaching new projects, we apply established analytic tools and also develop, implement and deploy customized tools depending on specific requirements. Current projects involve 1) cancer mechanisms; 2) stem cell epigenomics and biology; 3) cancer genome discovery in tumors and circulating tumor cells; 4) cancer cell line pharmacogenomics; 5) biomarker discovery and validation using data integration, meta-analysis, and predictive modeling.

Selected Publications:


*Co-authors