Systemic Effects of Cancer Think Tank

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ABSTRACTS

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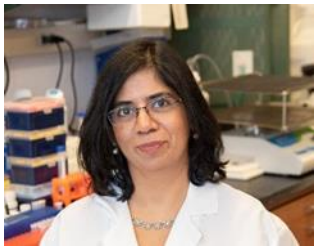


Our laboratory focuses on understanding the underlying mechanisms of cancer metastasis. We take a systemic approach to our research, studying how metastasis evolves in the context of the host. More than 90% of cancer-related deaths in solid tumors are due to metastasis rather than the primary disease. Therefore, a fundamental question arises: What makes metastatic disease lethal?

Several attributes contribute to the morbidity and mortality in cancer patients with metastasis:

1) Vital organ dysfunction: Metastatic cancer cells that invade and grow in vital organs such as the liver, bone, or brain can locally disrupt the normal physiological functions of these organs.
2) Therapy resistance: Patients with metastatic disease have limited surgical options. Therefore, systemic therapy represents the main clinical choice for treatment. However, metastatic tumors often show only partial responses to these treatments and acquire resistance, making them ultimately refractory to anti-cancer treatments. We investigate the mechanisms that contribute to the apparent intractability and therapy resistance of metastatic tumors.
3) Systemic effects: Cancer cells invade distant organs and remodel the local microenvironment to accommodate the needs of the expanding metastatic colonies. Extracellular matrix alterations, vascular remodeling, and immune polarization further shape the metastatic niche. As a consequence, metastatic tumors disrupt the metabolic homeostasis in the host, resulting in a debilitating muscle-wasting condition known as cachexia.

The incidence and severity of cachexia increase with metastatic progression, with nearly 80% of metastatic cancer patients developing cachexia. This suggests that the development of cachexia could be molecularly linked to the metastatic process. We aim to understand how changes in metastatic tumors, as well as signals from metastatic niches, trigger cachexia and contribute to lethality in metastatic cancer patients.

Our work has identified how changes in metastatic niches can deregulate zinc ion transport through ZIP14 upregulation in skeletal muscle and promote cachexia. We are developing therapeutic strategies to block ZIP14 function for treating cachexia in conjunction with anti- metastatic therapies.

Diana Cittelly
University of Colorado

The Cittelly group studies how interactions between specialized cells within the brain microenvironment and cancer cells contribute to brain metastatic progression, and how changes in the female hormonal milieu impact these interactions throughout the lifespan. Using a combination of spontaneous and experimental metastases models, ex vivo models (i.e. organotypic brain slices) and *in vitro* approaches, we aim to define mechanisms by which glial cells (astrocytes, microglia) and neurons communicate with disseminated cancer cells to promote or dampen brain metastatic colonization and response to treatments. We have shown that in mouse models mimicking breast cancer brain metastases in younger women, pre-menopausal levels of estrogen modulate estrogen receptors (ER) on reactive astrocytes, leading to upregulation of growth factors (i.e. EGF, BDNF), which in a paracrine manner, promote brain metastases from cancer cells that are -otherwise- estrogen unresponsive (i.e. triple-negative breast cancer, TNBC). Estrogens also promote an immunosuppressive brain niche by modulating ER+ microglia and suppressing recruitment of T and NK cells; and estrogen-suppression therapies restore anti- tumoral immune responses and sensitize brain metastases to radiation therapy. While these studies highlight the importance of estrogen in promoting metastatic progression in young women with TNBC, ongoing studies suggest that aging, and loss of E2 occurring with aging, supports brain metastatic progression from endocrine-resistant ER+ tumors through mechanisms involving non-canonical functions of membrane receptors upregulated in ER+ cancer cells following endocrine therapies. Thus, hormonal effects on the tumor microenvironment, both local and systemic, have significant impact in the progression of metastases.

Questions/Thoughts about systemic effects of cancer:

- While emerging evidence supports the notion that cancer cells hijack normal homeostatic mechanisms to growth at metastatic sites (i.e switch from anti to pro-tumoral neuroinflammatory responses in BMs), an integrated view of the changes in the TME occurring during metastatic progression (from seeding to outgrowth) remains poorly understood.
- How cancer therapies alter the TME (not only immune responses but specialized resident cells) and their impact in metastatic progression and response to treatment remains unexplored.
- Despite clinical and experimental evidence that hormones (male vs female, young vs old, stress, etc) impact progression of metastases, response to treatment, and are also altered during cancer progression/treatment, clinical and pre-clinical studies lack of a comprehensive examination of hormonal status that could help explain the heterogeneity in response to therapy observed clinically.

Karuna Ganesh
Memorial Sloan Kettering Cancer Center

Metastasis causes >90% of cancer death. The emergence, persistence and lethality of metastasis is driven by metastasis stem cells (MetSCs) — cells capable of self-renewal, slow cell-cycling, tumor re-initiation, and therapy resistance. The Ganesh lab focuses on understanding the molecular mechanisms, mediators, and consequences that underlie the emergence of regenerative and cell state plasticity during metastasis, with an eye toward developing effective strategies for eliminating colorectal cancer metastasis. Our mechanistic studies use patient- derived tissues (normal, primary tumor, metastatic tissue), organoids and mouse models of colorectal cancer and approaches involving lineage tracing, along with bulk and single cell transcriptomic, epigenomic, and immunophenotypic analyses, to: (1) elucidate how tumor invasion and dissemination induce phenotypic plasticity enabling the emergence of pro- metastatic regenerative traits; (2) dissect the role of stromal cells, including immune cells, in promoting and constraining MetSC plasticity; (3) define key signaling nodes that drive MetSC plasticity and develop therapeutic strategies for targeting such vulnerabilities; and (4) collaborate with clinicians to understand mechanisms of therapy resistance in metastasis.

Questions/Thoughts about systemic effects of cancer:

- How do we improve models of the tumor microenvironment and macroenvironment? Mouse vs Human? What is the knowledge gap and do we have appropriate technologies to address these?
- To what extent would curing cachexia benefit patients in the absence of “source control” i.e. disrupting the growth of the primary tumor?
- How do we tackle the microbiome – as an understudied variable in cancer models, as a target for cancer interventions, and the heterogeneity of the microbiome within and across individuals and populations with comparable disease phenotypes? Is this a tractable problem? How do we address it as a cancer research community?
- To what extent do differences in the host micro/macroenvironment account for disparities in outcomes across ethnic/racially diverse patient cohorts? How can we address this?

Ana Gomes
Moffitt Cancer Center

Despite aging being the major risk factor for cancer incidence, our understanding of how aging affects cancer progression, evolution, sensitivity to anti-cancer therapies and mortality is severely limited. Our published studies support this premise and revealed a causal link between the systemic metabolic reprogramming that occurs as a function of aging and the progression of cancer into metastatic disease, putting aging and the changes that this processes causes in the host at the center stage coordinating the different aspects required for the evolution of malignant phenotypes. Our subsequent studies show that in addition to systemic changes, changes in the old tumor microenvironment (TME) composition and functional state lead to changes in niche signaling and drive divergent lines of primary cancer evolution and metastatic adaptation than what occurs in the young lung TME, causing resistance to standard of care therapies. Understanding the changes in tumor evolution, adaptations and consequent liabilities imposed by the aging process are currently the main focus of our work.

Questions/Thoughts about systemic effects of cancer:

- Does aging select for specific oncogenic mutations and if so why?
- Does aging alter metastatic tissue tropism and if so why and how?
- What other aspects of host physiology interact with aging to affect tumor evolution, metastatic spread and their adaptations to the secondary organs (e.g. chronic stress, race, gender, metabolic/endocrine state)?
- Are there interactions between the tumor cells and the TME cells that give rise to pathological changes to the local organ and/or other organs to decrease quality of life and/or accelerate mortality in the elderly (e.g. cachexia, NAFLD/diabetes, COPD)?

Marcus Goncalves
Weill Cornell Medical College

Dr. Goncalves' lab explores the dynamics between cancer and systemic metabolism, with a focus on cancer-induced anorexia and cachexia. These conditions lead to severe muscle and fat tissue loss, which limits physical mobility, reduces quality of life, and contributes to worse overall mortality. We are interested in identifying the tumor cells and secreted factors that mediate anorexia and cachexia using mouse models and samples from human subjects. Once identified, our goal is to target these pathways using biologics and small molecules to enable rapid translation to human trials.

Systemic Metabolic Disruption: Our research emphasizes the systemic nature of metabolic dysfunction in cancer, where alterations in hepatic metabolism and hormonal imbalances contribute to muscle wasting, underscoring the interconnectedness of organ systems in cancer cachexia. It is unknown how much anorexia contributes to cachexia and whether hypermetabolism truly exists.

Therapeutic Strategy and Sex-specificity: Our work suggests that targeting metabolic pathways offers a promising avenue for cachexia treatment, with the necessity of considering sex-specific physiological differences in developing effective therapeutic strategies. It is unknown if mechanisms of cachexia in humans differ by sex.

Translational Potential: The identification of specific metabolic and molecular targets (PPARα, Activin A) in cachexia provides a foundation for translational research, aiming to bridge the gap between preclinical findings and clinical application, particularly in developing personalized medicine approaches in cancer care. It is unknown if the model systems reflect specific patient subsets.

Aaron Grossberg
Oregon Health Sciences University

The Grossberg lab is focused on studying the mechanisms that cause the cancer-associated wasting syndrome of cachexia. The aim is to better understand how cancer reprograms the adaptive host responses to normal physiological and environmental stressors. To achieve this, the lab uses syngeneic orthotopic and genetically engineered murine cancer models to induce cachexia and then subjects the mice to environmental, inflammatory, and metabolic challenges. This method accomplishes two goals: firstly, by controlling the environmental conditions, specific physiological responses to the stressor can be isolated and tested. Secondly, it elicits a measurable cachexia phenotype early in cachexia development, which is crucial in distinguishing between the drivers of wasting and the consequences of wasting in a physiologically compromised host. The lab is currently investigating the modification of lipid metabolism as an energy source during both acute and chronic periods of fasting or undernutrition. They believe this is due to mitochondrial dysfunction in tissues that require a high metabolic demand, such as skeletal muscle, liver, and heart.

The systemic effects of cancer often interfere with core functions of life such as metabolism, reproduction, homeostasis, and movement. This hierarchy that prioritizes the sickness response above these core functions is evolutionarily conserved among nearly all vertebrate organisms. Therefore, these effects must provide some evolutionary advantage, and the field may benefit from exploring the benefits of these effects on the host.

Ben Izar
Columbia University

Inspired by fundamental questions in cancer biology and challenges in the clinical care of patients with metastatic cancers, the Izar laboratory studies mechanisms of cancer immune evasion and metastatic organotropism. More specifically, we study interactions between cancer cells and the tumor microenvironment, and how these interactions define metastatic niches, response and resistance to cancer immunotherapies. We leverage, develop and implement single-cell genomics, including multi-modal single-cell sequencing and spatial transcriptomic tools, and dissect tumor heterogeneity and cellular interactions of human tissues across space and time and a spectrum of patient-derived models, with the goal to discover novel therapeutic dependencies. To understand why immune checkpoint inhibitor therapy can produce potentially durable responses in only some cancer patients, we identified a set of genes that are associated with drug resistance and use multi-scale genome-editing and single-cell genomics in patient-derived tumor/immune models to functionally to characterize putative drivers of resistance. To delineate why some tumors have a preference to metastasize to one organ over another, we apply single-cell genomics and imaging to defined genetic models of human and murine cancer precursors in tissue-engineered and pre-clinical in vivo models. Among metastatic niches, we are particularly interested in the brain and liver metastases, which are associated with lower drug response rates and major causes for morbidity and mortality across cancers.

Questions/Thoughts about systemic effects of cancer:

- Do different metastatic sites cause different systemic effects?
- How do systemically delivered drugs affect host responses and interactions with the tumor and thereby influence tumor growth and deleterious systemic effects?

Tobias Janowitz
Cold Spring Harbor Laboratory

We study mechanistic causes of the whole-body response to disease with a focus on cancer. A particular focus is the neuroendocrine biology during cytokine mediated cancer associated cachexia. We have shown that interleukin-6 downregulates hepatic ketogenesis and stimulates specific neurons in the area postrema. Neuronal circuitry to the paraventricular nucleus and to neurons producing corticotropin release hormone in conjunction lead to apathy and hypothalamic-pituitary-adrenal axis activation, inducing a sickness program characterized by reduced food intake and altered nutrient processing. The consequence of the negative energy balance and elevated glucocorticoid levels is a systemic immune suppression. Preclinical studies from our laboratory have shown that early intervention can recondition the host organism to facilitate more effective cancer immunotherapy.

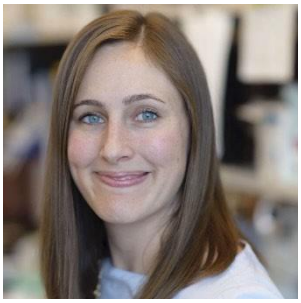
Conversely, dietary interventions can uncouple tumor response from overall survival. Administration of ketogenic diet at late time points in disease progression induces ferroptosis in cancer cells secondary to lipid peroxidation and depletion of NADPH. The oxidative effect is systemic leading to significant depletion of NADPH in the adrenal gland and failure of metabolically required corticosterone production in mice, resulting in early cachexia.

Together our studies highlight the complex and non-linear biology of cachexia and suggest that cachexia may be the consequence of an unsustainable biological adaptation process.

Questions/Thoughts about systemic effects of cancer:

- What is the dependency of treatment efficacy on duration of disease progression?
- What are the effects of dietary interventions on host biology?
- How can we best optimize translation of complex and time dependent combination therapies?

Ashley Laughney
Weill Cornell



My research program tackles the genotype-to-phenotype problem in cancer evolution. Predicting protein function from sequence, also known as *genotype-to-phenotype* mapping, remains a central challenge in biology. This is because most proteins are highly pleiotropic; meaning they can perform more than one function and participate in a wide range of biological processes. As such, perturbations to a single gene often affects multiple, independent cellular responses. Integrating innovative systems and synthetic biology approaches with a hypothesis-driven framework, my lab develops tools to map genome-encoded components to complex cellular and *in vivo* functions at scale. We focus on cancer metastasis as our model of a multicellular, evolutionary process and develop approaches that ask how activation of the very same protein or signaling pathway can lead to diverse functional outputs through *(i)* the evolution of distinct modular domains, (*ii*) *intra*-cellular genetic interactions (epistasis) and *(iii) inter*-cellular signaling networks (multicellular programs). We apply these emerging techniques to understand how highly pleiotropic proteins - such as an immune-related protein called Stimulator of Interferon Genes (STING) - switches from a tumor-suppressor to pro-tumoral function during the evolution of cancer metastasis. To effectively target pleiotropic regulators like STING, we must understand how protein and cellular components interact to produce multiple, distinct responses, and how proteins evolve these responses under certain selective pressures. Context is key and as we systematically map the context-dependent functions of proteins during cancer evolution; it will be important to model the long-range effects of inflammation, pregnancy, aging and obesity, among others.

Selma Masri
University of California, Irvine

The circadian pacemaker network governs a host of 24-hour physiological processes that encompass endocrine signaling, metabolic control, and immune regulation. The circadian clock is exquisitely sensitive to alterations in physiological homeostasis as the clock is essential in orchestrating systemic functions in a temporal manner. During cancer development, several of these clock-controlled pathways are altered or disrupted and the Masri lab has a long-standing interest in dissecting the mechanistic underpinnings of these pathways. Using genetically engineered mouse models, we focus on how the circadian clock can sense metabolic perturbations that are hallmark features of cancer-associated cachexia. We found that metabolic rewiring that involves an adipose tissue to liver axis is profoundly deregulated during the development of cachexia. Additionally, new studies from the Masri lab reveal how the epithelial cell clock communicates with immune cells in the tumor microenvironment to regulate time-of- day control of anti-tumor immunity. Taken together, our work places a central focus on daily biological rhythms in mediating tissue-tissue communication and how this crosstalk is disrupted or altered during tumor progression and the onset of cachexia.

Thales Papagiannokopoulos
New York University

Cancer-associated cachexia (CAC) is a multifactorial syndrome is driven by the combination of reduced food intake and altered systemic metabolism. Effective therapies to treat cancer-associated cachexia are currently lacking, with treatment focused on nutritional support and symptom mitigation. Approximately 80% of lung cancer patients display CAC. Efforts to understand CAC in lung cancer have been complicated by the high degree of genetic heterogeneity in this disease, the lack of pre-clinical models that accurately recapitulate CAC hallmarks, and limited information describing how nutrition may impact CAC. Therefore, there is a great need to develop physiologically relevant CAC animal models to understand the underlying mechanisms of this disorder, identify biomarkers, and develop new therapeutic strategies to prevent and reverse cachexia.

To address these key points, we generated genetically engineered mouse models (GEMMs) representing the most common and aggressive genetic subsets of *KRAS*-driven LUAD bearing *Lkb1* (KL), *Tp53* (KP*)* or *Cdkn2a/b* (KCC) driver co-mutations. We demonstrated that only KL GEMMs display symptoms of cachexia. Surprisingly, we observe that high caloric density diets, including high-fat or ketogenic diet dramatically exacerbates CAC without an impact on tumor burden. We are investigating how *LKB1* mutant tumors uniquely interact with high dietary fat to exacerbate CAC. We have uncovered novel mechanisms by which tumors process fat and signal locally to sensory neurons in the lung, which project directly to the brain in order to promote sickness behavior. Our results shed light into how tumors and diets may promote CAC by signaling directly to the somatosensory neuronal network.

Questions/Thoughts about systemic effects of cancer:

- Innervated tumors can directly wire into the somatosensory system and through the central nervous system impact multiple aspects of systemic physiology, including cachexia associated symptoms and more.
- Dietary interventions can be used to prevent or suppress the emergence of cachexia in patients.
- There may be multiple environmental factors, other than diet, that can impact the emergence of cachexia.

Erin Talbert
University of Iowa

The Talbert laboratory is interested in the cancer cachexia syndrome and mechanisms driving skeletal muscle wasting in cancer, with particular emphasis on identifying ways in which muscle loss can be prevented. Low muscularity and particularly skeletal muscle wasting are associated with poor outcomes for people with cancer, including shortened survival, increased treatment toxicity, and reduced quality of life, and preserving muscle mass is expected to improve these outcomes. The lab has a particular focus in how pancreatic cancer causes muscle loss due to both the poor outcomes for patients with pancreatic cancer and the high incidence and severity of tissue wasting in these patients. The lab seeks to utilize patient data and samples to inform our mechanistic work performed using animal, *ex vivo*, and cell culture models. Disparities between successful strategies to prevent muscle wasting in animal models of cancer cachexia and failed clinical trials has led to our efforts to improve mouse modeling of muscle wasting in PDAC to ensure mouse models reflect the human condition. Our patient data reveal significant heterogeneity in rates of muscle wasting and circulating factors associated with cachexia in pancreatic cancer patients, including accelerated muscle wasting in males and individuals with obesity, and reduced rates of muscle wasting in patients responding to treatment. Therefore, successfully treating muscle wasting in people with cancer likely will require personalization to patient's individual drivers of muscle wasting. Factors including sex, adiposity, tumor type, tumor inflammatory profile, and treatment response are likely to impact the success of a given therapeutic approach, with other currently unidentified factors also significantly impacting effective treatments.

Humsa Venkatesh
Brigham & Women's Hospital

The Venkatesh lab studies the reciprocal interactions between the nervous system and cancer. Our work emphasizes the electrical components of tumor pathophysiology and highlights the extent to which neural activity can control and facilitate disease progression both in and outside the brain. The understanding of these malignant mechanisms of co-opting neural plasticity has led to novel strategies to broadly treat cancers by disabling their ability to electrically integrate into neural circuitry. Our efforts in this emerging field of cancer neuroscience aim to harness the systems-level microenvironmental dependencies of tumor growth to develop innovative therapeutic treatments for various types of cancers. Our current work focuses on bidirectional neuron-cancer communication and network dynamics between the central and peripheral nervous systems throughout tumor development. By using systems neuroscience tools, we have begun to explore the role of innervation and the neuron-tumor specific structural, functional, and electrical interactions that occur within tumor microenvironments throughout the body.

Questions/thoughts on Systemic effects of cancer:

- How does nervous system signaling dictate remodeling of the tumor microenvironment in various organs?
- How can we best investigate the tumor-derived secretome that would have the most direct effect on various biological systems (ie. cytokines, hormones)?
- What tools would best enable whole body interrogation of disease progression over the course of tumor evolution?

Shizhen Emily Wang
University of California, San Diego

The Multi-organ and Multi-layered Effects of Cancer-derived Extracellular Vesicles

Our knowledge of short- and long-range intercellular communication had an exponential growth in the past decade partially owing to the discovery of the diverse functions of extracellular vesicles (EVs). EVs are a variety of membrane-enclosed nanosized particles that carry and transfer between cells functional cargoes including RNA, DNA, proteins, and lipids. Secretion of EVs is a fundamental and evolutionarily conserved biological process broadly found from bacteria to humans and in all cell types in a higher organism. Due to their bulk loading nature, EVs play a critical and versatile role in the intercellular communication perhaps in all physiological and pathological processes, including the cancer-host crosstalk. Research from our group and others has shown that cancer cell-secreted EVs partake in vascular remodeling, immunomodulation, and formation of pre-metastatic niches. Circulating EV-based biomarkers are being exploited for risk prediction, early diagnosis and prognosis of human diseases such as cancer. I will showcase recent studies from my group elucidating how EVs secreted by breast cancer cells influence a variety of non-cancer cell types in the brain, lungs, liver, muscle, endocrine tissues, and blood vessels to impair many aspects of normal physiological functions and facilitate tumor growth and metastasis. Research in my lab accentuates a holistic understanding of human diseases such as breast cancer, with a focus on EV-mediated cancer- host crosstalk.

Questions/Thoughts about systemic effects of cancer:

- To what degree do the systemic effects of cancer influence the clinical outcome of patients? While many are seeking a “cure” for cancer by killing cancer cells directly, how can we demonstrate the importance of targeting cancer’s systemic effects as animportant new part of clinical management?
- Could we form a consortium or forum to continue this collaborative effort and facilitate the growth of research in cancer’s systemic effects?

Yu Xin (Will) Wang
Sanford Burnham Prebys Medical Discovery Institute

Inflammation in neuromuscular regeneration and wasting conditions

Skeletal muscle mass and function are maintained by a combination of regenerative mechanisms to form new muscle fibers (myofibers) after injury, and proteostatic control of myofiber metabolism and mass. Both are regulated by interactions with motor neurons that innervate myofibers, and immune cells that infiltrate during local or systemic inflammation. My lab uses spatial -omics approaches, at single cell resolution, to investigate changes to the tissue microenvironment and architecture during regeneration and muscle wasting conditions (dystrophy, autoimmune disease, denervation, aging). These methods allow us to better understand the complex relationships across cell types and the interactions of muscle with distal immune organs. Specifically, we aim to resolve how dysregulated immune responses underly age-related muscle wasting and identify regulatory nodes that can be modulated to restore muscle mass and function. One such example is the pro-inflammatory signal, prostaglandin E2, that has potent pro-regenerative properties for stimulating neuromuscular regeneration that can overcome age-related muscle atrophy.

In the context of cancer-induced muscle wasting, known as cachexia, we are interested in how changes in the tumor-immune microenvironment (TIME) and systemic immune landscape alter how myofibers interact with supportive cell types, with an emphasis on innervation and neuropathic processes. We will apply our spatial technologies and expertise in tissue regeneration, immunity, and muscle pathologies to orient our interpretation of the diverse range of molecular phenotypes during cachectic muscle wasting.