Indian Institute of Science
Centre for BioSystems Science and Engineering
BSSE Seminar
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Imaging and Defining Dynamic Interactions in the Tumour microenvironment

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ABOUT THE SPEAKER

Dr. Arja Ray received his PhD in Biomedical Engineering from the University of Minnesota Twin Cities, studying the biophysical interactions of cancer cells and surrounding collagen by live imaging. In desmoplastic tumors, cancer cells rapidly invade surrounding tissues by directionally migrating along aligned collagen tracks by contact guidance. While the phenomenon of contact guidance had been described before, his work (*Ray et al., Nat. Commun., 2017: highlighted in F1000Prime*) elucidated a biophysical mechanism by which such guidance is orchestrated at the molecular level. In parallel, he developed engineered tissues (*Ray et al., Biophys. J., 2017; Ray et al., Integr. Biol., 2018*) and techniques enabling live two-photon imaging of cancer cell migration in tumor-mimetic 3D ECM (*Ray et al., Curr. Prot. Stem Cell Biol., 2018)*. Currently a postdoctoral scholar in Matthew Krummel's lab at the University of California, San Francisco, he studies fundamental aspects of tumor-infiltrating T cell biology using intravital imaging. His long-term goal is to utilize imaging-based approaches to unravel critical processes driving tumor progression and anti-tumor immunity.

ABSTRACT

Carcinoma cells in fibrotic breast tumors often disseminate from the primary tumor mass by utilizing aligned collagen fibers as tracks, eventually causing increased metastasis and affecting patient outcome. Likewise, in pancreatic ductal adenocarcinomas (PDA), cancer cells escape from ductal lesions into highly organized periductal collagen, which act as highways for local invasion. Yet, how cells sense, interact and follow these ECM pathways by the process of contact guidance is poorly understood. To study this process, we used 2D microfabricated substrates with micron-scale parallel ridges mimicking aligned collagen fibers. In addition, we engineered aligned collagen matrices by constrained fibroblast-mediated matrix compaction to simulate *in vivo*-like 3D ECM structures. Using these platforms in conjunction with live confocal and two-photon microscopy, we defined the molecular mechanism of contact guidance. We found that cell guidance on the aligned substrata is mediated by spatially constrained growth of focal adhesions on the structural discontinuities of the ECM, leading to anisotropic distribution of adhesions, F-actin and traction forces. In fact, such anisotropic forces also counteract the cell-cell forces in epithelial clusters and may initiate collective or single cell invasion at the tumor-stromal interface. Such invasive dissemination is often observed early in PDA development, leading to pre-malignant dissemination and metastasis. Importantly, abrogating such cell-ECM interactions through focal adhesion kinase (FAK) inhibition is sufficient to restrict early invasion and metastasis in PDA. While restricting metastasis is vital for controlling tumor progression, immunotherapy, through checkpoint blockade, has emerged as a potential treatment for some cancer types. To understand and overcome the limited success of cancer immunotherapy, it is imperative to define and decode the heterogeneous T cell dynamics in solid tumors. Currently, my efforts focus on defining the phenotypic and interactional landscape of functional T cells in tumors using a novel mouse model with endogenous labeling of activated T cells. Intravital imaging, flow cytometry and transcriptomic analysis of T cells from this mouse model enabled us to identify and capture the dynamics of anti-tumor T cells. Thus, we are defining the molecular signatures, key interaction partners and niches of functional T cells in a tumor, thereby providing new perspectives to enhance the anti-tumor function of T cells.