Indian Institute of Science
Centre for BioSystems Science and Engineering
BSSE Seminar
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Mechano-Immunology-Exploring the Physical Drivers of Macrophage Activation

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ABOUT THE SPEAKER

Dr. Nikhil Jain carried out his doctoral studies at the National University of Singapore under the supervision of Prof. Paul Matsudaira and G.V. Shivashankar (2008-2014). By combining microfabrication techniques, high-resolution-imaging and "omics" toolkit, he elucidated functional and regulatory coupling between cellular architecture and the gene expression program. Using genome-wide transcriptome analysis and by generating multi-dimensional plots, he linked specific gene clusters with distinct cell-geometries in fibroblast and stem cells. In 2014, he joined the laboratory of Prof. Viola Vogel as a postdoctoral fellow, where he contributed to the formulation of a new paradigm of homeostasis and inflammatory gene expression regulation of immune-cells by forces, which exist in healthy and diseased tissues. According to this, macrophage activation is directly regulated by spatial confinement. During his postdoctoral tenure, he was awarded an SNF fellowship followed by an EMBO fellowship to carry out a project to study epigenomic changes during macrophage inflammation in collaboration with Prof. Yuval Ebenstein at the Tel-Aviv University and Prof. Chuan He at the University of Chicago. His current research interest is towards understanding how physical forces, which exist in tissues, shape the behaviour of immune cells during different pathological conditions mainly aging and neuro-degenerative diseases.

ABSTRACT

Macrophages are unique in the sense that they perform their function under a variety of different physical environments. Macrophage-like microglia cells in the brain sense low ECM stiffness, within the vasculature, blood flow can critically affect macrophage survival and function, and macrophage like-osteoclasts are constantly subjected to mechanical loading in bone. A large amount of literature suggesting chemical/metabolic signals regulating macrophage tissue-specification and function is available, however, all these studies have so far not been able to clarify how macrophages acquire tissue-specific phenotypic and functional states. Further, even though it is now known that during the loss of cellular and tissue homeostasis and the onset of pathological conditions (fibrotic/atherosclerotic/cancerous), the physical properties of a tissue including stiffness, architecture and cellular composition change dramatically, it is poorly understood how these changes in the physical parameters co-regulate the pro-inflammatory and pro-healing activation of macrophages. Understanding the mechanisms how physical properties of the microenvironment can tune macrophages specification and activation is highly significant to better understand how macrophages drive the disease progression and vice-versa to learn how materials can be engineered to tune their phenotypes. I will show how macrophage spatial confinement, as imposed by micropatterning, 3D microporous substrates or cell crowding, suppresses inflammation related transcriptional programs by mechano-modulating chromatin compaction and epigenetic alterations. Mechanistically, confinement reduces actin polymerization, thereby lowers inflammation regulated nuclear translocation of MRTF-A. The MRTF-A–SRF complex activity is lowered and this subsequently downregulates the inflammatory response, as confirmed by chromatin immunoprecipitation coupled with quantitative PCR and RNA sequencing analysis and complemented with super resolution microscopy. Confinement thus downregulates pro-inflammatory cytokine secretion and the phagocytic potential of macrophages. I will introduce a new super-resolution epi-imaging technique, which we have developed to study DNA epigenetic modification and macrophage inflammation. All these findings and novel techniques developed will have broad implications in the context of inflammation and immunology, cellular reprogramming, tissue engineering and regenerative medicine and lastly, in the development of cell mechanics-based biomarkers.