Indian Institute of Science

Centre for BioSystems Science and Engineering

BSSE Seminar

At 3:00 PM on 30th November 2018

MRDG seminar hall, 1st Floor Biological Sciences Building

MMP-cytoskeletal crosstalk in cancer invasion

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Abstract

Cancer invasion through dense extracellular matrices (ECMs) is mediated by matrix metalloproteinases (MMPs) which degrade the ECM thereby creating paths for migration. Localized degradation by MMPs is mediated by invasive structures called invadopodia. However, how such localized degradation at invadopodia can create tracks amenable for cell invasion remains unknown. Also, it remains unclear if, in addition to mediating ECM degradation, MMPs play additional function in regulating the invasive phenotype of cancer cells is also not clear. Here, we address these questions by first studying the dependence of invadopodia activity on ECM properties, determining the role of membrane-bound versus soluble MMPs in mediating ECM degradation, and then probing the function of MMPs in regulating biophysical properties of cancer cells relevant to invasion. Our results suggest that cancer cells tune MMP secretion rate and inter-invadopodia spacing for creating wide pores conducive for invasion, with bulk of the degradation mediated by soluble MMPs. Further, we show that MMP catalytic activity regulates cell spreading, motility, contractility and cortical stiffness of highly invasive cancer cells by stabilizing integrins at the membrane and activating focal adhesion kinase. MMP inhibition causes a transition to a rounded amoeboidal phenotype through a combination of cytoskeletal disassembly-induced cell softening, and nuclear softening through increased phosphorylation of lamin A/C. Together, our results reveal an integrin mediated crosstalk between MMPs and the actomyosin cytoskeleton that enables invasion plasticity, i.e., switch from protease-dependent mesenchymal mode of migration to protease-independent amoeboidal mode of migration, by altering cell and nuclear properties.

About the Speaker

Dr. Shamik Sen is an Associate Professor at the Department of Biosciences and Bioengineering, IIT Bombay. One of the most important breakthroughs of this post-genomic era is the finding that in addition to chemical cues, cell behavior is equally susceptible to physical cues of the environment, including the geometry, topography and physical properties of the extracellular matrix (ECM). From embryonic development to cancer, physical forces play an important role in modulating cell processes including cell sorting, proliferation, differentiation and angiogenesis. The broad goal of his research plan is to understand how physical forces influence cell and matrix mechanics through a combination of experimental and computational techniques. To contribute to this understanding he explores how development and cancer progression are regulated by the physical crosstalk between the cell cytoskeleton and the ECM