GRK 2213

Joint guest lecture of the
Philipps-Universität Marburg and
Max-Planck-Institute for Heart & Lung Research

21st of June 2018

Guests are welcome

TOBIAS ZECH

Institute of Translational Medicine, University of Liverpool

"Mechanisms of 3D cell migration: Nuclear force coupling mediated cancer cell invasion"

Cells migrating through 3D matrices form hybrid adhesion structures, which display hallmarks of both focal adhesions and invadopodia. We have identified an interaction between beta-PIX (ARHGEF7; COOL-1) and Myosin18A (M18A) in proteomic screens of 3D matrix adhesion sites. Loss of beta-PIX /M18A abolished cancer cell invasion, but increased matrix degradation and pseudopod extension in collagen matrices. These seemingly contradictory results can be explained by our finding that beta-PIX is part of a betaPIX -M18A-nonmuscle myosin 2A (NM2A) recruitment cascade that is required for adhesion site turnover and nuclear-force coupling (NFC). The nucleus can act as limiting factor in 3D cell migration. Migrating cells need to actively squeeze the nucleus through matrix pores. Knockdown of nuclear envelope actin binding proteins called Nesprin-1 and -2 severely affect 3D cell migration. We have found a reciprocal regulation of Nesprin-2 and beta-PIX /M18A function. We can show using a novel nuclear membrane FRET/FLIM force biosensor, that direct force coupling from 3D adhesion sites to the nuclear membrane through beta-PIX/M18A is required for 3D cell migration. We propose that this mechanism establishes front-rear cell polarity during 3D cell migration through NM2 isoform polarisation. Front-rear polarity of migrating cells enables polarised recycling of pro invasive proteins like the metalloproteinase MT1-MMP in an actin dependant manner. We can show that ubiquitin mediated degradation and actin mediated receptor recycling are part of one connected sorting systems that is orchestrated by HRS (ESCRT-0) and the WASH complex to enable effective receptor recycling for invasive migration.

5:00 pm
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