University of Stuttgart

Stuttgart Research Center Systems Biology

SRC SB

Systems Biology Seminar Talk

The cell biology of PTEN loss-associated invasion in ovarian cancer

Prof. David Bryant
School of Cancer Sciences
University of Glasgow, UK

10.02.2025
14:00 CET
Host:
Prof. Monilola Olayioye
Lecture Hall 0.106
Allmandring 31
Stuttgart

Abstract:

Dysregulation of the PI3K/AKT pathway is a common occurrence in high-grade serous ovarian carcinoma (HGSOC), with the loss of the tumour suppressor PTEN in HGSOC being associated with poor prog- nosis. The cellular mechanisms of how PTEN loss contributes to HGSOC are largely unknown. We here utilise time-lapse imaging of HGSOC spheroids coupled to a machine learning approach to classify the phenotype of PTEN loss. PTEN deficiency induces PI(3,4,5)P3-rich and -dependent membrane protrusions into the extracellular matrix (ECM), resulting in a collective invasion phenotype. We identify the small GTPase ARF6 as a crucial vulnerability of HGSOC cells upon PTEN loss. Through a functional proteomic CRISPR screen of ARF6 interactors, we identify the ARF GTPase-activating protein (GAP) AGAP1 and the ECM receptor b1-integrin (ITGB1) as key ARF6 inter- actors in HGSOC regulating PTEN loss-associated invasion. ARF6 functions to promote invasion by controlling the recycling of inter- nalised, active b1-integrin to maintain invasive activity into the ECM. The expression of the CYTH2-ARF6-AGAP1 complex in HGSOC patients is inversely associated with outcome, allowing the identifi- cation of patient groups with improved versus poor outcome. ARF6 may represent a therapeutic vulnerability in PTEN-depleted HGSOC.

CV:

David Bryant’s laboratory studies how groups of cells assemble into tissues and how the rules for this in cancer are changed. In particular we make extensive use of 3-Dimensional culture as a tool for studying collective behaviours, including improving the tools and techniques for 3D culture. We use in vitro-to-in vivo approaches where we charactertise mechanisms of behaviour in vivo, and transplant organoid cultures in vivo to understand tumour formation and metastasis. Our work focuses on how changes in phosphoinositide signalling (the ‘PI3-kinase pathway’) controls cells growth and metastasis. I'm also a strong advocate for LGBT and minority group equality, and in working to make the workplace open and accepting to all.