

Seminar series TRR 305 – Striking a moving target: From mechanisms of metastatic organ colonisation to novel systemic therapies



Wednesday, 18 January 2023

15.00 h

hybrid (on site in Erlangen)

TRC Auditorium Translational Research Center, Raum 0.010
Schwabachanlage 12, 91054 Erlangen

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Fumarate hydratase loss as a paradigm of oncometabolism

The role of mitochondrial dysfunction in cancer has been debated for over a century. Recent bioinformatic data analyses revealed that mitochondrial genes are suppressed in cancer with poor clinical outcome. Furthermore, the fact that mutations of core metabolic enzymes in the mitochondria such as Fumarate Hydratase (FH) cause renal cancer strongly indicates that mitochondrial dysfunction can drive cancer. Today, I will provide an overview of our recent findings about the molecular mechanisms through which mitochondrial dysfunction can drive transformation. In particular, using a novel genetically modified mouse model, I will show that FH loss has different outcomes in different tissues, and whilst kidneys are very robust to FH loss, other tissues don't tolerate FH loss and here FH-deficient cells are negatively selected. Our work provides some insights into potential mechanisms of tissue-specific tumorigenesis based on metabolic permissiveness.

Ryan DG, Yang M, Prag HA, Blanco GR, Nikitopoulou E, Segarra-Mondejar M, Powell CA, Young T, Burger N, Miljkovic JL, Minczuk M, Murphy MP, von Kriegsheim A, Frezza C. Disruption of the TCA cycle reveals an ATF4-dependent integration of redox and amino acid metabolism. *Elife*. 2021 Dec 23;10:e72593. doi: 10.7554/eLife.72593. PMID: 34939929; PMCID: PMC8735863.

Sciacovelli M, Gonçalves E, Johnson TI, Zecchini VR, da Costa AS, Gaude E, Drubbel AV, Theobald SJ, Abbo SR, Tran MG, Rajeeve V, Cardaci S, Foster S, Yun H, Cutillas P, Warren A, Gnanapragasam V, Gottlieb E, Franze K, Huntly B, Maher ER, Maxwell PH, Saez-Rodriguez J, Frezza C. Fumarate is an epigenetic modifier that elicits epithelial-to-mesenchymal transition. *Nature*. 2016 Aug 31;537(7621):544-547. doi: 10.1038/nature19353. Erratum in: *Nature*. 2016 Dec 1;540(7631):150. PMID: 27580029; PMCID: PMC5136292.

Zoom-Meeting-Link

<https://fau.zoom.us/j/67221195153?pwd=MHZLZGNHa0RCbStnTEFZcG1FejhKUT09>

Meeting-ID: 672 2119 5153

Code: 721518