Seminar series FOR2127 – Selection and adaptation during metastatic cancer progression

Thursday, 06 Februar 2020
Kleiner Hörsaal, Klinikum
14.00 h

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"A Primary Mammary Organoid System to Trace Breast Cancer Treatment Reveals Molecular Targets to Interfere with Minimal Residual Disease"

Despite great advances in adjuvant therapies breast cancer reoccurrence remains the main cause of breast cancer related death. Recurrences are largely driven by minimal residual disease (MRD), which survives therapeutic intervention. However, the molecular and cellular mechanisms of MRD establishment have remained largely unexplored, mainly due to the difficulties in identifying and characterizing these cells in patients.
We employ tractable preclinical mouse models of breast cancer together with an organotypic primary 3D tissue culture approach to examine the nature of residual breast cancer cells following initial targeted therapy. Mammary organoids permitted to closely follow tumor cell fate after oncogene silencing and allowed the isolation of a population of residual cells. In depth characterization of MRD included transcriptomic, metabolomic and lipidomic measurements to perform multiomic overlay and flux modeling. In addition the treatment phase and establishment of MRD is followed with live cell imaging at a single cell resolution using Selective Plane Illumination Microscopy (SPIM) to monitor interference with candidate targets that allow survival of residual cells.
The residual cells exhibit a distinct transcriptional profile that distinguishes them from tumor- and normal cells. Strikingly, they bear metabolic resemblance to the tumor state, despite the absence of oncogene expression, normal proliferation rates and apparent normal, re-polarized phenotypic appearance. The MRD kept metabolic tumor hallmarks that were also observed in the breast tumor, as if MRD retains some kind of "oncogenic memory".
Integration of the multi-omics datasets, along with metabolite predictions, flux modeling and imaging, further defined hallmarks of MRD. We will discuss the identified targets and migration/survival patterns of residual cells to interfere with dormant disease.

Selected reading:

Jechlinger, M., Podsypanina, K., & Varmus, H. (2009). Regulation of transgenes in three-dimensional cultures of primary mouse mammary cells demonstrates oncogene dependence and identifies cells that survive deinduction. Genes & Development, 23(14), 1677–1688.

Havas K.M., Milchevskaya V., Radic K., Alladin A., Kafkia E., Garcia M., Stolte J., (...), Jechlinger M. (2017). Metabolic shifts in residual breast cancer drive tumor recurrence. Journal of Clinical Investigation,127(6), pp. 2091-2105.