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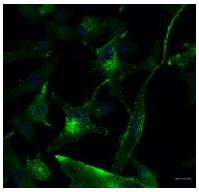

Tumor intrinsic mechanisms in melanoma and the dynamics between tumor and immune cells: the role of the endolysosomal machinery of melanoma cells

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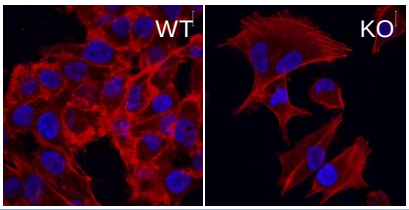
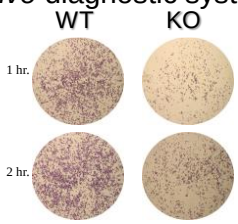
Background

In 2018, Denmark had the highest age-standardized rate of melanoma among women and placed 4th in overall incidence worldwide. Despite the impact of immunotherapy in recent years, melanoma remains the main cause for skin cancer-related deaths. Response to immunotherapy is limited to a third of patients, and acquired resistance poses a serious challenge. ***Hence, it is vital to advance our understanding of melanoma biology***.

Focusing on the biology of melanoma cells, we have established that melanoma tumors frequently acquire megalin expression, and in preliminary experiments using a megalin knock out model we have revealed that megalin is gatekeeper of melanoma phenotype and immunogenicity. Absence of megalin is associated dramatic changes of the endolysosomal machinery, the cytoskeleton, the phenotype, and with high invasiveness and low immunogenicity.

Leveraging a novel microfluidic culture system we intend to investigate our novel findings in a physiological 3D setting recapitulating the interactions between tumor cells and non-tumor cell elements of the tumor microenvironment. Beyond the fundamental biological insights gained, establishment of this technique will establish a sophisticated *ex vivo* diagnostic system.



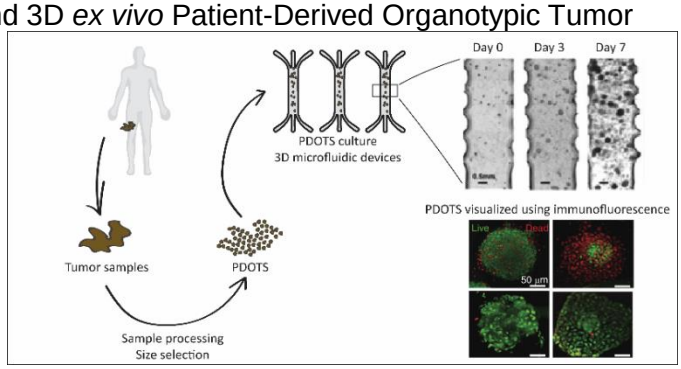


Projects

- Investigations of the dynamics between melanoma and immune cells and how their interactions affect melanoma phenotype and immunogenicity.
- Specifically we focus at the endolysosomal vesicular transport network in melanoma cells.
- Our overall aim is to deliver knowledge that will enable us to improve the response rate of immunotherapy and identify novel mechanisms for intervention with melanoma cancer.

Techniques

- *In vitro* cell lines modelling phenotype switching and immunogenicity dynamics (CRISPR/Cas9 mutated melanoma cell lines and melanoma cell lines exposed to various physiologically relevant signalling molecules).
- 2D co-cultures of melanoma cells and various types of immune cells.
- qPCR, cloning, immunoblotting, adhesion assays, wound healing assays, invasion assays, immunofluorescence and advanced imaging, flow cytometry.
- Immunohistochemistry and digital pathology (tissue analyses).
- Spheroid mono-cultures and co-cultures and 3D *ex vivo* Patient-Derived Organotypic Tumor Spheroids (PDOTS) as shown here:



Modified from Jenkins RW et al. Cancer discovery. 2018;8(2):196-215.

References:
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"Megalin is gatekeeper of the epithelial and immunogenic phenotype of melanoma cells and controls metastatic potential".
Julie Nelly Christensen/Martin Qvist Rasmussen, …, Søren Degn and Mette Madsen. In preparation 2019.