Metabolism and cancer cell plasticity

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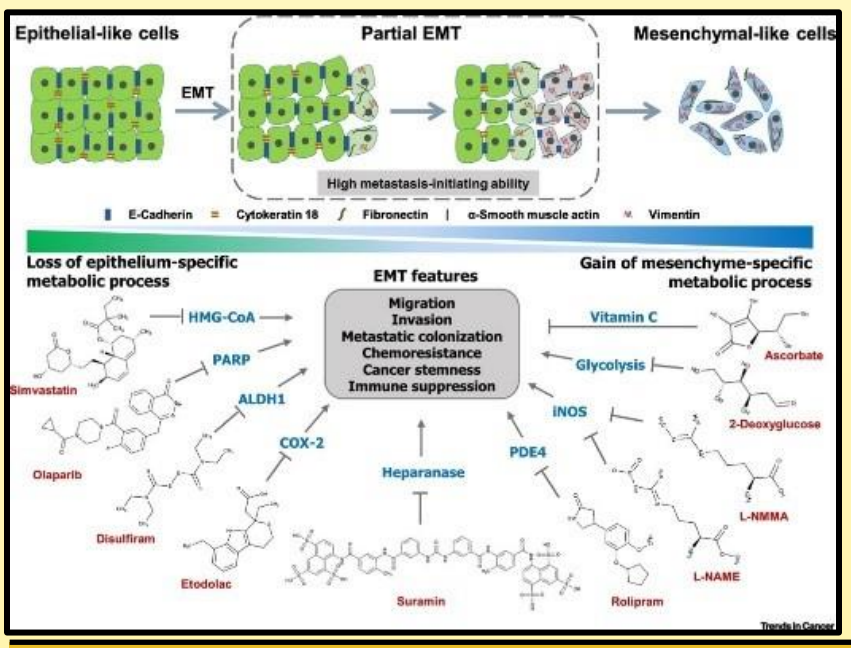
Gruppens kerneforskningsområder

The most lethal features of cancer are chemoresistance and metastatic dissemination. In many cases, both are attributed to the presence of cells driven by up-regulation of nucleotide metabolism (NM) and by the de-differentiation process of epithelial-to-mesenchymal transition (EMT), which can foster chemoresistance and clinical relapse. Recently, our lab and others showed that some metabolic pathways can exert a powerful regulatory role on cancer cell de-differentiation and promote cancer aggressiveness by driving NM and EMT. Metabolism-based therapeutic strategies could contribute to reduce the devastating effects of aggressive cancers. Our group employs several cell and molecular biology techniques, mouse models, high-throughput approaches, bioinformatics and the analysis of human samples.

Er du interesseret i at skrive projekt i gruppen, så kontakt pceppi@bmb.sdu.dk



Incucyte S3 live cell imager

Projekter	Beskrivelse
Repurposing anti-metabolism drugs to target EMT and cancer aggressiveness	Epithelial-to-mesenchymal transition (EMT) represents an attractive target in oncology. However, direct targeting of EMT is, in most cases, pharmacologically challenging. Since emerging research has highlighted the distinct metabolic circuits involved in EMT, we will test the use of metabolism-specific inhibitors as a drug repurposing approach to target cancer EMT and aggressive features. The project involves cell cultures, live cell imaging, anti-metabolic drugs and metabolic assays in vitro. See Ramesh et al. *EMBO Mol Med* 2023.
Role of thymidylate synthase in chemoresistance, dedifferentiation and tumor progression	Cancer cells frequently boost nucleotide metabolism (NM) to support their increased proliferation, but the consequences of elevated NM on tumor de-differentiation are mostly unexplored. We identified a proliferation-independent role for thymidylate synthase (TS), a NM enzyme and established drug target, in cancer cell de-differentiation. We aim to determine the mechanistic and metabolic details of this phenomenon with several potential clinical implications in solid cancers. The project involves cell cultures, live cell imaging, the use of anti-metabolic drugs and interfering oligonucleotides in vitro. See Siddiqui et al. *Molecular Metabolism* 2020 and *British Journal of Cancer* 2021.
Single cell transcriptomics analysis of tumor microenvironmental cells' contribution to contact-mediated pyrimidine transfer in non-small cell lung cancers	Cancer cells rely on a permanent supply of nucleotides (purines and pyrimidines), which they continuously synthesize to drive DNA replication. Our preliminary unpublished data show that pyrimidine metabolites could be transported across cells, providing survival benefit to the cell that are deficient in synthesizing their own pyrimidine molecules. The present project aims to explore a big dataset comprising single cell RNA-seq information from non-small cell lung cancer patients to identify the potential partners in the nucleotide exchange and the underlying mechanisms and implications. The project primarily involves advanced computational methods like single cell and bulk RNA-seq sequencing analyses, Geneset enrichment analysis and pathway-based approaches utilizing different platforms such as R, Python, Linux and GSEA.