Metabolism and cancer cell plasticity

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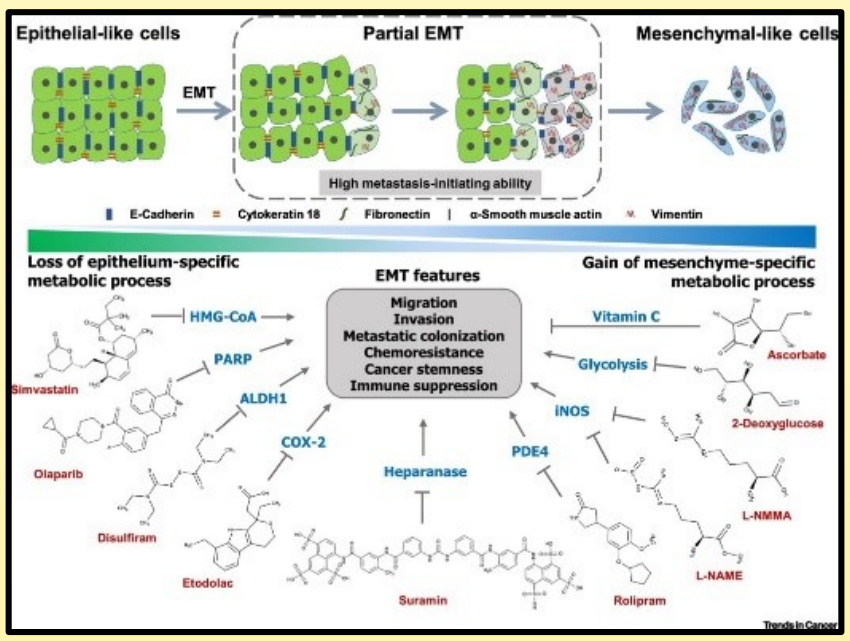
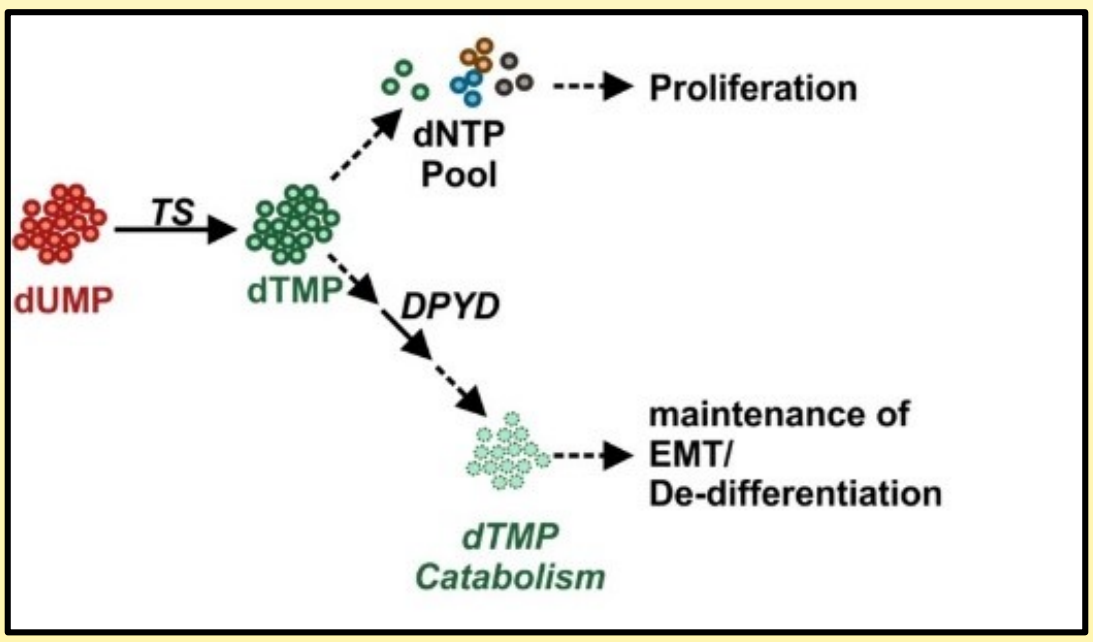
Gruppens kerneforskningsområder

The most lethal features of cancer are chemoresistance and metastatic dissemination. In many cases, both are attributed to the presence of cells driven by de-differentiation processes like the epithelial-to-mesenchymal transition (EMT) and the cancer stem cell (CSC) program, which can foster a 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 EMT/CSC. Identifying the whole network of metabolic pathways controlling the de-differentiation processes could be highly impactful in the field of drug repositioning because, in contrast to currently known EMT effectors and mediators, several inhibitors for metabolism enzymes are already in clinical use for the treatment of not tumor-related diseases. Metabolism-based therapeutic strategies could contribute to reduce the devastating effects of aggressive cancers.

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





Projekter	Beskrivelse
Repurposing anti-metabolism drugs to target EMT	Epithelial-to-mesenchymal transition represents an attractive target in oncology. However, direct targeting of EMT effector molecules 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, FDA approved or under clinical trials, as a drug repurposing approach to target EMT in cancer.
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 and determined its clinical significance in breast and lung cancer. We aim to determine the mechanistic and metabolic details of this phenomenon with several potential clinical implications in solid cancers.
Understanding EMT biology by mapping the micro-RNAs regulatory network	EMT is essential for numerous developmental processes and holds a central role in tissue regeneration and disease. MicroRNAs (miRNAs) are a class of small non-coding regulatory RNAs that target gene expression to regulate cellular functions. Some miRNAs tightly control EMT, but the global network of EMT regulation orchestrated by miRNAs is currently unresolved, mainly because of the lack of tools to unbiasedly identify the upstream molecular events controlling miRNA expression/activity. By using a novel high-throughput and high-resolution approach to measure the activity of miRNAs in living cells, we propose here to resolve for the first time the entire EMT regulatory circuitry and interfere with the EMT process in vivo in a disease-relevant model. Mapping the whole EMT regulatory network could be game-changing in physiology and disease, opening new avenues in the treatment of EMT-related conditions, like fibrotic disorders and solid tumors.