"In 2019, the BCCRU finalised its characterisation of fatty acid synthase as a key mediator of breast epithelium transformation. This opens up an unprecedented opportunity for cancer prevention."

RESEARCH HIGHLIGHTS

Contrary to what was previously known, we have found that fatty acid synthase (FASN, an enzyme with low expression in healthy tissue but high expression in epithelial malignancies) exerts a key role during the early steps of cancer initiation, but not when the cancer is established. In vitro and in vivo models of breast carcinogenesis cannot undergo transformation in the absence of FASN; however, its deletion after the cancer is established has little effect. Mechanistically, this preventive role is independent of its biosynthetic product. FASN consumes acetyl-CoA, which unlocks reductive isocitrate dehydrogenase-dependent carboxylation. This allows the production of the reductive power necessary to quench the reactive oxygen species (ROS) produced during the 2D–to–3D growth transition. This necessary hallmark of cancer is abrogated in the absence of FASN due to intramitochondrial ROS accumulation, which disrupts the mitochondrial respiratory supercomplexes and results in cell death. These findings open up therapeutic opportunities in the preventive phase of breast cancer.

Our previous findings about the metabolic adaptation of tumours in response to metabolic-normalising antiangiogenics were confirmed in a clinical trial, where patients with early HER2-negative breast cancer were treated with bevacizumab alone or bevacizumab plus a mitochondrial inhibitor. The latter patients experienced a 3-fold decrease in the Ki67 replicative fraction.

Finally, we worked on the search for predictive markers of activity of anti-PD-L1 agents. In patients with advanced breast cancer, we found that those with a baseline higher quotient of T-effector/T-memory populations had a higher chance of response to durvalumab.