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REDOX AND METABOLIC REPROGRAMMING OF BREAST CANCER CELLS AND ASSOCIATED ADIPOSE TISSUE - THE CORNERSTONES OF ADAPTIVE TUMOUR BEHAVIOUR

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A high proliferation rate and the malignancy of cancer cells are favoured by redox and metabolic plasticity, which is determined by the co-evolution of cancer cells with their host microenvironment. The tight functional connections between the mammary glands' epithelium and adipose tissue (AT) allow breast cancer cells to subjugate the AT and form a protumorigenic cancer-associated adipose tissue (CAAT). Our findings in luminal invasive ductal carcinomas in premenopausal women confirmed key cancer cell strategies - the Warburg effect, increased mitochondrial metabolism and redox adaptability, which are associated with a specific shift in the metabolic and redox phenotype of CAAT. Notably, the upregulated master redox-sensitive transcription factor Nrf2 appears to be responsible for the cancer cell-induced redox and metabolic shift of CAAT. We also investigated the role of Nrf2 in the metabolic co-evolution of cancer cells and CAAT during disease progression. Our results in the orthotopic breast cancer mouse model and in the co-culture of breast cancer cells with adipocytes confirmed the different spatiotemporal redox and metabolic properties of cancer cells and CAAT, established with respect to the Nrf2-coupled/uncoupled tumour microenvironment. The uncovered metabolic and redox strategies adopted by breast cancer cells according to CAAT properties and at different disease stages have helped to better understand the biology of the aggressive disease and to identify breast cancer vulnerabilities that could become therapeutic targets.

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