Poster

Characterising the role of palmitoylation in metastatic breast cancer

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ABSTRACT

Motivation: Metastasis is the final stage and main cause of cancer-related deaths. In a study by Altea Manzano et al., they observed that increased dietary fat uptake can facilitate metastasis of the primary breast tumour in the lung. Primary breast cancer tumour cells can promote increased palmitate production in the lungs, creating a premetastatic niche that allows the colonisation and growth of tumour cells in the lung. This excess of palmitate can be used by tumour cells as an energy source or to activate oncogenic pathways. In this context, this study aims to characterise the role of palmitoylation in metastatic breast cancer. Protein S-palmitoylation is a reversible posttranslational modification where the fatty acid palmitate is attached to a specific cysteine residue in the target protein. Palmitoylation affects the localisation, trafficking, stability and activity of hundreds of proteins and is mediated by the ZDHHC family of proteins, while the depalmitoylation process is carried out by depalmitoylases. Proteins that are encoded by oncogenes and tumour suppressor genes are palmitoylated and dysregulation of protein palmitoylation could be related to metastatic invasion.

Methods: We performed 3D in vitro cultures of mouse (4T1 and D2.A1) and human (HCC1428 and MCF10A-HRas) breast cancer cell lines to determine the role of palmitate in tumour spheroid growth. We also generated knockdown cell lines for a specific depalmitoylase to study how this modification affects the growth of 3D spheroids. We also tested a chemical inhibitor for the depalmitoylase enzyme to determine if the effect of the inhibition in the 3D spheroids growth is similar to the effect of the knockdown.

Results: Cell lines were cultured with different concentrations of palmitate and we observed that breast cancer spheroids showed an increase in 3D growth in the presence of 75 μM of palmitate. We also found that higher concentrations than 75 μM are no longer beneficial for 3D growth. We also tested D2.A1 3D growth upon depalmitoylation inhibition (knockdown and chemical inhibition). Notably, we found that inhibiting depalmitoylation prevents the growth advantage conferred by palmitate supplementation.

Conclusions: Palmitate promotes the growth of 3D tumour spheroids, and this effect is dependent on depalmitoylase enzymes. When depalmitoylases are inhibited, 3D spheroids are not able to grow using palmitate, which may be related to a reduced ability to form metastases.

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