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Development of an *in vitro* tumour model to evaluate drug efficacy and epidermal mesenchymal transition in triple negative breast cancer

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Introduction: The advent of diverse methods for 3-dimensional (3D) cell culture has allowed scientists to address some of the limitations of conventional 2D methods. 3D cell culture systems attempt to mimic the in vivo tumour microenvironment accurately allowing more physiological studies of cancer cell response to treatment (1). A major component of the tumour microenvironment overlooked during past years of drug discovery and cancer studies is the interstitial fluid pressure (IFP) (2). Despite recent increased interest in this area many aspects of the biophysical effect of IFP on cancer development, particularly in solid tumours, remains unknown. The aim of this project is to study breast cancer cell behaviour in terms of invasion and drug responses in a more physiologically relevant environment taking into account the effect of IFP and fluid flow.

Method: The MDA-MB231 breast cancer cell line was chosen as it is a triple negative breast cancer subtype. In the 3D system MDA-MB231 cells were seeded in a dense (80 mg/ml) collagen scaffold and surrounded by stromal collagen forming an artificial cancer mass (ACM) enabling the invasive properties of the cancer cells to be studied. The proliferation/metabolic activity of the cells in 2D, 3D, static and dynamic flow conditions (flow of 100 and 500 µl/min and pressure of 19 mmHg), were evaluated using an Alamar Blue assay and confocal microscopy. Markers of epidermal-mesenchymal transition (EMT) were evaluated using q-RT-PCR and responsiveness of cells to doxorubicin was assessed.

Results: MDA-MB231 cells showed a reduction in metabolic activity when cultured in 3D compared to 2D. In contrast, gene expression levels for markers of EMT demonstrated that the dynamic 3D environment promoted a switch to a mesenchymal phenotype with increased expression-levels of mRNA for Snail, vimentin but not MMP14, a membrane type matrix metalloprotease involved in collagen type I degradation. Doxorubicin treatment was less effective when MDA-MB231 cells were grown in 3D and cultured under flow conditions.

Conclusion: The results obtained in this study show that the metabolic activity and drug responsiveness of the cancer cell line MDA-MB231 varies according to the different microenvironments in which the cells are cultured. Applying flow and the implementation of IFP affects the expression levels of EMT related markers.

References:

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