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Obesity and cancer: role of adipose cells in preventing the transition from *in situ* to invasive breast cancer in a two-cell fluorescent spheroid model

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Introduction: The incidence of ductal carcinoma *in situ* (DCIS) has increased in recent years. During the transition from DCIS to invasive ductal carcinoma (IDC), the disorganisation or even disappearance of myoepithelial cells (MECs) is observed, enhancing the ability of the cancer cells to migrate. As no marker has been defined to identify which DCIS will evolve into IDC, the understanding of this transition seems to be of major importance for better patient management. Moreover, many studies have shown the role of **obesity** and **adipose microenvironment** in breast cancer progression. In particular, our team has recently shown that adipose cells may be able to modify the functional characteristics of MECs leading to an invasion process.

Objective: Our objective is to identify preventive factors involved in the transition from DCIS to IDC in **overweight or obese women** by assessing the impact of the inflammatory adipose microenvironment on MECs by developing 3D models.

Methods: A fluorescent 2-cell spheroid model reproducing the pathology of DCIS is being developed. For this purpose, *in situ* cancer cells (MCF10DCIS-RFP) are first seeded in agarose moulds that do not allow cell adhesion. After obtaining spheroids, MECs (Hs578Bst-GFP) are added to our model, the objective being to obtain a continuous layer of MECs around the previously formed spheroids. By confocal imaging, the organisation of the cells in the spheroids as well as the rupture of the continuous MEC layer is visualised. The impact of the inflammatory adipose microenvironment will then be assessed using conditioned media derived from the culture of adipose stem cells or mature adipocytes from overweight/obese women.

Results: For the design of fluorescent cell lines, a lentiviral transduction approach was used to obtain a stable expression of the fluorescent proteins (integrative system). MCF10DCIS cells were transduced with a RFP (Red Fluorescent Protein) gene, while MECs were transduced with a GFP (Green Fluorescent Protein) gene. These genes are under the control of constitutive promoters (EF1a or CMV type), clones of MCF10DCIS and MECs constitutively expressing GFP or RFP, respectively, which will allow to distinguish them directly under the fluorescence microscope. The 2-cell spheroid mimicking DCIS will now be reconstituted and the impact of adipose cells from women of normal-weight and obese women will be evaluated.

Conclusion: This project could ultimately help prevent the progression of ductal cancer *in situ* (DCIS) to invasive ductal cancer (IDC) and lead to the development of new therapeutic strategies for the management of overweight women with DCIS at high or low risk of developing IDC.