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Title: Investigation of signaling pathways activated in breast cancer cell lines after adipocyte co-culture
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Sponsor: Cancer Society of New Zealand, Canterbury-West Coast Division Inc. Cancer Society Rangiora Group

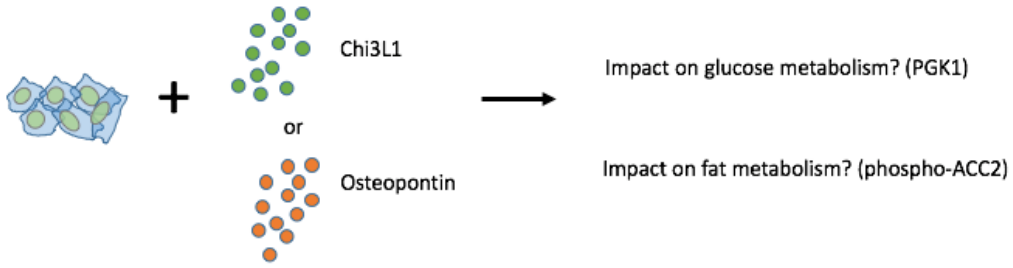
Introduction: Breast cancer is the most commonly diagnosed cancer in New Zealand women and a leading cause of cancer death in women worldwide. Obesity, a modifiable factor, is associated with worse outcome in patients with breast cancer. The tumour microenvironment plays an important role in cancer development and progression and represents a way in which obesity can have a local effect on breast cancer. In particular, the growth of breast cancer cells and adipocytes (fat cells) together has been shown to have a substantial impact on the phenotype of both cell types. Fat cells lose fat and become thinner developing into, what is termed, cancer associated adipocytes (CAAs). These CAAs secrete factors which can make breast cancer cells more aggressive, invasive and resistant to treatment options such as chemotherapy.

Previous research conducted within the Mackenzie Cancer Research Group has looked at the growth of breast cancer cells with fat cells using a transwell system in which the cells can interact but do not come into direct contact. Two key metabolic enzymes were found to be highly upregulated in breast cancer cells. Firstly, phosphoglycerate kinase 1 (PGK1), which drives the metabolism of glucose and secondly, phospho Acetyl-CoA carboxylase (p-ACC2), which drives the metabolism of fat. As well as this, two key factors known to increase breast cancer cell migration and survival (osteopontin and chitinase 3 like 1 (Chi3L1)) were found to be released by fat cells. However, the impact of these factors on breast cancer cells and more precisely the signaling pathways activated in breast cancer cell lines after adipocyte co-culture are yet to be determined, an area we aim to explore in this project.

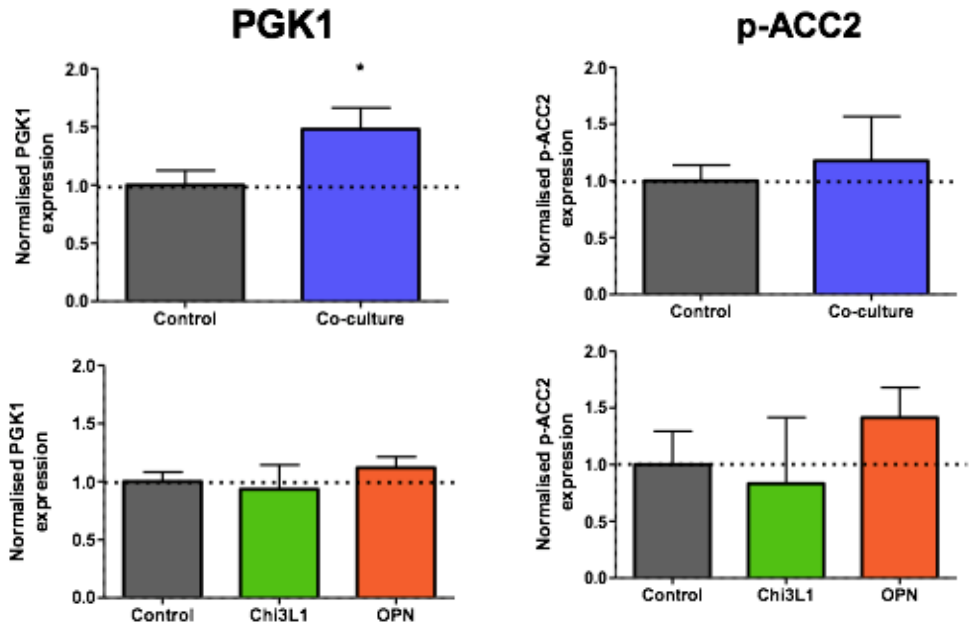
Aim: Our main aim was to investigate the potential impact of factors secreted by cancer-associated adipocytes on the breast cancer cell metabolism. In particular, we aimed to use western blotting to measure key metabolic proteins (PGK1 and p-ACC2) in MCF7 breast cancer cells treated with chitinase 3 like 1 (Chi3L1) or osteopontin. It was hypothesized that Chi3L1 and/or osteopontin may give a survival advantage to breast cancer cells through changing either glucose metabolism or fat metabolism.

Impact: (in lay terms): This research has increased our understanding of cancer cell biology in the context of being grown in fat rich tissue and together with research ongoing in the Mackenzie Cancer Research Group, may lead to more effective treatments for early-stage breast cancer patients.

Method: In this project, human breast cancer cells (MCF7) were grown and stimulated with chitinase 3 like 1, osteopontin or received no stimulation (control). Following a 3-day incubation period, cells were lysed and cell lysates were collected. Western blotting analyses were used to investigate levels of metabolic proteins involved in glucose metabolism (PGK1) and fat metabolism (phospho-ACC2).



Results: Both PGK1 and p-ACC2 expression increased in breast cancer cells co-cultured with fat cells, compared to control breast cancer cells. Osteopontin treated breast cancer cells showed an increasing trend in PGK1 and p-ACC2 levels. The expression of PGK1 and p-ACC2 showed no change in chitinase 3 like 1 treated cells.



Conclusion: This study indicated osteopontin may have a role in the regulation of metabolism in breast cancer cells cultured with fat cells. Osteopontin treated breast cancer cells showed a trend to increase in levels of PGK1 (glucose metabolism) and phospho-ACC2 (fat metabolism). Therefore, osteopontin released from fat cells may give breast cancer cells a survival advantage, by allowing them to metabolise both glucose and fat. In this study, we found chitinase 3 like 1 did not alter the metabolic proteins we looked at (PGK1 or p-ACC2). However, this protein has previously been shown to increase migration and chemo-resistance and therefore may act in other ways through alternative pathways and could be explored further in future research.