Göteborg, 2019

Metabolic and immunological interactions between adipose tissue and breast cancer

Implications of obesity in tumor progression

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, den 22 november 2019, klockan 13:00

Av Peter Micallef

Fakultetsopponent: Ann Rosendahl, docent

Onkologi och Patologi, Kampradlab

Lunds Universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. Antioxidant treatment induces reductive stress associated with mitochondrial dysfunction in adipocytes. Peris, E., **Micallef, P**., Paul, A., Palsdottir, V., Enejder, A., Bauzá-Thorbrügge, M., Olofsson, C.S., Wernstedt Asterholm, I. *Journal of Biological Chemistry, 294 (7), pp. 2340-2352 (2019).*

II. The adipokine C1QTNF3 increases in breast cancer-associated and high fat diet-induced obese subcutaneous adipose tissue, and pushes M2-type macrophages towards an M1-like phenotype. **Micallef, P**., Wu, Y., Peris, E., Wang, Y., Li, M., Chanclón, B., Rosengren, A., Ståhlberg, A., Cardell, S., Wernstedt Asterholm, I. *Submitted.*

III. Adipose tissue - breast cancer crosstalk leads to increased tumor lipogenesis associated with enhanced tumor growth. **Micallef, P**., Chanclón, B., Stensöta, I., Wu, Y., Peris, E., Wernstedt Asterholm, I. *Manuscript.*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

Göteborg, 2019

Metabolic and immunological interactions between adipose tissue and breast cancer

Implications of obesity in tumor progression

Peter Micallef

Enheten för metabol fysiologi, Fysiologi, Neurovetenskap och fysiologi, Sahlgrenska akademin, Göteborgs universitet, Sverige.

Abstract

Triple-negative breast cancers have fewer treatment options than other breast cancers. The overall goal of this research is to identify new pharmaceutical targets for triple-negative breast cancer through studies of the tumor-promoting crosstalk between tumor and surrounding adipose tissue. In **paper I**, we established extracellular flux analyzer-based methodology to evaluate metabolic function of cultured cells, used in **paper II** and **III**. In **paper II**, we identified the C1q/TNF-related protein family member *C1qtnf3* as one of the most upregulated secreted proteins in E0771 triple negative breast cancer-associated mouse adipose tissue – in particular in the obese setting. Antibody-mediated blockage of C1QTNF3 reduced macrophage infiltration in breast cancer-associated adipose tissue in mice. In cultured macrophages, C1QTNF3 decreased oxidative phosphorylation and enhanced M1-polarization. In **paper III**, we demonstrated that E0771 breast cancer tumors grew faster, associated with increased de novo lipogenesis from glucose, if transplanted orthotopically into adipose tissue than if transplanted outside adipose tissue. Based on our vitro data, we propose that adipose tissue-produced lactate triggers the observed increase in de novo lipogenesis in the tumor. In conclusion, paracrine interactions between adipose tissue and breast cancer involve both immunological and metabolic processes, associated with enhanced tumor progression. In the future, we hope that pharmaceutical targeting of these interactions, in combination with conventional therapy, will improve the survival of breast cancer patients.

Keywords: Breast cancer, Adipose tissue, Macrophage, Metabolism, Paracrine.

ISBN: 978-91-7833-518-3 (PRINT) http://hdl.handle.net/2077/60812
ISBN: 978-91-7833-519-0 (PDF)