

# **The breast cancer microenvironment and cancer cell secretion - specific effects on cancer progression and subtypes of cancer cells**

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, den 12e februari 2021, klockan 13.00

av Emma Persson

Fakultetsopponent: Professor Maréne Landström, Umeå Universitet, Sverige

## **Avhandlingen baseras på följande delarbeten**

- I. Jacobsson H., Harrison H., Hughes É., Persson E., Rhost S., Fitzpatrick P., Gustafsson A., Andersson D., Gregersson P., Magnusson Y., Ståhlberg A., Landberg G. Hypoxia-induced secretion stimulates breast cancer stem cell regulatory signalling pathways. *Mol. Oncol.* 2019; 13(8): 1693-1705
- II. Landberg G., Fitzpatrick P., Isakson P., Jonasson E., Karlsson J., Larsson E., Svanström A., Rafnsdottir S., Persson E., Gustafsson A., Andersson D. Rosendahl J., Petronis S., Ranji P., Gregersson P., Magnusson Y., Håkansson J. and Ståhlberg A. Patient-derived scaffolds uncover breast cancer promoting properties of the microenvironment. *Biomaterials* 2020; 235; 119705
- III. Persson E., Gregersson P., Gustafsson A., Fitzpatrick P., Rhost S., Ståhlberg A., Landberg G. Patient-derived scaffolds influence secretion profiles in cancer cells mirroring clinical features and breast cancer subtypes. *Manuscript*
- IV. Berger K\*, Persson E\*, Gregersson P., Jonasson E., Ståhlberg A., Landberg G., Rhost S. Interleukin-6 induces stem cell propagation through liaison with the sortilin-progranulin axis in breast cancer. *\*Equal contribution. Manuscript*

# **The breast cancer microenvironment and cancer cell secretion - specific effects on cancer progression and subtypes of cancer cells**

**Emma Persson**

Avdelningen för Laboratoriemedicin, Institutionen för Biomedicin,  
Sahlgrenska akademien, Göteborgs universitet, Sverige, 2021.

## **Abstract**

Breast cancer is the cancer form responsible for the most cancer-related deaths among women worldwide, and novel targeted therapies are highly needed. The tumor microenvironment consists of several components, including different cell types, extracellular matrix, oxygen and nutrient gradients and soluble factors that plays a key role in cancer progression. Cancer cell secretion affects tumor characteristics, such as proliferation, migration, invasion and priming of the pre-metastatic niche. In this thesis, we have investigated the effect of tumor microenvironmental-induced secretion by studying hypoxia and the extracellular matrix and the induction of secretion in relation to cancer progression and subpopulations of breast cancer cells. We demonstrated that hypoxia-induced secretion affects the cancer stem cell subpopulation, but in opposing directions depending on estrogen receptor status. Moreover, by developing a novel *in vivo*-like model based on decellularized breast cancer tissue we could show induced changes in reintroduced cell lines in gene expression and cell secretion, both towards a more dedifferentiated cell state compared to monolayer cells. In addition, we demonstrated that one subgroup of decellularized breast cancers induced secretion of proteins such as interleukin-6, chemokine (C-C motif) ligand 2 and plasminogen activator inhibitor 1, all associated with cancer stem cell characteristics and priming of the pre-metastatic niche. This subgroup also included tumors of higher grade and with shorter patient relapse-free survival, further displaying the aggressiveness of these microenvironments. Further, we revealed that the well-known cancer stem cell inducing cytokine interleukin-6 increased after treatment with the hypoxia-induced growth factor progranulin and that interleukin-6 increased the cancer stem cell propagation in a sortilin dependent way. In conclusion, in this thesis we explored the importance of the tumor microenvironment and continued to unravel the complex network of tumor microenvironmental-induced secretion and the significance for breast cancer progression and patient outcome.

**Keywords:** Breast cancer, cancer microenvironment, secretion, hypoxia

ISBN: 978-91-8009-182-4 (TRYCK)

ISBN: 978-91-8009-183-1 (PDF)