

The impact of the progranulin-sortilin axis on breast cancer stem cell activity and patient outcome

Akademisk avhandling

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av Karoline Berger

Fakultetsopponent:

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Avhandlingen baseras på följande delarbeten:

- I. Rhost S, Hughes É, Harrison H, Rafnisdóttir S, Jacobsson H, Gregersson P, Magnusson M, Fitzpatrick P, Andersson D, **Berger K**, Ståhlberg A and Landberg G. **Sortilin inhibition limits secretion-induced progranulin-dependent breast cancer progression and cancer stem cell expansion.**
Breast Cancer Res. 2018 Nov 20;20(1):137.
- II. **Berger K**, Rhost S, Rafnisdóttir S, Hughes É, Magnusson Y, Ekholm M, Stål O, Rydén L and Landberg G. **Tumor co-expression of progranulin and sortilin as a prognostic biomarker in breast cancer.**
BMC Cancer. 2021 Feb 22;21(1):185.
- III. **Berger K***, Persson E*, Gregersson P, Jonasson E, Ståhlberg A, Landberg G and Rhost S. **Interleukin-6 induces stem cell propagation through liaison with the sortilin-progranulin axis in breast cancer.**
*Authors contributed equally. (*Manuscript*)
- IV. **Berger K***, Rhost S*, Hughes É, Gregersson P and Landberg G. **Granulin peptide domains induce breast cancer stem cell propagation via sortilin.**
*Authors contributed equally. (*Manuscript*)
- V. **Berger K**, Pauwels E, Parkinson G, Landberg G, Le T, Demillo V.G, Lumangtad L.A, Jones D.E, Islam M.A, Olsen R, Kapri T, Intasiri A, Vermeire K, Rhost S and Bell T.W. **Reduction of Progranulin-Induced Breast Cancer Stem Cell Propagation by Sortilin-Targeting Cyclotriazadisulfonamide (CADA) Compounds.**
(*Manuscript under revision*)

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN**



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Abstract

Breast cancer is the most common cancer in women worldwide. Still today, despite current breast cancer therapies, many patients experience treatment resistance and relapse, which are believed to be due to failure in targeting treatment-resistant cancer stem cells. Cytokines and growth factors secreted by various cell types present in the tumor microenvironment have the potential to affect this challenging cell subpopulation. This thesis focuses on a complex cellular communication system based on hypoxia-induced secretion, where we identified the growth factor progranulin as one of the key mediators driving cancer stem cell propagation. In this thesis, we demonstrate that progranulin mediates cancer stem cell propagation in various breast cancer cell lines. By chemically degrading and modulating sortilin expression, or using a small sortilin binding molecule, AF38469, we could reduce the progranulin-induced cancer stem cell propagating effect *in vitro*, suggesting that the progranulin-induced cancer progression is dependent on sortilin. Importantly, using breast cancer xenograft models, we were able to confirm the progranulin-mediated cancer stem cell propagating effect *in vivo*. Strikingly, progranulin induced a significant increase in lung metastasis, which could be reduced by oral administration of AF38469. Moreover, when investigating the mechanisms behind sortilin-driven progranulin-induced cancer stem cell activation, we found that progranulin induced secretion of the inflammatory cytokine interleukin-6 and could demonstrate a crosstalk between progranulin and interleukin-6 protein expression. Similar to progranulin, interleukin-6 affected breast cancer stem cell expansion via sortilin, altogether suggesting that sortilin is a highly relevant biological target in breast cancer. Furthermore, in a tissue microarray of breast cancer patients, high co-expression of progranulin and sortilin defined a novel and highly malignant subgroup of breast cancer, suggesting that these proteins can be used as prognostic biomarkers. Combined, results presented in this thesis propose that targeting the progranulin-sortilin communication axis represents a potential novel breast cancer therapeutic approach, inhibiting tumor progression driven by secretion and microenvironmental influences. Accordingly, we are currently in the process of developing sortilin-targeting drugs for the treatment of breast cancers with high expression of progranulin and sortilin.

Keywords: Breast cancer, biomarker, cancer stem cells, microenvironment, progranulin, sortilin, interleukin-6, targeted therapy, prognostic