

Evaluation of regulator of G-protein signaling 2 (RGS2) at different stages of prostate cancer

Significance and clinical potential

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i Ragnar Sandberg hörsal, Medicinaregatan 7A, onsdagen den 5 juni 2019, klockan 9.00 av Anna Linder

Fakultetsopponent:

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Lunds Universitet, Sverige

Avhandlingen baseras på följande delarbeten

- I. Linder A, Hagberg Thulin M, Damber JE, Welén K. Analysis of regulator of G-protein signalling 2 (RGS2) expression and function during prostate cancer progression. *Scientific reports*. 2018; 8: 1-14
- II. Linder A, Larsson K, Welén K, Damber JE, RGS2 is prognostic for development of castration-resistance and cancer-specific survival in CRPC. *Manuscript*
- III. Linder A, Spyratou V, Stattin P, Granfors T, Egevad L, Linxweiler J, Jung V, Junker K, Saar M, Hammarsten P, Bergh A, Welén K, Damber JE, Josefsson A. Prognostic value of stromal expression of regulator of G protein signaling 2 (RGS2) and androgen receptor (AR) for men with prostate cancer followed with expectancy management. *Manuscript*
- IV. Linder A, Hagberg Thulin M, Welén K, Damber JE. Importance of RGS2 in prostate cancer bone metastases. *Manuscript*

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER**



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Significance and clinical potential

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ABSTRACT

Prostate cancer (PC) is often a slow-growing and symptom-free disease with good prognosis. However, a substantial number will progress, ultimately metastasize if left untreated and finally kill the patient. The standard treatment for these stages of PC is androgen deprivation therapy (ADT), which generally has an initially good clinical response. However, ADT drives development of highly aggressive forms of castration-resistant PC (CRPC) and promote development of bone metastases. Thus, early detection of resistance is invaluable considering the incurability of these stages once they are established.

The purpose of the present thesis was to assess the regulation and significance of regulator of G-protein signaling (RGS2) in PC; with focus on PC progression, and development of CRPC and bone metastases. Furthermore, evaluate its potential as a prognostic biomarker for hormone-naïve prostate cancer (HNPC) and in association to development and progress of CRPC. This, as the new era of treatment options calls for stable reliable biomarkers for adequate treatment decisions.

The principal findings from this work suggest that, RGS2 was highly expressed in both advanced HNPC and CRPC. The significance of this was reflected by the association between high levels of RGS2 and poor clinical outcome in both of these stages. Moreover, experimental data suggest that RGS2 expression is regulated by hypoxia and HIF1. The implication of different levels of RGS2 was assessed with RGS2 knockdown in the PC cell line LNCaP. The results show that low and high RGS2 expressing PC cells have distinct PC phenotypes, resembling early low-risk tumors and advanced PC, respectively. Furthermore, the data suggests that by mediating the effect of hypoxia, RGS2 has significant tumor promoting roles in HNPC. Additionally, induced RGS2 expression, in response to ADT, was found predictive of decreased time to relapse in association with resumed androgen-receptor (AR) signaling. The stromal expression of RGS2 display a contrasting expression pattern compared to the epithelial, with decreased expression in association with more advanced disease, the relevance of this was suggested by a prognostic property of stromal RGS2 expression. Finally, high RGS2 expression levels were noticed in human PC bone metastases, and found to be essential for the tumor cells ability to establish in the bone, as well as endorsing of the sclerotic phenotype that is associated with PC bone metastases.

In conclusion, the present thesis suggests a tumor-promoting function for RGS2, associated with PC progress and development of CRPC and PC bone metastases. Furthermore, the results suggest that RGS2 has potential as a prognostic and treatment-predictive biomarker in PC.

Keywords: Prostate cancer, regulator of G-protein signaling 2, castration-resistance, androgen receptor, prostate cancer bone metastases