Setanaxib attenuates NADPH oxidase 4-driven activation of prostate cancer-associated fibroblasts and alters signaling pathways involved in cellular adhesion and migration

Background

The development and progression of prostate cancer (PCa) is highly influenced by a pro-tumorigenic environment, where cancer-associated fibroblasts (CAFs) influence cancer cell proliferation, metastatic progression and therapy resistance through secretion of soluble factors and remodeling of the extracellular matrix. We previously showed that the H_2O_2-producing enzyme NADPH oxidase 4 (Nox4) is crucial for the transformation of benign fibroblasts to a CAF phenotype and that its increased expression is associated with biochemical relapse and poor survival of PCa patients. The current study aims to evaluate the potential of pharmacological Nox4 inhibition as an adjuvant therapeutic strategy for PCa and to identify Nox4-induced molecular players in the tumor microenvironment that promote tumor development and progression.

Methods

To test the therapeutic application of Nox4 inhibition, primary prostate CAFs and *ex vivo* cultured human PCa tissue were treated with Setanaxib, a dual Nox1/Nox4 inhibitor, and ROS levels, expression of reactive stroma markers and PCa progression markers were determined. In a next step we aim to identify Nox4 effectors and their key regulators via an integrative “omics” approach encompassing the secretome, proteome and transcriptome of primary prostate CAFs and patient-matched normal fibroblasts treated with Setanaxib.

Results

Pharmacological Nox4 inhibition decreased the expression of CAF markers and PCa progression markers in primary CAFs and *ex vivo* tissue cultures, respectively. Notably, treatment with Setanaxib also attenuated the secretion of PSA, a key clinical biomarker of PCa progression. Integrative bioinformatics suggests that Nox4 influences various pathways in the tumor microenvironment, including the secretion of paracrine factors and signaling pathways involved in cellular adhesion and migration. This is supported by functional assays which showed that Nox4 inhibition reduces CAF adhesion and migration, which is directly implicated in facilitating tumor cell migration and metastasis.

Conclusion & Outlook

Current data suggest that Nox4 is a central mediator of stromal-epithelial crosstalk in the PCa microenvironment and thus represents a promising therapeutic target. Candidate Nox4-regulated effectors identified by large scale analyses will be further validated at the functional level to determine their effects on tumor development and progression.