

GDNF as Collateral Damage of Prostate Cancer Chemotherapy

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The majority of prostate cancer deaths result from metastatic disease, which tends to initially respond well to chemotherapeutic agents that damage DNA yet prostate cancers often acquire resistance. It is therefore important to understand the effects of DNA damaging agents in not only the prostate cancer cells themselves, but also in the benign cell types that surround the tumor, which are collectively referred to as the tumor microenvironment. Previous work in Dr. Pete Nelson's Laboratory (Human Biology and Clinical Research Divisions) tested the hypothesis that treatment-induced DNA damage in benign cells promote therapy resistance and tumor progression. This work identified over 40 secreted proteins that are induced in benign fibroblasts in response to chemotherapy with potential of affecting prostate cancer cells. The proteins collectively form the DNA damage secretory program (DDSP; Sun *et al.*, 2012).

A new Fred Hutch study led by former postdoctoral fellow Dr. Roland Huber in Dr. Nelson's lab and published in *Oncotarget* addressed the functions of one such protein, GDNF, in both fibroblasts and prostate cancer cells. GDNF, Glial Cell-derived Neurotrophic Factor, was first identified as a growth factor for neurons but is now known to promote proliferation of other cell types. "I think the most important aspect of our work is that we learn how a tumor reacts to a treatment. Initial responses are often good in prostate cancer, but resistance and treatment failure are very common. So by understanding what happens during and after treatment will help us understand these active (non pre-existing) resistance mechanisms much better and could, mid to long term, lead to improved combination therapies," said Dr. Huber.

The study began by confirming that both the expression and secretion of GDNF were elevated in prostate fibroblasts (PSC27) in response to a wide range of DNA-damaging agents (bleomycin, mitoxantrone, radiation and docetaxel). Importantly, GDNF expression was also elevated in cancer-associated fibroblasts micro-dissected from men undergoing a clinical trial that combined mitoxantrone with docetaxel. Next, the authors examined the effects of GDNF in prostate fibroblasts which showed that GDNF exposure results both in increased stimulation of downstream protein kinases, such as SRC and ERK, and increased replicative potential. Curiously, fibroblasts from the

bone marrow also secreted GDNF but did not exhibit the same downstream responses. Because GDNF is a secreted protein, the investigators tested the effect of GDNF exposure in a range of different prostate cancer cell lines, and found that the subset of cell lines that exhibited increased proliferation and invasive behavior also expressed GFRA1, a GDNF receptor. Strikingly, prostate cancer cells that were stimulated with GDNF were found to be resistant to DNA-damaging agents.

To elucidate the gene expression program downstream of GDNF, the authors performed whole-genome microarrays in prostate cancer cells and fibroblasts exposed to GDNF. This analysis revealed that GDNF stimulation was associated with reduced activity of the retinoblastoma tumor suppressor with concomitant increases in the activities of the transcriptional regulators E2F1 and androgen receptor (AR). "As previous studies have shown that E2F1 promotes AR activity, GDNF may provide a link for interactions between the tumor microenvironment and maintenance of the AR program, a crucial driver of prostate cancer growth," said Dr. Nelson. "GDNF however is only one of probably hundreds of factors, so we do have a lot of work ahead of us to understand the collective effects of all these factors. I hope, that in the long run this will help to improve treatment success," said Dr. Huber. In summary, while it's tempting to pursue therapeutics that inhibit GDNF, perhaps a more viable long-term strategy would be to target the DDSP more broadly in order to limit the treatment-induced damage to the tumor microenvironment.

[Huber RM, Lucas JM, Gomez-Sarosi LA, Coleman I, Zhao S, Coleman R, Nelson PS](#). 2014. DNA damage induces GDNF secretion in the tumor microenvironment with paracrine effects promoting prostate cancer treatment resistance. *Oncotarget* 6(4): 2134-47.

See also:

[Sun Y, Campisi J, Higano C, Beer TM, Porter P, Coleman I, True L, Nelson PS](#). 2012. Treatment-Induced Damage to the Tumor Microenvironment Promotes Prostate Cancer Therapy Resistance Through WNT16B. *Nat Med* 18(9):1359-68.

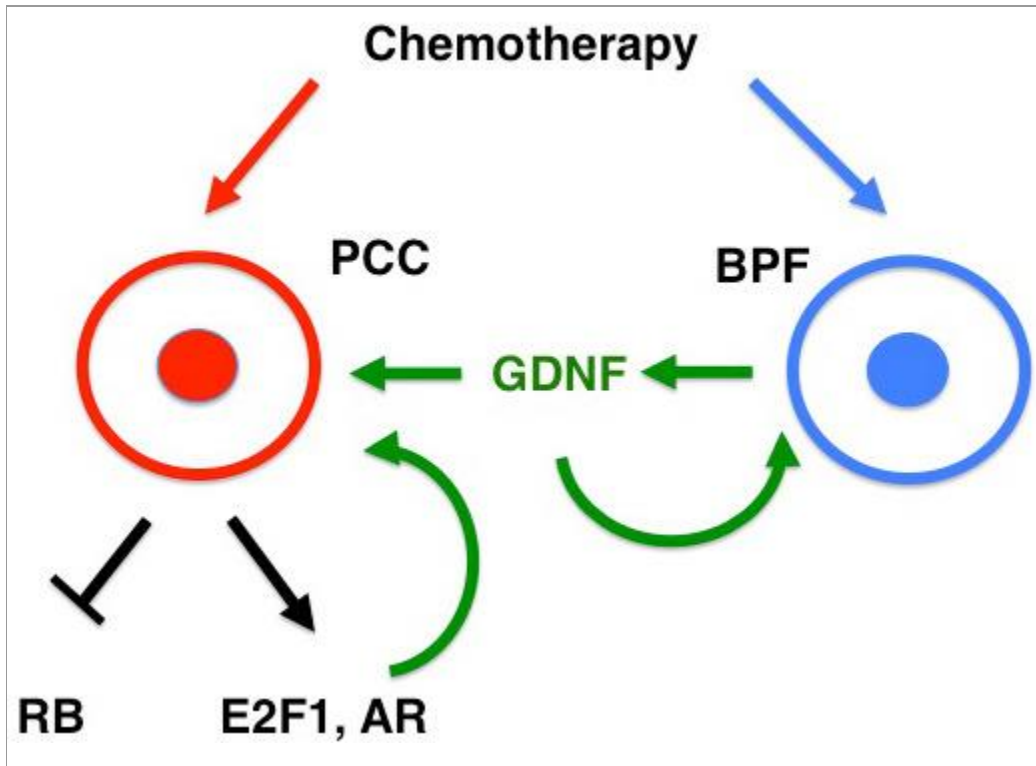


Image by Dr. Alexandre Neves

Prostate cancer chemotherapy induces DNA damage in both prostate cancer cells (red; PCC) and benign prostate fibroblasts (blue; BPF). BPF respond to DNA damage by secreting the Glial-cell Derived Neurotrophic factor (GDNF). GDNF, in turn, stimulates proliferation of both BPF and PCC and inhibits the tumor suppressor retinoblastoma protein (RB), while activating the oncogenic transcription factors E2F1 and androgen receptor (AR) in PCC. AR, activated by E2F1, promotes both survival and growth of PCC.