TMPRSS2 & COVID-19

TMPRSS2 [transmembrane protease, serine 2] has been a recurrent topic in the PCa literature for a while. Close to a thousand papers reference it - all within the past 20 years - & over 700 papers refer to TMPRSS2-ERG fusion that is common in PCa - all within the past 15 years. The Wikipedia page is short but pithy [1]:

"**ERG gene fusion**

"TMPRSS2 protein's function in prostate carcinogenesis relies on overexpression of ETS transcription factors, such as ERG and ETV1, through gene fusion. TMPRSS2-ERG fusion gene is the most frequent, present in 40% - 80% of prostate cancers in humans. ERG overexpression contributes to development of androgen-independence in prostate cancer through disruption of androgen receptor signaling.

"**Relation to coronaviruses**

"Some coronaviruses, e.g. both the SARS coronavirus of 2003 and the novel coronavirus of 2019/20 are activated by TMPRSS2 and can thus be inhibited by TMPRSS2 inhibitors. "SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming. A TMPRSS2 inhibitor approved for clinical use blocked entry and might constitute a treatment option."

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The subject of TMPRSS2 is heating up, but Dr. Michael Glode deserves a mention for his March 29 vlog post [2], in which he hypothesized that ADT might be protective, because of the inhibitory effect on TMPRSS2.

(These things don't come out of the blue - there is a SARS-TMPRSS2 paper from 2010.)

It's worth noting - from a 2018 PCa paper [3]:

"TMPRSS2-ERG-positive and -negative prostate cancer specimens have distinct intratumoral androgen profiles, *possibly due to activation of testosterone-independent DHT biosynthesis via the alternative pathway in TMPRSS2-ERG-positive tumors*. Thus, patients with TMPRSS2-ERG-positive prostate cancer may benefit from novel inhibitors targeting the alternative DHT biosynthesis."

Bottom Line:

Men on Abiraterone [Zytiga] may be better protected than men on Lupron, say.

& men on Avodart may be protected from the "alternative pathway".

-Patrick

[1] en.wikipedia.org/wiki/TMPRSS2

[2] prost8blog.com/2020/03/29/c...

[3] pubmed.ncbi.nlm.nih.gov/297...

Endocr Relat Cancer

. 2018 Sep;25(9):807-819. doi: 10.1530/ERC-18-0148. Epub 2018 May 17.

Intratumoral Androgen Levels Are Linked to TMPRSS2-ERG Fusion in Prostate Cancer

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PMID: 29773553 DOI: 10.1530/ERC-18-0148

Abstract

Intratumoral androgen biosynthesis is one of the mechanisms involved in the progression of prostate cancer, and an important target for novel prostate cancer therapies. Using gas chromatography-tandem mass spectrometry and genome-wide RNA sequencing, we have analyzed androgen concentrations and androgen-regulated gene expression in cancerous and morphologically benign prostate tissue specimens and serum samples obtained from 48 primary prostate cancer patients. Intratumoral dihydrotestosterone (DHT) concentrations were significantly higher in the cancerous tissues compared to benign prostate ($P < 0.001$). The tissue/serum ratios of androgens were highly variable between the patients, indicating individual patterns of androgen metabolism and/or uptake of androgens within the prostate tissue. An unsupervised hierarchical clustering analysis of intratissue androgen concentrations indicated that transmembrane protease, serine 2/ETS-related gene (TMPRSS2-ERG)-positive patients have different androgen profiles compared to TMPRSS2-ERG-negative patients. TMPRSS2-ERG gene fusion status was also associated with an enhanced androgen-regulated gene expression, along with altered intratumoral androgen metabolism, demonstrated by reduced testosterone concentrations and increased DHT/testosterone ratios in TMPRSS2-ERG-positive tumors. TMPRSS2-ERG-positive and -negative prostate cancer specimens have distinct intratumoral androgen profiles, possibly due to activation of testosterone-independent DHT biosynthesis via the alternative pathway in TMPRSS2-ERG-positive tumors. Thus, patients with TMPRSS2-ERG-positive prostate cancer may benefit from novel inhibitors targeting the alternative DHT biosynthesis.

Keywords: TMPRSS2-ERG; androgen; cancer; intratumoral; prostate.

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