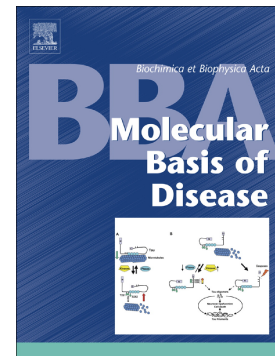


Accepted Manuscript

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PII: S0925-4439(17)30320-4
DOI: doi: [10.1016/j.bbadis.2017.09.005](https://doi.org/10.1016/j.bbadis.2017.09.005)
Reference: BBADIS 64888

To appear in:

Received date: 2 June 2017
Revised date: 16 August 2017
Accepted date: 7 September 2017

Please cite this article as: Aine G. O'Sullivan, Sarah B. Eivers, Eamon P. Mulvaney, B. Therese Kinsella, Regulated expression of the TP β isoform of the human T Prostanoid receptor by the tumour suppressors FOXP1 and NKX3.1: Implications for the role of Thromboxane in Prostate Cancer, (2017), doi: [10.1016/j.bbadis.2017.09.005](https://doi.org/10.1016/j.bbadis.2017.09.005)

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Regulated expression of the TP β isoform of the human T Prostanoid Receptor by the tumour suppressors *FOXP1* and *NKX3.1*: Implications for the role of Thromboxane in Prostate Cancer.

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Key words

Thromboxane receptor; prostate cancer; Forkhead box protein P1 (FOXP1); NKX3.1 homeobox protein; tumour suppressor gene; CpG methylation.

Abstract

The prostanoid thromboxane (TX)₂ signals through the TP α and TP β isoforms of T Prostanoid receptor (TP) that are transcriptionally regulated by distinct promoters termed Prm1 and Prm3, respectively, within the *TBXA2R* gene. We recently demonstrated that expression of TP α and TP β is increased in PCa, differentially correlating with Gleason grade and with altered CpG methylation of the individual Prm1/Prm3 regions within the *TBXA2R*. The current study sought to localise the sites of CpG methylation within Prm1 and Prm3, and to identify the main transcription factors regulating TP β expression through Prm3 in the prostate adenocarcinoma PC-3 and LNCaP cell lines.

Bisulfite sequencing revealed extensive differences in the pattern and status of CpG methylation of the individual Prm1 and Prm3 regions that regulate TP α and TP β expression, respectively, within the *TBXA2R*. More specifically, Prm1 is predominantly hypomethylated while Prm3 is hypermethylated across its entire sequence in PC-3 and LNCaP cells. Furthermore, the tumour suppressors FOXP1 and NKX3.1, strongly implicated in PCa development, were identified as key transcription factors regulating TP β expression through Prm3 in both PCa cell lines. Specific siRNA-disruption of FOXP1 and NKX3.1 each coincided with up-regulated TP β protein and mRNA expression, while genetic-reporter and chromatin immunoprecipitation (ChIP) analyses confirmed that both FOXP1 and NKX3.1 bind to *cis*-elements within Prm3 to transcriptionally repress TP β in the PCa lines. Collectively these data identify Prm3/TP β as a *bona fide* target of FOXP1 and NKX3.1 regulation, providing a mechanistic basis, at least in part, for the highly significant upregulation of TP β expression in PCa.

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