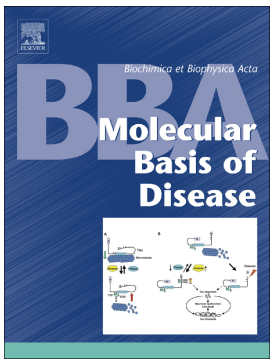

Regulated expression of the TPβ isoform of the human T Prostanoid receptor by the tumour suppressors FOXP1 and NKX3.1: Implications for the role of Thromboxane in Prostate Cancer

Aine G. O'Sullivan, Sarah B. Eivers, Eamon P. Mulvaney, B. Therese Kinsella

PII: S0925-4439(17)30320-4
DOI: doi: 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 TPβ 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

BBADIS_64888_original

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

Aine G. O'Sullivan, Sarah B. Eivers, Eamon P. Mulvaney and B. Therese Kinsella

UCD School of Biomolecular and Biomedical Sciences, UCD Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Belfield, Dublin 4, Ireland

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)A_2 signals through the TPα and TPβ 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 TPα and TPβ 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 TPβ 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 TPα and TPβ 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 TPβ expression through Prm3 in both PCa cell lines. Specific *si*RNA-disruption of FOXP1 and NKX3.1 each coincided with up-regulated TPβ 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 TPβ in the PCa lines. Collectively these data identify Prm3/TPβ 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 TPβ expression in PCa.