The role of PTEN as a cancer biomarker


Published in:
Oncoscience

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
Copyright 2016 The Authors
This is an open access article published under a Creative Commons Attribution License (https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution and reproduction in any medium, provided the author and source are cited.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.
The role of PTEN as a cancer biomarker

Nuala McCabe, Richard D. Kennedy, Kevin M. Prise

THE PTEN TUMOUR SUPPRESSOR GENE

The phosphatase and tensin homologue, PTEN, was identified in 1997 and later found to be frequently disrupted in multiple sporadic tumour types and targeted by germline mutations in patients with cancer predisposition syndromes such as Cowden disease [1]. The principal catalytic function of PTEN is to dephosphorylate phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P3), which is a potent activator of 3-phosphoinositide-dependent kinase (PDK) and AKT. As a consequence, loss of PTEN function leads to increased levels of PtdIns(3,4,5)P3 and activation of the phosphoinositide 3-kinase (PI3K)–AKT pathway which stimulates cell growth and survival. Additionally, recent data demonstrate that nuclear PTEN has now been demonstrated to maintain genomic stability through regulation of RAD51, a key protein involved in double-strand break (DSB) repair and stabilisation of replication fork during replication stress [2]. These distinct functions of PTEN and associated cancer predisposing mutations, has caused great interest in PTEN as a cancer biomarker.

PTEN AS A BIOMARKER IN ESTIMATING RISK

Germline mutations of PTEN are the underlying genetic causes of related disorders clinically referred to as PTEN hamartoma syndromes (PHTS) including Cowden syndrome. Mutations responsible for these syndromes result in a non-functional or absent protein, which causes uncontrolled cell growth, leading to tumour (either benign or malignant) growth. Additionally these patients have a predisposition for cancer with increased lifetime risks for breast (85%), thyroid (35%), renal (33%), and endometrial (28%) cancers, colorectal cancers (9%) and melanoma (6%) [3].

PTEN AS A PROGNOSTIC BIOMARKER

The cloning of the PTEN gene to human chromosome 10q23.3, was accompanied by detection of various types of mutations including homozygous deletion, frameshift, inframe deletion, truncation and point mutation [1]. Additionally post-translational modifications including phosphorylation, acetylation, methylation, oxidation have also been implicated in the loss of PTEN function and in the initiation of tumourigenesis [4]. Whether through mutation or epigenetic regulation, the loss or aberration of the PTEN gene/protein can have prognostic impact in the cancers which manifest these alterations. PTEN loss has been shown to be associated with poor outcome in a variety of cancers including prostate cancer (PCa), glioblastoma and colorectal cancer [1, 4]. For example approximately 2–14% of prostate cancer specimens were shown to harbour PTEN mutations, and 12–41% have copy number loss [4]. It has been demonstrated that there was a higher frequency of PTEN loss in more advanced castrate resistant PCa (CRPC) cases and that PTEN loss was associated with shorter progression-free survival time [4].

PTEN AS A PREDICTIVE BIOMARKER

PTEN has been associated with response to conventional standard of care chemotherapy. PTEN-negative tumours have also been shown to have shorter survival in the post-docetaxel abiraterone treatment setting compared with cases with preserved PTEN expression [5]. Additionally PTEN loss has previously been reported to be prognostic for outcome following radiotherapy in prostate cancer [4]. PTEN expression also shows promise as a predictive marker for targeted therapeutic agents including anti-EGFR mAbs [6], trastuzumab-based chemotherapy in breast cancer [7]. Additionally PTEN loss has been demonstrated to induce sensitivity to PARP1/2 inhibition in cell line models, however recent findings from TOPARP trial (NCT01682772) indicate that PTEN loss does not confer sensitivity to PARP inhibition using olaparib [8] suggesting that a greater understanding of the role of PTEN in DNA repair and therefore PARP inhibitor sensitivity will need to be gained. Additionally our lab has demonstrated a function for PTEN in controlling oxidative DNA damage was recently demonstrated and therapeutically exploited using an ataxia telangiectasia mutated (ATM) inhibitor [9]. We have demonstrated that the sensitivity of PTEN null cells to ATM inhibition was dependent of the generation of oxidative DNA damage, and independent of RAD51 function, suggesting further nuclear roles for PTEN.

The utility of using PTEN as a biomarker of prognosis or predictor for drug response clearly needs further investigation. Only through a greater understanding
of the function played by PTEN in regulating various biological functions will its role as a biomarker be fully realised. Additionally it will be imperative to evaluate the monopoly of cancer associated mutations and post-translational modifications which target these functions in clinical samples. This will be important in defining the best methods for detecting PTEN aberration for best clinical impact.

CONFLICTS OF INTEREST

Nuala McCabe and Richard D. Kennedy are employees of Almac Group.

Kevin M. Prise: Center for Cancer Research & Cell Biology, Queens University Belfast, UK.
Correspondence: Kevin M. Prise, email k.prise@qub.ac.uk

Keywords: PTEN, predictive biomarker, tumour suppressor gene

Received: November 26, 2015
Published: March 03, 2016

REFERENCES