PTEN and Cancer

Subjects: Oncology

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The *PTEN* gene is an important and well-characterised tumour suppressor, known to be altered in many cancer types. Interestingly, the effect of the loss or mutation of *PTEN* is not dichotomous, and small changes in PTEN cellular levels can promote cancer development.

Keywords: PTEN ; PTENP1 ; ceRNA networks ; microRNAs

1. Introduction

The phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*), also known as mutated in multiple advanced cancers 1 (MMAC1) and TGFß-regulated and epithelial cell-enriched phosphatase 1 (TEP-1) [1][2][3], is a well-known tumour suppressor gene located on chromosome 10q23.31 [2]. The gene and its protein product play a vital role in cell proliferation, migration, and survival [2][4][5][6][7]. As an antagonist of phosphoinositide 3-kinase (PI3K), PTEN dephosphorylates its substrate PIP_3 to PIP_2, thereby negatively regulating the pro-proliferative and anti-apoptotic PI3K/Akt pathway to maintain cellular homeostasis [8][9]. The regulation of PTEN cellular levels is critical in the negative modulation of tumorigenesis with disruption of PTEN signalling leading to significant cellular changes. Interestingly, subtle decreases in cellular levels of PTEN can result in malignancy and tight regulation of the expression, function, and cellular half-life of PTEN, at the transcriptional, post-transcriptional, and post-translational levels is necessary in the prevention of carcinogenesis [10][11]. *PTEN* is frequently mutated and/or deleted in the inherited PTEN hamartoma tumour syndromes (PHTS) [12][13] and multiple sporadic human malignancies, including those from the brain, breast, prostate [1], endometrium [14], skin (melanoma) [15], and colon [6].

Less well-known regulatory mechanisms of *PTEN* with emerging importance include the *PTEN*–miRNA–*PTENP1* axis, which has been shown to play a critical role in the fine tuning of PTEN regulation and cellular integrity. *PTENP1* is a processed pseudogene of *PTEN* termed the phosphatase and tensin homolog pseudogene 1 (*PTENp1*, *PTENpg1*, *PTENP1*, *PTH2*, and *ψPTEN*), which is located on 9p13 (Gene ID: 101243555) [16][17][18]. This pseudogene is transcribed to produce sense and antisense transcripts with the sense transcript showing high sequence similarity with the *PTEN* transcript; however, unlike *PTEN*, this transcript is not translated to produce a protein [19]. Although PTENP1 protein is undetected in cells, when transcribed *in vitro* as a fusion protein, the product is viable and has comparable phosphatase activity to the wild-type PTEN [19]. The sense and antisense long non-coding RNAs (lncRNA) produced from *PTENP1* are important in the modulation of *PTEN* expression at the transcriptional and post-transcriptional levels, respectively. The *PTENP1* sense transcript (*PTENP1-S*), acting as a competitive endogenous RNA (ceRNA) of *PTEN*, leads to alterations in PTEN cellular abundance. The characteristics of this *PTEN* pseudogene lncRNA include similarities in their microRNA (miRNA) binding sites, and as such, *PTENP1* can act as a decoy or ‘sponge’, competing for miRNAs that target *PTEN*. Disruption of the *PTEN*–miRNA–*PTENP1* axis and ceRNA networks in carcinogenic progression is contemporary and is an exciting area in the discovery of regulatory mechanisms that are altered in cancer. In addition to its regulation of *PTEN* expression, *PTENP1* is able to act as a tumour suppressor independent of its *PTEN* regulatory function as described in a recent review of the role of *PTENP1* in human disorders with a focus on its tumour suppressor functionality [20].

2. PTEN and Cancer: From Mutations to a Continuum Model of Tumorigenesis

Germline and somatic mutation of *PTEN* is known to contribute to many cancers, highlighting the importance of this tumour suppressor in cancer initiation, progression, and metastasis. Germline mutations of *PTEN* are the cause of four autosomal dominant inherited syndromes: Cowden syndrome (CS) [21], Bannayan–Riley–Ruvalcaba syndrome (BRRS) [22][23], Proteus syndrome (PS), and PS-like syndrome [24], which share common features, including the development of multiple benign hamartomas, and are all classified under the umbrella term of the PTEN hamartoma tumour syndromes (PTHSs) [12][13]. PTHS patients have an increased lifetime risk of developing specific malignancies, mainly breast cancer

(approximately 80%) [12][13], thyroid cancer (approximately 30%) [12][13], renal cell carcinoma (approximately 34%) [13], endometrial cancer (approximately 28%) [13], and colorectal cancers (approximately 9%) [13]. In individual PHTS patients exhibiting clinical phenotypes, *PTEN* germline mutations are reported in 25-85% of CS patients [21][25][26], 60% of BRRS [21][22][25][27], up to 20% of PS [28], and between 50 and 67% of PS-like syndrome patients [24]. Interestingly, germline *PTEN* mutations are also associated with a subset of patients with autistic behaviour and extreme macrocephaly [29].

Somatic mutations of *PTEN* are frequently associated with tumorigenesis with somatic alterations of *PTEN* being described in over 50% of cancers of various types [30]. *PTEN* somatic mutations are most prevalent in prostate cancer [31], endometrial cancer [32], melanoma [33][34], non-small-cell lung cancer [35][36], kidney [37], breast cancer [38], and glioblastoma [39]. *PTEN* somatic alterations include the complete loss or inactivation of one allele (functional haploinsufficiency) due to point mutations and/or deletions and/or epigenetic silencing through hypermethylation of the *PTEN* promoter, which is characteristic of some advanced and metastatic cancers [1][4]. Deletion of both alleles of *PTEN* occurs at a lower incidence but is seen mostly in metastatic breast cancer, melanomas, and glioblastomas [1][4][40]. In contrast, a recent study showed that patients with high PTEN expression levels in endometrial cancer had low tumour malignancy, decreased cancer cell proliferation and a better prognosis [41]. There are different mechanisms of PTEN loss or inactivation, with some being more prevalent in specific tumour types (**Table 1**) [30][42][43].

Table 1. Mechanism and frequency (%) of *PTEN* loss in various cancer types.

Cancer Type	Mutation		Deletion		Loss of Protein		Promoter Methylation	
Glioblastoma	**30%**	[2][3][42][44][45][46]	**78%**	[44][45][46][47]	**65%**	[48]	**6%**	[49]
Breast	**3%**	[42][50][51]	**27%**	[38][52]	**40%**	[42]	**35%**	[53][54]
Prostate	**13%**	[55][56][57][58]	**51%**	[56][57][58]	**54%**	[55][56][57][58]	**<5%**	[42][59][60][61]
Colorectal	**7%**	[6][42][62][63][64][65][66]	**8.7%**	[42][62][63]	**40%**	[67]	**17%**	[68]
Lung	**8%**	[42]	**34%**	[42]	**56%**	[42]	**38%**	[69]
Endometrial	**41%**	[14][42][70]	**48%**	[14][42][70]	**45%**	[14][41]	**19%**	[42][71]
Ovarian	**16%**	[42][43][72][73][74][75][76]	**48%**	[42][43][72][73][74][75][76]	**44%**	[42][43][72][73][74][75][76]	**10%**	[42][77]

Note: Where multiple references are provided, the frequencies of mutation, deletion, and promoter methylation are an approximate average across the relevant publications.

The effect of the loss or mutation of *PTEN* is not dichotomous, and subtle changes in PTEN cellular levels have been shown to lead to deleterious consequences relating to tumour incidence, penetrance, and aggressiveness in several epithelial cancers [11][78]. In the hypomorphic transgenic *Pten* mouse, it has been shown that in susceptible organs such as the prostate, PTEN protein expression levels need to reach dramatically low levels (reduced by 70% compared to normal levels) to initiate tumorigenesis, however, in the mammary glands, a more subtle reduction (reduced by 20% compared to normal levels) can initiate tumorigenesis [78]. Thus, *PTEN* does not follow the ‘two-hit’ paradigm or stepwise model of tumour suppressor gene function but rather presents a new continuum model of tumorigenesis whereby tumorigenesis occurs in an incremental dose-dependent manner [11][78]. This has been evidenced in gastric cancer, where *PTEN* expression was shown to gradually decrease with increasing gastric cancer progression [79].

PTEN Loss, Tumour Immune Evasion, and Therapy Resistance

There are several recent studies that have explored the relationship between PTEN loss and tumour immunity, showing PTEN loss contributes to alterations in the tumour microenvironment (TME) to produce an immunosuppressive niche. The evidence suggests that PI3K signalling may influence the composition and functionality of the TME, thereby modulating the immune response in cancer. Vidotto et al. (2023) analysed PTEN copy number in 9793 cases from 30 tumour types, derived from the Cancer Genome Atlas, and showed that reduced tumour *PTEN* expression occurs with hemizygous loss leading to tumour anti-cancer immune responses [80]. In another integrative analysis of TCGA samples, Lin et al. (2021) found that both PTEN loss and activation of the PI3K pathway were associated with reduced T-cell infiltration and an enhanced immunosuppressive status in multiple tumour types [81]. Overall, the effect of PTEN loss of function in the different cellular compartments swings the balance towards an immunosuppressive TME [82]. There was also a correlation between PTEN loss and poor response to immunotherapy [81]. Interestingly, PTEN loss has also been shown to promote resistance to therapy in breast cancer. Reducing PTEN levels in breast cancer cells conferred resistance to trastuzamab,

and patients with PTEN-deficient breast cancers showed poorer therapeutic responses with this drug. Thus, PTEN deficiency has become a good predictor for trastuzumab resistance [83][84]. Reduced *PTEN* expression has been shown in vivo, in mouse models, to be due to specific miRNAs. An example being PTEN as a target of mi-R22 in breast and prostate cancers, which have been shown to have a strong influence in a cancer immune TME, playing a role in cancer initiation, progression, and metastasis [85]. Importantly, in vivo, knockdown of miR-22 appears to invoke tumour resistance in an immunocompetent environment [85]. These findings open new avenues for immuno-targeting, such as modulating miRNAs targeting PTEN, hence improving the efficacy of immunotherapy and overcoming therapy resistance.

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