Phosphatase and tensin homologue deleted on chromosome 10

Imran Haruna Abdulkareem, Maria Blair[1]

Department of Trauma and Orthopaedics Surgery, Leeds University Teaching Hospitals, Leeds, LS9 7TF West Yorkshire, [1]Biomedical Research Centre, Sheffield Hallam University, Sheffield, UK

ABSTRACT

Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) is a tumor suppressor gene deleted or mutated in many human cancers such as glioblastoma, spinal tumors, prostate, bladder, adrenals, thyroid, breast, endometrium, and colon cancers. They result from loss of heterozygosity (LOH) for the PTEN gene on chromosome 10q23. Previous studies reported that various drugs, chemicals, and foods can up-regulate PTEN mRNA and protein expression in different cell lines, and they may be useful in the future prevention and/or treatment of these cancers. PTEN has also been observed to have prognostic significance and is gradually being accepted as an independent prognostic factor. This will help in monitoring disease progression and/or recurrence, with a view to improving treatment outcomes and reducing the associated morbidity and mortality from these cancers. Neprilysin (NEP) is a zinc-dependent metallopeptidase that cleaves and inactivates some biologically active peptides thus switching off signal transduction at the cell surface. Decreased NEP expression in many cancers has been reported. NEP can form a complex with PTEN and enhance PTEN recruitment to the plasma membrane as well as stabilize its phosphatase activity. MicroRNA-21 (miR-21) post-transcriptionally down-regulates the expression of PTEN and stimulates growth and invasion in non-small cell lung cancer (NSCLC) (lung Ca), suggesting that this may be a potential therapeutic target in the future treatment of NSCLC. PTEN is a tumor suppressor gene associated with many human cancers. This has diagnostic, therapeutic, and prognostic significance in the management of many human cancers, and may be a target for new drug development in the future.

Key words: Disease monitoring, human cancers, novel treatment, prognosis, phosphatase and tensin homologue deleted on chromosome 10, tumor suppressor

Address for correspondence:
Dr. Imran Haruna Abdulkareem, Department of Trauma and Orthopaedics Surgery, Registrars' office, B Floor Clarendon Wing, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, West Yorkshire, UK.
E-mail: imranharuna@yahoo.com

INTRODUCTION

Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) is a tumor suppressor gene,[1] which is deleted or mutated in approximately 45% of uterine endometrial cancers,[2] 30% of glioblastomas and spinal tumors,[3] and less commonly cancers of the prostate,[4] bladder,[5] adrenal glands,[6] thyroid, breast,[7,8] skin (melanomas) and colon.[9-11]

Discovery of phosphatase and tensin homologue deleted on chromosome 10

This tumor suppressor gene (PTEN) was discovered in 1997,[12,13] and it was observed that chromosome 10 was partially or completely lost in glioblastoma, bladder, prostate, colon and breast cancers.[14] The most common region of LOH was identified to be 10q23.[1] Further evidence suggested that a tumor suppressor gene may be found at this location, which was later confirmed by the discovery of a 403-amino acid open reading frame.[13] Sequence analysis revealed that the gene encoded a protein tyrosine phosphatase with similarity to chicken tensin,[15] and so it was named PTEN for phosphatase and tensin homologue deleted on chromosome 10.[12,13,14]

Access this article online	
Quick Response Code:	Website: www.nigeriamedj.com
	DOI: 10.4103/0300-1652.110033

STRUCTURE AND FUNCTION

Phosphatase domain

This tumor suppressor protein consists of four hundred and three amino acids. It contains an N-terminal phosphatase domain with homology to auxillin and tensin.[16] This phosphatase domain spans residues 1-185, and it has a wider catalytic active site compared to other protein phosphatases. Three positively charged amino acids (one histidine and two lysine residues at positions 3, 125 and 129, respectively) are

important here.[17] The enlarged active site accommodates phosphatidylinositol 3, 4, 5-triphosphate (PIP3) substrates and accounts for the ability of PTEN to function as a lipid phosphatase.[18] The positively charged residues may explain the preference of PTEN to act on highly acidic substrates and the phosphatase domain is essential for the tumor suppressor function of PTEN, especially the lipid phosphatase activity, cell cycle arrest and apoptosis.[12,19,20]

C2 domain

Lee *et al*.[18] reported the crystal structure of a protein fold C2 domain between residues 186-351 which contains β strands. This C2 domain binds to membrane phospholipids and is responsible for the regulation of PTEN's sub-cellular localisation and catalytic activities.[16,17] Reduced affinity to membrane phospholipids was observed in mutated C2 domains in glioma cells.[1] in addition to a reduction in growth suppression which resulted in increased cellular proliferation and anchorage-independent growth.[18]

C-terminal tail domain

The C-terminal region follows the C2 domain and contains 50 amino acids, including two degradation motifs and a PDZ domain.[16] These degradation motifs are situated between residues 350-375 and 379-396, and they target proteins with short intracellular half-lives for degradation.[21] This domain has a significant role in the maintenance of PTEN stability and enzymatic activity.[22] It also contains serine 370, and serine/threonine clusters (Ser380, Thr382, Thr383, and Ser385).[21] Specific mutations in these clusters are associated with protein instability, reduction in half-life and level of PTEN, accompanied by an increased activity.[19]

A three amino acid PDZ domain (TKV-COOH) makes up the carboxy terminal part of the PTEN protein.[17] This is responsible for interactions with other proteins and is involved in interactions between different proteins by binding to S/TXV motifs of PDZ domain containing proteins.[21] The epithelial cell tight junctions contain membrane-associated guanylate kinase inverted (MAGI) proteins,[23,24] which contain multiple PDZ domains.[25] These associate with PTEN to form complexes at the cell membrane, which stabilize PTEN and enhance its ability to inhibit Akt.[26] Figure 1 illustrates the various parts of the PTEN protein.

This illustrates the domain structure of PTEN. The N-terminal phosphatase domain is required for both membrane-binding and catalytic activity. The C2 domain represents a membrane-binding domain. The PDZ-binding domain is thought to affect the sub-cellular localisation of the molecule.[27]

Localisation of phosphatase and tensin homologue deleted on chromosome 10

Cell survival and proliferation may depend on PTEN expression, and this is important in cancer pathogenesis.[19]

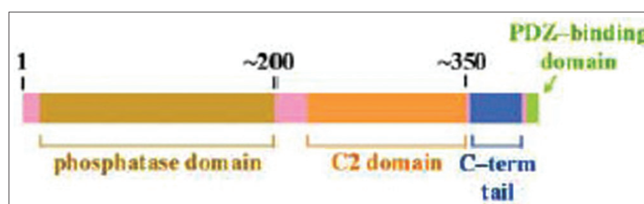

Figure 1: Structure and function of phosphatase and tensin homologue deleted on chromosome 10

PTEN has been observed to be expressed both in embryonic and extra-embryonic tissues during embryogenesis, but its expression within the embryo changes at different times of development. Initially, PTEN is expressed in all tissues, but later it becomes restricted to only certain tissues and organs.[28]

It has also been observed that in late development, the protein is most highly expressed in the central nervous system, liver, heart, skin and gastrointestinal tract.[29] At the sub-cellular level, PTEN has been reported to localize in the cytoplasm and occasionally the nucleus and the plasma membrane (where the main substrate PIP_3 is located).[1]

Moreover, the exact sub-cellular location of this protein varies in different tissues,[16] since it has mainly been found in the cytoplasm of epithelial cells like skin, colon, breast and prostate, whereas it is mostly located in the nucleus of neurons, fibroblasts and adrenal medulla. This protein (PTEN) has also been reported to be present in cell-cell tight junctions of polarized Madin Darby canine kidney cells.[1]

Overall, these different localisations are determined by the C-terminal domain of PTEN. Ginn-Pease and Eng[30] reported that the levels of PTEN in the nucleus rise during the cell cycle and this parallels the cytoplasmic levels, and the highest concentrations were recorded during the G_0-G_1 phase of the cell cycle. This suggests that the nuclear PTEN plays a significant part in G_1 arrest and sub-cellular localisation of PTEN protein during the different stages could reflect its role in cellular function and development.[31,32]

Furthermore, the sub-cellular localisation of this protein has been noted to vary between malignancies and normal tissues. This was seen in normal pancreatic islet cells which had nuclear localisation of PTEN, but endocrine pancreatic tumors were observed to have cytoplasmic localisation. This change in localisation has been related to the process of tumorigenesis.[1,16]

Phosphatase and tensin homologue deleted on chromosome 10 mutations

Many human cancers are associated with somatic deletions or mutations of the PTEN gene. This makes it the most commonly mutated tumor suppressor gene after p53.[17] Glioblastoma multiforme (brain tumor), prostate cancer

and endometrial cancer have the highest frequency of PTEN mutations which are accompanied by loss of LOH leading to inactivation of the phosphatase activity of PTEN, as well as loss of PTEN mRNA or protein expression.[1]

A common example is uterine endometrial carcinoma, which has PTEN mutations in about 50% of the cases,[33] complete loss of PTEN expression in 61% of cases and decreased expression in 97% of cases.[34,21] Other tumors such as colon, bladder, breast and lymphatic cancers have been reported to have lower frequencies of PTEN mutations.[16,35]

Four rare autosomal dominant syndromes have been associated with germline mutations of PTEN[10] and these include Cowden's disease, Bannayan-Zonana syndrome, Lhermitte-Duclos syndrome, and Proteus syndrome.[17] Cowden's disease which was the first to be linked with PTEN mutation, is a harmatomatous disorder associated with multiple harmatomas and high risk of malignancy involving the skin, breast, thyroid, oral mucosa and intestinal epithelium.[15] The locus for this disease is on chromosome 10q23 and it was discovered that 81% of 37 families with Cowden's disease were carrying the PTEN mutations[36] and these mainly affected the phosphatase domain of the protein.[21]

Rychahou and colleagues demonstrated that non-steroidal anti-inflammatory drugs up-regulate PTEN mRNA and protein expression in human colon cancer cell lines, and that this explains the ability of these drugs to inhibit cancer cell growth and proliferation.[37] This forms a novel mechanism for the inhibition of colon cancer cell growth by these drugs, therefore emphasizing the therapeutic importance of the PI3K/Akt pathway in targeting colorectal carcinoma for possible chemoprevention and treatment in future.[11,37] Other workers have also published data on the induction of apoptosis in colorectal cancer cells by peroxisome proliferator-activated receptor gamma activation, up-regulation of PTEN and inhibiting PI3K activity and these revealed promising results.[26]

REGULATION OF PI3K/Akt SIGNALLING PATHWAY

PTEN has a protein tyrosine phosphatase domain[38] homologous to dual-specificity phosphatases,[37] which can dephosphorylate substrates that are phosphorylated on their tyrosine, serine and/or threonine residues.[17] It has been reported that PTEN has protein and lipid phosphatase activity *in vitro*,[12,38] but has revealed mostly lipid phosphatase activity *in vivo*[39,29] with less protein phosphatase activity.[40] These contradictory findings may be explained by the preference of PTEN to act on highly acidic substrates[17] the commonest of which is PIP3.

This substrate is a product of phosphatidylinositol-3-kinase (PI3K), and is found in low concentrations in normal cells.[11,41] PI3K is recruited to the cell membrane by activation of cell surface receptors by growth factors leading to cell growth and differentiation[13,42] PI3K phosphorylates phosphatidylinositol 4, 5-diphosphate (PIP2) at the cell membrane leading to the formation of the potent second messenger PIP3.[19]

However, the role of PTEN is to dephosphorylate PIP_3 by specifically removing the D3 phosphate from the inositol ring[1] and therefore reduces the levels of PIP_3 on the membrane. In addition to that, PTEN also dephosphorylates phosphatidylinositol 4, 5-diphosphate and 3, 4-diphosphate to form the monophosphates, but this is to a lesser extent compared to PIP_3 dephosphorylation.[15] Because PI3K is important in regulating cell growth, by causing signal transduction, disruption of this pathway by PTEN has an inhibitory effect on cell growth, migration, death, differentiation and development.[29] This is illustrated in Figure 2.

Consequently, PTEN deficiency in mutant cells leads to the accumulation of PIP_3 as a result of its decreased dephosphorylation by PTEN.[43] This is why cancer cells have elevated levels of PIP_3 which allows uncontrolled cellular growth and proliferation in addition to prevention of apoptosis.[44] PIP_3 usually binds to proteins containing a Pleckstrin homology (PH) domain, especially the serine/threonine kinase Akt, and so accumulation of PIP_3 on the cell membrane results in the translocation of Akt to the membrane.[37]

Phosphatidylinositol-dependent kinases (PDKs) also contain a PH domain, and activation of PDK by PIP3 results in phosphorylation and subsequent activation of Akt kinase,[45] which has anti-apoptotic activity favouring oncogenesis.[13] This anti-apoptotic activity therefore protects the cells from programmed cell death by blocking the release of cytochrome C from the mitochondria and phosphorylating a number of Akt substrates.[44] These substrates include the pro-apoptotic

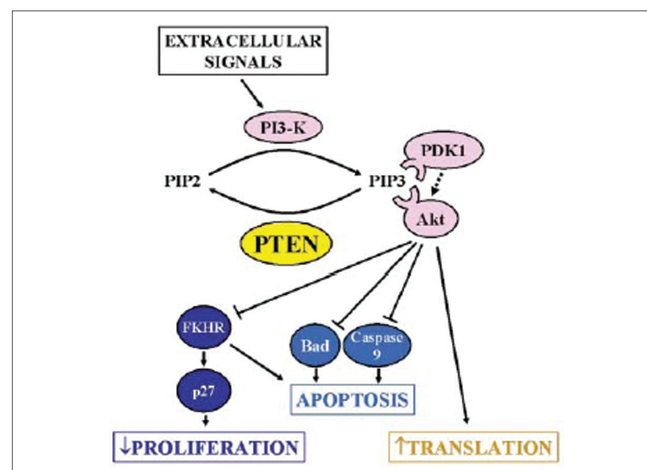

Figure 2: The phosphatidylinositol-3-kinase/Akt signaling pathway

factors Bad, caspase 9 and forkhead transcriptional factors responsible for regulating the expression of genes necessary for apoptosis.[17] As a result of the phosphorylation and substrate inactivation by Akt, changes result in sub-cellular localisation, as well as activity and half-life,[45] therefore altering cell metabolism, death, cell cycle progression and differentiation in favour of oncogenesis.[29]

Many studies have been carried out to examine the wild type (WT) and mutant PTEN in cells as well as the PI3/Akt pathway in order to provide better understanding of the role of these mutations in tumorigenesis. One of the studies[46] revealed that heterozygous mutants of PTEN (PTEN+/–) have increased levels of PIP_3 and activated Akt compared to the WT controls.

PIP_3 and Akt levels in homozygous PTEN mutant (PTEN–/–) cells are also elevated compared to the heterozygotes. PTEN is therefore accepted as a negative regulator of the PI3/Akt pathway and by blocking Akt activation; it also regulates cell cycle progression and apoptosis.[43,47] This figure illustrates PTEN activity in mammalian cells.[27]

CELL CYCLE ARREST AND APOPTOSIS

The ability of PTEN to cause cell cycle arrest and apoptosis has been studied in a number of cell lines.[48,8] This tumor suppressor gene was re-introduced into glioma cells lacking its expression and this led to growth inhibition of the cells.[12] This was observed to result in arrest in the G1 phase of the cell cycle. Similarly, growth suppression was also noticed in breast cancer cells, but via apoptosis instead of cell cycle arrest.[49] Loss of PTEN leads to a constitutively active PI3/AKt pathway resulting in increased levels of PIP_3 and activated Akt, thereby protecting the cells from the apoptotic stimuli by inactivation of the pro-apoptotic factors such as Bad and caspase 9.[47,35] This also leads to phosphorylation and inactivation of 4EBPI, an mRNA translation repressor protein.[21]

PDK activated by PIP_3, along with mammalian target of rapamycin (mTOR) and PIP_3, in turn activate S6 kinase (S6K), and regulate cell growth and translation.[1] Re-introduction and expression of PTEN inhibits activation of Akt and therefore results in suppression of cell cycle progression as well as apoptosis.[38] Studies were carried out[50] on PTEN+/– and PTEN–/– mouse models to investigate the role of PTEN in embryo development and found that this tumor suppressor is essential in embryogenesis. The PTEN null mice died during embryogenesis and did not survive 9.5 days post-coitum. They also revealed abnormal differentiation and disorganized pattering of the three germ layers, especially the ectodermal and mesodermal ones. Suzuki *et al*.[51] noticed over-proliferation and expanded cephalic and caudal regions of the mice used for their study and concluded that embryogenic lethality may be due to abnormal tissue and organ development. It was also observed that heterozygous mice survived embryogenesis, but had increased risk of tumor development in multiple tissues such as prostate, thyroid, and colon.[1,16,52] This was also observed in lymphocytes and was attributed to reduced sensitivity of the PTEN heterozygous cells to apoptotic stimuli.[50]

Furthermore, it was observed that in some cancers like glioma and breast, over-expression of recombinant PTEN (rPTEN) resulted in dephosphorylation of PIP_3 and inactivation of Akt.[53] This induced a specific apoptotic pathway initiated by cell detachment from the extracellular matrix. In cells expressing PTEN the PI3/Akt signalling pathway is inhibited and survival signals and protection against apoptosis are lost.[19,54] PTEN thus regulates cell death when loss of contact with the extracellular matrix occurs by inducing apoptosis. Cells lacking PTEN expression also have enhanced anchorage-independent growth, which could explain the association of PTEN mutations with the invasive tumor phenotype.[48]

ORGAN SIZE

PTEN controls cell number and size by inhibiting cell cycle progression, inducing apoptosis, and regulating protein translation.[55] The development of multi-cellular tissues and organs is related to size regulation and it has recently been suggested that the insulin and IGF-1 signalling pathways may be responsible for organ size control in *Drosophila melanogaster* fly.[56] It has also been revealed that *Drosophila* PTEN (dPTEN) protein, cloned in 1999 contains a highly conserved amino terminal region which shares 65% homology with the human PTEN protein.[57] *Drosophila* PTEN is a negative regulator of the insulin and IGF-1 signalling pathway, and causes growth suppression when expressed in cells.

Bohni and colleagues[56] studied the loss of dPTEN and revealed increased cell size, organ size and animal size following loss of the gene. Huang *et al.*[57] and Gao *et al.*[58] carried out similar studies but only observed eye and wing size in somatic dPTEN–/– cells and revealed that these clones lacking PTEN expression were larger in size compared to the WT control. The findings of Stiles *et al*.[29]; Stiles *et al*.[59]; and Suzuki *et al*.[51] were in support of this and demonstrated organomegaly in liver, brain, heart and skin following loss of the gene. Consequently, over-expression of dPTEN in the fly was observed to have the opposite effects and inhibited cell proliferation during eye development.[57]

STEM CELL FUNCTION

Stem cell function is also known to be regulated by PTEN,[10] and it is agreed that stem cells play essential roles in development by producing cellular diversity and order within an individual and allowing procreation from one generation

to another.[29] Stem cells have the ability to differentiate into multi-lineages to produce organs and tissues.

In studies of mutant mice brain development using embryonic stem cells, Grozer *et al*.[60] found that PTEN protein expression was specifically absent in the brain during mid-embryonic development, producing mice with enlarged brains as a result of increased cell proliferation, decreased cell death and enlarged cell size.[59,29]

The same studies also revealed abnormalities in the brain structure, but PTEN deletion did not change overall differentiation[35] recently observed that PTEN-deficient intestinal stem cells initiated intestinal polyposis, and this further supports the role of PTEN mutations or deletions in the pathogenesis of colorectal and other malignancies.

MIGRATION

PTEN negatively controls cell migration,[1] and this has been thought to result from the direct dephosphorylation of focal adhesion kinase by PTEN,[24] as well as inhibition of integrin-mediated cell spreading, migration and MAP kinase activation.[61]

It was also observed that altered actin fibres and cell migration resulted from re-introduction of PTEN into PTEN null tumor cells.[62] Over-expression of PTEN in glioblastoma and other cell lines also led to inhibition of cell migration and down-regulation of focal adhesions.[62] Stiles *et al.*[29] observed that PTEN controls cell migration by down-regulating Rac 1 and Cdc42, two small GTPases that mediate cell migration. In addition, Rho small GTPases also control intracellular localisation of PTEN.[63]

During chemotaxis in PTEN-expressing cells, chemoattractants activate RhoA and Cdc42, members of the Rho family of small GTPases, and localize to the posterior edge of the chemotaxing cell which is opposite to the migration-leading edge. Iijima and Devreotes[64] also reported that in *Dictyostelium*, deletion of PTEN results in broadened PH domain relocation and actin polymerization responses.

INTERACTION BETWEEN PTEN AND NEPRILYSIN (CD 10)

Neural endopeptidase (NEP or CD 10) is a 90-110 kDa zinc-dependent metallopeptidase, and a type II integral membrane protein. It cleaves and inactivates a number of biologically active peptides, thus switching off signal transduction at the cell surface. Decreased expression of NEP in several types of human cancer, such as prostate, lung and endometrium, has been reported.[65]

A loss of NEP activity has been suggested to be involved in the transition of androgen-dependent prostate cancer into androgen-independent prostate cancer. Aberrant cellular distribution of this protein in cancer cells has also been described. Modulation of its expression mainly at the transcriptional level, by factors such as androgens, progesterone and TGF-β1, which can influence tumorigenic transformation, has been reported.[66] However, while steroids up-regulate transcription of NEP mRNA, TGF-β1 decreased its level in cells.

Unexpectedly, it was recently described that NEP can form a complex with the tumor suppressor PTEN protein through electrostatic interactions between a highly basic residue stretch in the intracellular domain of NEP and the major phosphorylation site in PTEN's tail. This enhances PTEN recruitment to the plasma membrane, as well as its stability and phosphatase activity.[67]

THE ROLE OF microRNAs (miRNAs) ON PHOSPHATASE AND TENSIN HOMOLOGUE DELETED ON CHROMOSOME 10

A study was recently carried out[68] to look at the role of microRNA-214-targeting PTEN in advanced glycation end (AGE) product-induced apoptosis delay in monocytes. Luciferase reporter assay showed that miR-214 specifically binds to the phosphatase and tensin homologue (PTEN) mRNA 3′-untranslated region, implicating PTEN as a target gene of miR-214. PTEN expression is inversely correlated with miR-214 level in monocytes. Compared with normal monocytes, AGE-treated monocytes and monocytes from chronic renal failure patients exhibited lower PTEN levels and delayed apoptosis. Over-expression of pre-miR-214 led to impaired PTEN expression and delayed apoptosis of THP-1 cells, whereas knockdown of miR-214 level largely abolished AGE-induced cell survival. These findings define a new role for miR-214-targeting PTEN in AGE-induced monocyte survival.

This has also been demonstrated in a similar study by Zhang *et al.*[69] who investigated the expression of microRNA-21 (miR-21) and PTEN in twenty (20) non-small cell lung cancer (NSCLC) and adjacent non-tumor lung tissues by qRT-PCR and Western blotting respectively. They looked at the effect of miR-21 on PTEN expression with miR-21 inhibitor to decrease miR-21 expression, and observed that miR-21 post-transcriptionally down regulates the expression of PTEN tumor suppressor, and stimulates growth and invasion in NSCLC. They concluded that, this may be a potential therapeutic target for non-small cell lung tumor (NSCLC).

PROGNOSTIC SIGNIFICANCE OF PTEN

Zhang *et al.*[70] recently reported the effect of reduced expression of PTEN protein and its prognostic significance in gastrointestinal stromal tumors (GISTs). They

retrospectively reviewed the clinico-pathological features of tumors through patient's medical records, and observed that reduced PTEN expression was significantly associated with tumor diameter, mitotic figure count, metastasis and pathological staging of the tumor, but was not related to age, gender, or tumor site. They also observed that the three year survival of these patients with reduced PTEN expression was much lower than those with higher or normal expression of PTEN. As a result of these findings, they concluded that the expression of PTEN gene was strongly linked to the progression and metastasis of GISTs and so it (PTEN) should be considered an independent prognostic factor.

This is supported by a more recent study,[71] which reviewed PTEN protein expression in post-menopausal steroid receptor-positive early breast cancer patients treated with adjuvant Tamoxifen. This group observed that there was no association between PTEN protein expression and tumor histology, size, grade, or receptor (ER, PR, and HER2) expression. However, they observed that patients with PTEN (–) tumors had much shorter disease-free intervals, and decreased overall survival, compared to patients with PTEN (+) breast cancers. Therefore, they also agreed with the earlier suggestion that PTEN protein expression might be of prognostic significance in post-menopausal steroid receptor positive breast cancer patients treated with adjuvant Tamoxifen.

However, Liu *et al.*[72] had earlier suggested that PTEN plays less prognostic role than P53 tumor suppressor in diffuse large B cell-lymphoma. They revealed that results of multi-variate analysis showed that P53 mutation but not PTEN loss was associated with decreased survival in this group of patients. They further revealed that PTEN status had no effect on P53 mutation-associated poor survival, and so these workers concluded that PTEN may play less prognostic role than P53, and mutation of the latter should be considered as a predictive factor of the need for more aggressive treatment of diffuse B cell-lymphoma patients who express P53. They argued that this is not true for PTEN, and further studies are required in future to confirm the role of PTEN as a prognostic marker of human cancers.

CONCLUSION AND FUTURE PERSPECTIVES

PTEN tumor suppressor plays a significant role in cellular processes like cell cycle progression, translation, apoptosis, cell size, growth, proliferation and migration, by negatively controlling the PI3/AKt pathway. When the PTEN gene becomes mutated or deleted, this affects the normal cellular development leading to tumorigenesis. Recent studies have supported the role of PTEN protein as a prognostic indicator in many human cancers, and therefore knowledge of its role in cellular processes will provide a better understanding of cancer pathogenesis and possibly provide targets for novel drug development, cancer prevention and treatment in future. It is possible that routine laboratory testing and localisation of this gene and protein (PTEN) may become a reality in the near future, which will make screening, diagnosis, treatment, prognostication and follow-up of many human cancers much easier, with attendant decreased morbidity and mortality.

REFERENCES

1. Sulis ML, Parsons R. PTEN: From pathology to biology. Trends Cell Biol 2003;13:478-83.
2. Norimatsu Y, Moriya T, Kobayashi TK, Sakurai T, Shimizu K, Tsukayama C, *et al*. Immunohistochemical expression of PTEN and beta-catenin for endometrial intraepithelial neoplasia in Japanese women. Ann Diagn Pathol 2007;11:103-8.
3. You Y, Geng X, Zhao P, Fu Z, Wang C, Chao S, *et al*. Evaluation of combination gene therapy with PTEN and antisense hTERT for malignant glioma *in vitro* and xenografts. Cell Mol Life Sci 2007;64:621-31.
4. Priulla M, Calastretti A, Bruno P, Azzariti A, Paradiso A, Canti G, *et al*. Preferential chemosensitization of PTEN-mutated prostate cells by silencing the Akt kinase. Prostate 2007;67:782-9.
5. Herlevsen M, Oxford G, Ptak C, Shabanowitz J, Hunt DF, Conaway M, *et al*. A novel model to identify interaction partners of the PTEN tumor suppressor gene in human bladder cancer. Biochem Biophys Res Commun 2007;352:549-55.
6. Lázcoz P, Muñoz J, Nistal M, Pestaña A, Encío IJ, Castresana JS. Loss of heterozygosity and microsatellite instability on chromosome arm 10q in neuroblastoma. Cancer Genet Cytogenet 2007;174:1-8.
7. Tokunaga E, Oki E, Kimura Y, Yamanaka T, Egashira A, Nishida K, *et al*. Coexistence of the loss of heterozygosity at the PTEN locus and HER2 overexpression enhances the Akt activity thus leading to a negative progesterone receptor expression in breast carcinoma. Breast Cancer Res Treat 2007;101:249-57.
8. Nakajima H, Sakaguchi K, Fujiwara I, Mizuta M, Tsuruga M, Magae J, *et al*. Apoptosis and inactivation of the PI3-kinase pathway by tetrocarcin A in breast cancers. Biochem Biophys Res Commun 2007;356:260-5.
9. Teng DH, Hu R, Lin H, Davis T, Iliev D, Frye C, *et al*. MMAC1/PTEN mutations in primary tumor specimens and tumor cell lines. Cancer Res 1997;57:5221-5.
10. Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, *et al*. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet 1997;16:64-7.
11. Jin X, Gossett DR, Wang S, Yang D, Cao Y, Chen J, *et al*. Inhibition of AKT survival pathway by a small molecule inhibitor in human endometrial cancer cells. Br J Cancer 2004;91:1808-12.
12. Li DM, Sun H. TEP1, encoded by a candidate tumor suppressor locus, is a novel protein tyrosine phosphatase regulated by transforming growth factor beta. Cancer Res 1997;57:2124-9.
13. Li J, Yen C, Liaw D, Podsypanina K, Bose S, Wang SI, *et al*. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 1997;275:1943-7.
14. Steck PA, Pershouse MA, Jasser SA, Yung WK, Lin H, Ligon AH, *et al*. Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet 1997;15:356-62.
15. Chu S, Li L, Singh H, Bhatia R. BCR-tyrosine 177 plays

an essential role in Ras and Akt activation and in human hematopoietic progenitor transformation in chronic myelogenous leukemia. Cancer Res 2007;67:7045-53.
16. Gericke A, Munson M, Ross AH. Regulation of the PTEN phosphatase. Gene 2006;374:1-9.
17. Di Cristofano A, Pandolfi PP. The multiple roles of PTEN in tumor suppression. Cell 2000;100:387-90.
18. Lee JO, Yang H, Georgescu MM, Di Cristofano A, Maehama T, Shi Y, *et al*. Crystal structure of the PTEN tumor suppressor: Implications for its phosphoinositide phosphatase activity and membrane association. Cell 1999;99:323-34.
19. Leslie NR, Downes CP. PTEN: The down side of PI 3-kinase signalling. Cell Signal 2002;14:285-95.
20. Chu EC, Chai J, Tarnawski AS. NSAIDs activate PTEN and other phosphatases in human colon cancer cells: Novel mechanism for chemopreventive action of NSAIDs. Biochem Biophys Res Commun 2004;320:875-9.
21. Simpson L, Parsons R. PTEN: Life as a tumor suppressor. Exp Cell Res 2001;264:29-41.
22. Vazquez F, Ramaswamy S, Nakamura N, Sellers WR. Phosphorylation of the PTEN tail regulates protein stability and function. Mol Cell Biol 2000;20:5010-8.
23. Torres J, Pulido R. The tumor suppressor PTEN is phosphorylated by the protein kinase CK2 at its C terminus. Implications for PTEN stability to proteasome-mediated degradation. J Biol Chem 2001;276:993-8.
24. Kotelevets L, van Hengel J, Bruyneel E, Mareel M, van Roy F, Chastre E. Implication of the MAGI-1b/PTEN signalosome in stabilization of adherens junctions and suppression of invasiveness. FASEB J 2005;19:115-7.
25. Wu X, Hepner K, Castelino-Prabhu S, Do D, Kaye MB, Yuan XJ, *et al*. Evidence for regulation of the PTEN tumor suppressor by a membrane-localized multi-PDZ domain containing scaffold protein MAGI-2. Proc Natl Acad Sci U S A 2000;97:4233-8.
26. Delves PJ, Martin SJ, Burton DR, Roitt IM. Roitt's Essential Immunology. 11th ed. Oxford: Blackwell Publishing; 2006.
27. Goberdhan DC, Wilson C. PTEN: Tumour suppressor, multifunctional growth regulator and more. Hum Mol Genet 2003;12 Spec No 2:R239-48.
28. Risinger JI, Hayes AK, Berchuck A, Barrett JC. PTEN/MMAC1 mutations in endometrial cancers. Cancer Res 1997;57:4736-8.
29. Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, *et al*. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst 2000;92:924-30.
30. Marsh DJ, Coulon V, Lunetta KL, Rocca-Serra P, Dahia PL, Zheng Z, *et al*. Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. Hum Mol Genet 1998;7:507-15.
31. Rychahou PG, Jackson LN, Silva SR, Rajaraman S, Evers BM. Targeted molecular therapy of the PI3K pathway: Therapeutic significance of PI3K subunit targeting in colorectal carcinoma. Ann Surg 2006;243:833-42.
32. Zhang QG, Wu DN, Han D, Zhang GY. Critical role of PTEN in the coupling between PI3K/Akt and JNK1/2 signaling in ischemic brain injury. FEBS Lett 2007;581:495-505.
33. Maehama T, Dixon JE. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. J Biol Chem 1998;273:13375-8.
34. Stiles B, Groszer M, Wang S, Jiao J, Wu H. PTENless means more. Dev Biol 2004;273:175-84.
35. Wen S, Stolarov J, Myers MP, Su JD, Wigler MH, Tonks NK, *et al*. PTEN controls tumor-induced angiogenesis. Proc Natl Acad Sci U S A 2001;98:4622-7.
36. Minaguchi T, Nakagawa S, Takazawa Y, Nei T, Horie K, Fujiwara T, *et al*. Combined phospho-Akt and PTEN expressions associated with post-treatment hysterectomy after conservative progestin therapy in complex atypical hyperplasia and stage Ia, G1 adenocarcinoma of the endometrium. Cancer Lett 2007;248:112-22.
37. Song Z, Saghafi N, Gokhale V, Brabant M, Meuillet EJ. Regulation of the activity of the tumor suppressor PTEN by thioredoxin in Drosophila melanogaster. Exp Cell Res 2007;313:1161-71.
38. Arico S, Petiot A, Bauvy C, Dubbelhuis PF, Meijer AJ, Codogno P, *et al*. The tumor suppressor PTEN positively regulates macroautophagy by inhibiting the phosphatidylinositol 3-kinase/protein kinase B pathway. J Biol Chem 2001;276:35243-6.
39. Chen WC, Lin MS, Bai X. Induction of apoptosis in colorectal cancer cells by peroxisome proliferators-activated receptor gamma activation up-regulating PTEN and inhibiting PI3K activity. Chin Med J (Engl) 2005;118:1477-81.
40. Kim S, Domon-Dell C, Wang Q, Chung DH, Di Cristofano A, Pandolfi PP, *et al*. PTEN and TNF-alpha regulation of the intestinal-specific Cdx-2 homeobox gene through a PI3K, PKB/Akt, and NF-kappaB-dependent pathway. Gastroenterology 2002;123:1163-78.
41. Wu X, Senechal K, Neshat MS, Whang YE, Sawyers CL. The PTEN/MMAC1 tumor suppressor phosphatase functions as a negative regulator of the phosphoinositide 3-kinase/Akt pathway. Proc Natl Acad Sci U S A 1998;95:15587-91.
42. Wang Q, Wang X, Hernandez A, Kim S, Evers BM. Inhibition of the phosphatidylinositol 3-kinase pathway contributes to HT29 and Caco-2 intestinal cell differentiation. Gastroenterology 2001;120:1381-92.
43. Haier J, Nicolson GL. Time-dependent dephosphorylation through serine/threonine phosphatases is required for stable adhesion of highly and poorly metastatic HT-29 colon carcinoma cell lines to collagen. Anticancer Res 2000;20:2265-71.
44. Li DM, Sun H. PTEN/MMAC1/TEP1 suppresses the tumorigenicity and induces G1 cell cycle arrest in human glioblastoma cells. Proc Natl Acad Sci U S A 1998;95:15406-11.
45. He XC, Yin T, Grindley JC, Tian Q, Sato T, Tao WA, *et al*. PTEN-deficient intestinal stem cells initiate intestinal polyposis. Nat Genet 2007;39:189-98.
46. Li G, Robinson GW, Lesche R, Martinez-Diaz H, Jiang Z, Rozengurt N, *et al*. Conditional loss of PTEN leads to precocious development and neoplasia in the mammary gland. Development 2002;129:4159-70.
47. Suzuki A, de la Pompa JL, Stambolic V, Elia AJ, Sasaki T, del Barco Barrantes I, *et al*. High cancer susceptibility and embryonic lethality associated with mutation of the PTEN tumor suppressor gene in mice. Curr Biol 1998;8:1169-78.
48. Okamura H, Yoshida K, Sasaki E, Qiu L, Amorim BR, Morimoto H, *et al*. Expression of PTEN and Akt phosphorylation in lipopolysaccharide-treated NIH3T3 cells. Cell Biol Int 2007;31:119-25.
49. Cheung SM, Kornelson JC, Al-Alwan M, Marshall AJ. Regulation of phosphoinositide 3-kinase signaling by oxidants: Hydrogen peroxide selectively enhances immunoreceptor-induced recruitment of phosphatidylinositol (3,4) bisphosphate-binding PH domain proteins. Cell Signal 2007;19:902-12.
50. Lim S, Clément MV. Phosphorylation of the survival kinase Akt by superoxide is dependent on an ascorbate-reversible oxidation of PTEN. Free Radic Biol Med 2007;42:1178-92.
51. Furnari FB, Lin H, Huang HS, Cavenee WK. Growth suppression of glioma cells by PTEN requires a functional phosphatase catalytic domain. Proc Natl Acad Sci U S A 1997;94:12479-84.
52. Böhni R, Riesgo-Escovar J, Oldham S, Brogiolo W, Stocker H, Andruss BF, *et al*. Autonomous control of cell and organ size by CHICO, a Drosophila homolog of vertebrate IRS1-4. Cell 1999;97:865-75.

53. Huang H, Potter CJ, Tao W, Li DM, Brogiolo W, Hafen E, *et al*. PTEN affects cell size, cell proliferation and apoptosis during Drosophila eye development. Development 1999;126: 5365-72.
54. Gao X, Neufeld TP, Pan D. Drosophila PTEN regulates cell growth and proliferation through PI3K-dependent and -independent pathways. Dev Biol 2000;221:404-18.
55. Stiles B, Gilman V, Khanzenzon N, Lesche R, Li A, Qiao R, *et al*. Essential role of AKT-1/protein kinase B alpha in PTEN-controlled tumorigenesis. Mol Cell Biol 2002;22:3842-51.
56. Groszer M, Erickson R, Scripture-Adams DD, Lesche R, Trumpp A, Zack JA, *et al.* Negative regulation of neural stem/progenitor cell proliferation by the Pten tumor suppressor gene *in vivo*. Science 2001;294:2186-9.
57. Tamura M, Gu J, Matsumoto K, Aota S, Parsons R, Yamada KM. Inhibition of cell migration, spreading, and focal adhesions by tumor suppressor PTEN. Science 1998;280:1614-7.
58. Leslie NR, Yang X, Downes CP, Weijer CJ. PtdIns (3,4,5) P (3)-dependent and -independent roles for PTEN in the control of cell migration. Curr Biol 2007;17:115-25.
59. Li Z, Dong X, Wang Z, Liu W, Deng N, Ding Y, *et al*. Regulation of PTEN by Rho small GTPases. Nat Cell Biol 2005;7:399-404.
60. Iijima M, Devreotes P. Tumor suppressor PTEN mediates sensing of chemoattractant gradients. Cell 2002;109:599-610.
61. Podsypanina K, Ellenson LH, Nemes A, Gu J, Tamura M, Yamada KM, *et al.* Mutation of Pten/Mmac1 in mice causes neoplasia in multiple organ systems. Proc Natl Acad Sci U S A 1999;96:1563-8.
62. Ginn-Pease ME, Eng C. Increased nuclear phosphatase and tensin homologue deleted on chromosome 10 is associated with G0-G1 in MCF-7 cells. Cancer Res 2003;63:282-6.
63. Gimm O, Attié-Bitach T, Lees JA, Vekemans M, Eng C. Expression of the PTEN tumour suppressor protein during human development. Hum Mol Genet 2000;9:1633-9.
64. Freeman DJ, Li AG, Wei G, Li HH, Kertesz N, Lesche R, *et al.* PTEN tumor suppressor regulates p53 protein levels and activity through phosphatase-dependent and -independent mechanisms. Cancer Cell 2003;3:117-30.
65. Casey ML, Smith JW, Nagai K, Hersh LB, MacDonald PC. Progesterone-regulated cyclic modulation of membrane metalloendopeptidase (enkephalinase) in human endometrium. J Biol Chem 1991;266:23041-7.
66. Casey ML, Smith JW, Nagai K, MacDonald PC. Transforming growth factor-beta 1 inhibits enkephalinase (EC 3.4.24.11) gene expression in human endometrial stromal cells and sex skin fibroblasts in culture. J Clin Endocrinol Metab 1993;77:144-50
67. Sumitomo M, Iwase A, Zheng R, Navarro D, Kaminetzky D, Shen R, *et al*. Synergy in tumor suppression by direct interaction of neutral endopeptidase with PTEN. Cancer Cell 2004;5:67-78.
68. Li LM, Hou DX, Guo YL, Yang JW, Liu Y, Zhang CY, *et al*. Role of microRNA-214-targeting phosphatase and tensin homolog in advanced glycation end product-induced apoptosis delay in monocytes. J Immunol 2011;186:2552-60.
69. Zhang Y, Yu D, Li X, Hu J, Gong J. Reduced expression of PTEN protein and its prognostic significance in the gastrointestinal stromal tumor. J Huazhong Univ Sci Technolog Med Sci 2010;30:165-9.
70. Zhang JG, Wang JJ, Zhao F, Liu Q, Jiang K, Yang GH. MicroRNA-21 (miR-21) represses tumor suppressor PTEN and promotes growth and invasion in non-small cell lung cancer (NSCLC). Clin Chim Acta 2010;411:846-52.
71. Milovanovic Z, Dzodic R, Susnjar S, Plesinac-Karapandzic V, Juranic Z, Tatic S. PTEN protein expression in postmenopausal steroid receptor positive early breast cancer patients treated with adjuvant tamoxifen. J BUON 2011;16:46-51.
72. Liu YY, Yao SN, Zhao Y, Yao ZH, Ma J, Xia QX, *et al*. PTEN tumor suppressor plays less prognostic role than P53 tumor suppressor in diffuse large B-cell lymphoma. Leuk Lymphoma 2010;51:1692-8.

How to cite this article: Abdulkareem IH, Blair M. Phosphatase and tensin homologue deleted on chromosome 10. Niger Med J 2013;54:79-86.

Source of Support: Nil, **Conflict of Interest:** None declared.