Research article

Loss of phosphatase activity in PTEN (phosphatase and tensin homolog deleted on chromosome ten) results in endometrial carcinoma in humans: An in-silico study

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ABSTRACT

The tumour suppressor gene, PTEN (Phosphatase and Tensin homolog deleted on chromosome Ten), can act as both protein phosphatase and lipid phosphatase, is known to play a vital role in Pi3k signalling pathway. In humans, it is located at 10q23. Loss of its phosphatase and catalytic activity is associated with various types of cancers. This study focuses on evolution, understanding the somatic missense mutation in a particular residue of PTEN and understanding the molecular mechanism that leads to endometrial carcinoma through molecular docking. Mutational analysis of H123 position indicates that the missense mutation at first position of the codon CAC by G or T, result in aspartic acid or tyrosine instead of histidine and can have negative effect on the function of PTEN. Alongside, structural analysis showed mutated PTEN has lower stability than the normal. Additionally, SNPs dataset for endometrial carcinoma suggests H123 as strongly mutated residue. The mutation in phosphatase domain of PTEN along with its effect and interaction with substrate TLA1352 were systematically studied through molecular docking. Molecular interaction study reveals that the optimal substrate binding site in PTEN is unable to interact with the substrate in the mutated condition. This observation drew attention on the impact of mutation on disease biology and enabled us to conduct follow-up studies to retrieve novel molecular targets, such as mutated protein domain and modified Asp and Tyr sites, to design effective therapies to either prevent endometrial carcinoma or impede its progression.

1. Introduction

Phosphatase and tensin homologue deleted on chromosome10 or PTEN is a tumor suppressor gene, which has been found to be frequently mutated in patients suffering from various cancers like: glioblastomas, endometrial carcinomas, prostate carcinomas, and melanoma cases in human. This cytosolic protein with dual-specificity phosphatase activity, can act on both polypeptide and phosphoinositide substrates. These 403 amino acids are separated into two major domains i.e., N terminal phosphatase domain (residue 7-185) and a C terminal C2 domain (residue 186-351). The phosphatase domain is composed of five central β-sheets with one α-helix in one side and four on another side and also similar to the specificity phosphatase (Yuvaniyama et al., 1996). The C2 domain is composed of two antiparallel β-sheets with two small α-helix strands. The C2 domain play vital role in binding between protein and phospholipid membrane and phosphatase terminal has an important role in interaction between ligand and phosphate head. However, these two domains and also their interactions are controlled by the P loop (H123CKAGKGR130), WPD loop (residues 88–98), and TI loop (residues 160–171) which contain residues that are involved in catalysis (Lee et al., 1999). The phosphatase binding P-loop act as conserver and that has been reflected in nuclear binding properties. The function of the amino acids within P-loop allow for anchoring and help to detect the P-loop anchors in the several GTPase and ATPase. Glycine and histidine stabilize

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the major structure of P-loop by creating the interaction between adjacent helix C (Mercier et al., 2015).

Different sites of PTEN are responsible for developing cancer. Different types of mutated amino acid residues are present in each loop and they are responsible for decrease the protein activity. P-loop (residues 123-130) contains four mutation residues; His123, Lys125, Gly127 and Lys128, those play role for change in confirmation of this loop (Barford et al., 1994; Schubert et al., 1995) and also decrease the protein activity about 50–60%. The Ti loop contains 4 conserved residues Val166, Thr167, Ile168 and Gln171 in contact with phosphatase domain and C2 domain. Among them, Thr167 and Gln171 are the mutated residues within Ti loop. However, these mutations result in 60–75% loss of functions in human. In WPD loop, residue His93 showing the same effect on the protein activity is known to reduce about 75% of functionality. Moreover, the frequent mutation at D5 position may develop cancer (Lee et al., 1999). Loss of heterozygosity of chromosome 10q has been reported in cases of endometrial carcinomas (Dinulescu et al., 2005; Zhang et al., 2010). Some datas are also available which suggested that PTEN is more commonly mutated than any other gene which includes Kras and p53 (Maxwell et al.,

Figure 1. (A) Human PTEN protein entire structure (PDB ID: 1D5R); (B) PTEN structure showing P, Ti and WPD loop.

Figure 2. The heat map representation of the gene expression level, modelled by biological condition against disease experiment.
One of many early events in endometrial hyperplasia and development of endometrial and ovarian cancers include inactivation of PTEN (Montgomery et al., 2008).

Mutations of PTEN lead to increased cell proliferation and reduced cell death and aids in tumor development. But these negative effects are not limited to the genome inactivation only. There are many studies, which showed the repression of PTEN gene expression, rather than only mutations and deletions, are associated with tumorigenesis. Studies showed, besides mutations in some important domains within PTEN, various molecular mechanisms, which can cause changes in PTEN protein levels, location, and/or enzymatic activity can have negative effects on PTEN normal functioning in sporadic cancers, and other diseases (Stambolic and Woodgett, 2006; Milella et al., 2015). Decreased PTEN transcript levels were found to be associated with PTEN promoter methylation in melanoma. Almost 30-60% of the melanomas are related to loss of functioning of PTEN (Mirmohammadsadegh et al., 2006; Hollander et al., 2011). Kuchay et al., in 2017, found that PTEN competes with FBXL2 for IP3R3 binding. IP3R3 acts as a receptor for inositol 1,4,5-trisphosphate, which acts as a second messenger and mediates the release of intracellular calcium. They found that the FBXL2-dependent degradation of IP3R3 is associated with Pten−/− mouse embryonic fibroblasts and PTEN-null cancer cells. Decreased levels of PTEN promote IP3R3- and Ca2+-mediated apoptosis (Kuchay et al., 2017).

Figure 3. Domain DSPC and C2 of PTEN gene.

Figure 4. DSPC domain region (67-173) source: COSMIC. Organism: Homo sapiens; Source: pfam (PF00782); Coordinates: 67–173 (alignment region 101–159). The amino acid position range mentioned within bracket.
1.1. Function of termini and domains of PTEN as tumour suppressor

Previous studies revealed that among the Carboxyl terminal and N terminal domains, the C2 domain of C-terminal play a vital role in tumour suppressor activity (Lee et al., 1999, Georgescu, 2010). The three amino acids of C terminus can bind to PDZ domain to facilitate the interaction with phospholipid membranes that control the activity of the lipid binding which is important for its tumour suppressor function. Precedent studies confirmed that the mutated residues are not involved in structural stabilizing and also growth suppressor function is not responsible for the decrease of protein level, but short chain of PI(3,4,5)P3 analog have similar phosphatase activity level in wild type PTEN. Mutation in C2 terminal of the protein PTEN results in misfolding. Thus C terminal is involved in both protein stability and PTEN function. Mutation in the C terminal results in loss of stability but not loss in function (Vazquez et al., 2000). Most of the mutations are observed in phosphatase domain that are situated in the N terminal of PTEN collected from primary tumor and tumor cell line. A previous studies elaborated that mutation in N terminal leads to the reduction of the phosphatase activity. The structure of the PTEN (Figure 1) reveals that insertion of P loop and Ti loop residues (Gly129, Lys125 and Lys128) and WPD loop (His93) are evolutionary conserved. These conserved sites are the target for mutation to develop various cancers by reducing the PI(3,4,5)P3 phosphatase activity (Lee et al., 1999). Previous studies suggested that dephosphorylation of PI(3,4,5)P3 is more essential. This systematic study is carried out to understand the somatic missense mutation associated with the loss of phosphatase activity of PTEN that causes endometrial carcinoma and its effect on structure and predicting the molecular mechanism of interaction with the substrate.

2. Materials and methods

2.1. Collection of data and gene expression analysis

Based on the key role of PTEN in PI3k signalling pathway and vital role for tumor suppression in human, PTEN gene has been chosen as study of interest. Annotated amino acid sequence of the PTEN gene

![Figure 5. C2 domain region (188–349) Source: COSMIC. Organism: Homo sapiens; Source: pfam (PF10409); Coordinates: 188–349 (alignment region 188–349). The amino acid position range mentioned within bracket.](image)

![Figure 6. The change in residue and allele and from SNP to mRNA in forward direction (Source: DisGeNET).](image)
were retrieved from NCBI (https://www.ncbi.nlm.nih.gov). Gene expression data provide information about wide type of the species under different biological conditions (Mondal and Sen; 2018; Mondal et al., 2015). Expressional data of PTEN in different developmental condition along with various disease condition from different tissues and organs of human was collected from the Expression Atlas-EMBL-EBI (Papatheodorou et al., 2017, url: https://www.ebi.ac.uk/gxa/home). Then, the expression datas were represented by heatmap, generated through R (version 3.2.2) software (Mondal and Roy, 2017; Mondal, 2015; Mondal et al., 2013).

2.2. Somatic Mutation and SNP analysis

Somatic mutations within PTEN gene for endometrial carcinoma and other cancers were retrieved from Catalogue of Somatic Mutations in Cancer (COSMIC, ver-85) databases (Forbes et al., 2014). Then, the SNP dataset for this gene and their disease relation specifically for endometrial carcinoma were collected from DisGeNET (url: http://www.disgenet.org/web/DisGeNET, Pinero et al., 2015).

2.3. Collection of protein structure and structure alignment

The three dimensional (3D) crystallized protein structure of the wild type human PTEN with TLA (PDB ID: 1D5R, tertrate) was downloaded from RCSB PDB (Berman et al., 2003, url: http://www.rcsb.org/pdb) along with other information like: secondary structure content and responsible region within protein sequence to give different secondary structure, domain architecture, active sites, binding sites etc. Then two mutant (H > D or H > Y) amino acid sequence of PTEN at position 123 was submitted to the online server I-TASSER (Yang et al., 2015, url: https://zhanglab.ccmb.med.umich.edu/I-TASSER) for the prediction of 3D structure from amino acid sequence and results were obtained. The visualization tool Chimera (Pettersen et al., 2004) was used to detect the changes in bond length between the interacting amino acids within the

Figure 7. PTEN sequence view from RCSB PDB. In this picture SCOP and DSSP annotated two domains along with their different secondary structure conforming regions, TLA binding site were displayed.
protein structure for some specific region. To visualize the changes within mutated protein structures, the wild type PTEN structure was aligned with the mutated one through PyMOL (DeLano, 2002).

2.4. Protein – ligand interaction study

After obtaining the result files of the wild type and two mutated protein sequences, protein – ligand interaction study was conducted to know the effect of the mutation on PTEN protein structure and its consequence on molecular interaction. For this, TLA was chosen as ligand and PTEN (wild type or mutant – one at a time) as receptor molecule. The molecular docking study was done by using AutoDock (version 4) software. Furthermore, we had used, LIGPLOT v.4.5.3 to plot the protein-ligand interactions. It is freely available from https://www.ebi.ac.uk/thornton-srv/software/LIGPLOT/(Wallace et al, 1995).

3. Results and discussions

3.1. Analysis of gene expressions data

The gene expression level of PTEN is represented through heatmap (Figure 2) where gene expression values were converted into a colour-scale image, providing a visual representation of gene expression levels across different biological conditions. Endometrial carcinoma (expression level 19 TPM), is a cancer that arises from the endometrium (the lining of the uterus or womb). It is the result of the abnormal growth of cells that have the ability to invade or spread to other parts of the body. The first sign is most often vaginal bleeding not associated with a menstrual period. Previous study had reported that deletion or heterozygosity in chromosome 10q23.3 position is occupied by PTEN gene, has been reported in approximately 40% of endometrial carcinomas (Tashiro et al., 1997). Different sites of PTEN are responsible for developing cancer. Figure 2 is a representation of the gene expression level of PTEN, modelled by biological condition against disease experiment.

Previous studies revealed that some commonly affected signaling pathways such as TGFβ suppresses PTEN expression, inhibition of RAS/ERK activity, RAS/ERK signalling facilitates TGFβ-induced PTEN suppression; have a number of implications in pancreatic adenocarcinoma (Chow et al., 2007). Ovarian adenocarcinoma occurs in organ of ovary (expression level 84 TPM). Previous study provided that micro RNA-214 is of vital in chemoresistance of human ovarian cancer. Down-regulation of PTEN largely correlates with elevated levels of miRNA-214 in ovarian cancer (Yang et al., 2008). In case of Chronic Lymphocytic leukemia, micro RNA also play a vital role in gene expression, cell proliferation etc. but it's down regulation in signaling pathway involved in malignancy and represent downstream targets of activated oncogenic pathways, or that target protein-coding genes involved in cancer (Iorio and Croce, 2009). In case of Lymphoma, PTEN and phosphorylated AKT protein expression within subset nucleus of cell lines that abnormal nucleocyttoplasmic shuttling of key signalling molecules may play a role in the development of malignant neoplasms (Abbott et al., 2003). The loss of PTEN gene expression is correlated with native estrogen and progesterone status and caused in late event of breast carcinogenesis (Perren et al., 1999). In case of hepatocellular carcinoma, up-regulated expression of micro RNA-21 is caused of effect in biological function of target gene PTEN and involved in contribution of hepatocellular carcinoma growth and spread by modulating PTEN expression and PTEN-dependent pathways involved in mediating phenotypic characteristics of cancer cells such as cell growth, migration, and invasion (Meng et al., 2007). Previous allelic related studies have suggested that loss of heterozygosity or deletion of both alleles in seven out of 26 (27%) cause of follicular thyroid cancer which inactive the expression of PTEN tumor suppressor gene (Halachmi et al., 1998). Head and neck squamous cell carcinoma or HNSCC (expression level 30 TPM) that are begins in the lungs considered lung cancer. Esophageal adenocarcinoma (expression level 24 TPM) is a type of cancer arising
from esophagus. Some nuclear studies have reported that PTEN expression may be a favorable biologic marker and a useful prognostic indicator in human with esophageal adenocarcinoma. The down regulation of PTEN was correlated with advancement of the disease process and associated with advance stage esophageal adenocarcinoma. However, PTEN does not play a major role in carcinogenesis of esophageal adenocarcinoma (Tachibana et al., 2002). Clinicopathological studies have reported that loss of nuclear PTEN expression was a marker of poor clinical outcome in human with stage II colorectal adenocarcinoma (Kim et al., 2009).

3.2. Interpretation of cosmic result

3.2.1. Gene view

The gene view histogram (Figure 3) is a graphical view of mutations across PTEN. These mutations are displayed at the amino acid level across the full length of the gene by default. On the basis of the functionality of the PTEN gene, entire sequence (source org. Ovisaries) is divided into dual specificity phosphatase, catalytic domain [DPSc] and the C2 domain [PTEN_C2]. DUSPs (dual-specificity phosphatases) are a heterogeneous group of protein phosphatases that can dephosphorylate both phosphotyrosine and phosphoserine/phosphothreonine residues within the one substrate (Bermudez et al., 2010; Patterson et al., 2009). However, certain DUSPs whose phosphatase domain belongs in N terminal can act preferably on one type of residue. In crystal structure of PTEN it has been observed that the domain occupied 67-173 residue and the active site structures are more variable amongst the DUSPs members. From the following graphical data of mutation (Figure 4), it can be suggested that mostly mutation occur at the 1st position of the codon of an amino acid. PTEN binds the membrane through both of its phosphatase and C2 domains and bringing the active site to the membrane-bound PIP3 for its dephosphorylation, moreover it is involved in catalytic function. The mutational graphical chart suggests that most of the mutation occur in 1st position of amino acid of C2 domain (Figure 5).

3.3. SNP study with focus on His123 residue

Cancer cells are generally skips their normal growth cycle by acquisition of mutation. PTEN has marked as the tumor suppressor in human cancers. Few datas are available about the role of PTEN in endometrial carcinoma. Single Nucleotide Polymorphisms (SNP) analysis has been performed to explore the possible association between genotypic and phenotypic variation. Previous in silico study for the screening of missense or non-synonymous SNP within the protein coding region has been done using sequence based information and structural analysis. DisGeNET (http://www.disgenet.org/web/DisGeNET) was used to collect SNP related data of PTEN gene. Endometrial carcinoma (Disease id: C0476089, score: 0.519, PMIDs: 136) is one of them with SNP ID: rs786204931 (missense variant). The details (chromosome no., chromosome position, contig, contig position etc.) of position of acquisition of mutation within the genome for the said SNP are shown within the picture along with the position within mRNA and protein sequence. It was observed that that the nucleotide Cat position 1398 within mRNA is being mutated into G or T and this leads to the missense mutation as codon CAC which is the codon of positively charged R group containing Histidine converted to codon GAC (codon of negatively charged R group containing Aspartic acid) or to TAC (codon of aromatic R group containing Tyrosine) at position 123 within the protein sequence. Previous studies indicate that these two divergent mutation i.e., H \( \rightarrow \) D or H \( \rightarrow \) Y at position 123 of the PTEN protein has significant impact on endometrial carcinoma by loss of phosphatase activity (Figure 6).

3.4. Crystal structure of PTEN

The sequence view reveals that PTEN tumor suppressor (Phosphoinositide phosphatase), C-terminal domain contains 133 residues and Phosphoinositide phosphatase PTEN (PTEN tumor suppressor), N-terminal domain contains 174 residues on the basis of SCOP annotation. The DSSP annotation tells that PTEN contains 23% helical (8 helices; 77 residues) and 31% beta sheet (20 strands; 101 residues) (Figure 7). The site record information tells that it has binding site for residue TLA A. SNP data shows different site where mutation takes place and change in different position in amino acid residue. His123 residue positioned within phosphatase domain in N terminal was chosen as the study of interest due to its relation with disease. The local structure of PTEN and also interaction around their mutated residue in Phosphatase domain of PTEN were observed. The mutated position was mapped to the three-dimensional structure of PTEN.

Figure 10. Structure of Wild type and Mutated Asp and Tyr.
Different types of association with their severe phenotypes that are clustered within the active pocket located near N terminal was observed. Different types of mutations are involved in different type of cancer such as: R173C is cause of endometrial hyperplasia, ovarian cancer; residues C124 an R130 are play an important role in catalytic activity and protein function etc. The residue of interest His123 implicates the loop motion. From all these observations, it can be said that there is a possibility of involvement of the P, WPD, Ti loops and their mutation can change the positive charge of active site and loss the function of PTEN and leads to the tumor generation with different type of severe phenotypes.

3.5. Interpretation of I-TASSER structural result

To understand the structural changes in the mutated protein the mutated (replaced the H123 by D or by Y) protein sequences were submitted to I-TASSER server for the pdb structures. From the I-TASSER result, it was found that the amino acid at site 123 within the protein PTEN (in both wild and mutated) is in buried condition and are unable to bind with outer particles such as other macromolecule or ligand. I-TASSER result also indicates that the predicted structure is more stable in both and easy to target and the position 123 is conserved. In addition to the previous structural analysis, it was also viewed that the three dimensional structure of the wild type and those two mutated type using UCSF Chimera along with intramolecular hydrogen bonding which play important role to gives the proper three dimensional structure of the protein. The residue His123 within wild type forming hydrogen bond with the residue Leu70 and Tyr68 with bond length 2.051 Å and 1.975 Å respectively. In the mutated structure, the similar interaction persist with little bit changes in the bond length as follows: Asp123 to Leu70 and Tyr68 are 2.156 Å and 1.963 Å respectively and Tyr123 to Leu70 and Tyr68 are 2.058 Å and 1.947 Å. The above results indicate that in the mutated structures the hydrogen bond length between D123 or Y123 to Leu70 becomes longer and hydrogen bond length between D123 or Y123 to Tyr68 becomes shorter. These changes in the intramolecular bond length may lead to the changes in the structural conformation of the active site of the phosphatase domain and ultimately the substrate might not bind to this active site properly and de-phosphorylation may not take place (Figures 8, 9, 10, and 11). The Root Mean Square Deviation (RMSD) values obtained through structural alignments between wild type to mutate by D123 and to mutate by Y123 are 0.928 and 0.876 respectively (Figure 12). These RMSD values

![Figure 11. The hydrogen bond distance between (A) wild type His to Leu70 and Tyr68 (B) Mutated Asp to Leu70 and Tyr68 and (C) Mutated Tyr to Leu70 and Tyr68.](image)

![Figure 12. Structure alignment between wild type to (A) mutated by D (RMSD 0.928) and (B) mutated by Y (RMSD 0.876) at 123th position of amino acid sequence.](image)
indicates that the structural distortions in the mutated proteins are very less.

3.6. Molecular docking study of PTEN

Mutation causing human cancers like H123D and H123Y in endometrial carcinoma in complex with PTEN modulates endometrium tissue in a regulation dependent manner, and several drugs stabilize an open form of the endometrial carcinoma (Li et al., 2015). H123D and H123Y missense mutation in human cancers (from the COSMIC cancer mutation database) (Jubb et al., 2017) lies juxtaposed to an interfacially-binding approved drug molecule, PTEN (PDB: 1D5R). H123D and H123Y lines a large pocket in which three PTEN molecules stabilize the formation of an endometrial carcinoma N-terminal domain homodimer interface (Figure 13). Analysis of intermolecular interactions formed by H123D and H123Y at the PTEN binding site suggest that mutation to histidine in cancer may affect drug binding by ablating intermolecular aromatic ring interactions, in addition to altering a number of intramolecular interactions in the residues forming the binding pocket. The following tables (Tables 1, 2, and 3) show the parameters that were used. The results of interaction studies were mapped by using LIGPLOT software, which are provided in Figure 14.

4. Conclusion

The computational study approach in determining the PTEN has provided some interesting information on its structural and functional properties. In addition to that, it further shows the expression of PTEN gene in different biological conditions create various type of dangerous disease. The result also showed that the particular mutated region in the amino acid codon position that's already known from COSMIC result. Previous studies elaborated that various active site residues in the phosphatase domain with N-terminal and also including P loop are frequently mutated and developed severe human-related cancer. Although we cannot reach our goals through our results, we have found some results that conduct follow-up studies to retrieve novel molecular targets. Apart from this, some previous studies (Lee et al., 1999; Walker et al., 2004, Smith and Briggs, 2016) have shown that in the N terminal's active site residues, most of the mutations are seen. Additionally, we indicate H123 position is a strongly mutated residue by SNPs dataset, which also has shown as MMAC site of human PTEN protein sequence by NCBI data. I-TASSER information has helped us to understand that there is less stability in the mutated conditions than the normal condition, because of decrease of distance (1Å) between target residue and adjacent residue indicated loss of stability. Again, target residue in mutated condition, interaction with an unknown ligand is not seen in normal condition and distortion of active site in Y123 residue confirmed that the residue position of H123 is connected with developing endometrial cancer in mutated condition. Minimum distance between normal His123 with Lue70 show a positive interaction as the free electron of hydrogen are in a stable condition, whereas the mutated proteins are not so interactive due to this unstable distances. This suggests that PTEN might also affect the function by changing long-range structural elements. Docking study help us to assess the molecular effects of mutations including their molecular interaction of PTEN with the ligand TLA1352, this is also drawing an attention on the impacts of mutations on disease biology. These findings will enable us to conduct follow-up studies to retrieve novel molecular targets, such as mutated protein domain and modified Asp and Tyr sites, to design effective therapies to either prevent Endometrial Carcinoma or impede its progression. From the molecular docking result, it was analyzed that mutated D123 show RMSD value greater than Y123. So, mutated Asp is more stabilized than mutated Tyr align with wild type means H123. And also from confirmation information table of wild type and two mutated type, at a certain estimated state, the macromolecule TLA ligand bind with Wild type, but in case of mutated type (Asp or Tyr), it loses its ability to bind. So from that, it was understood that in the mutated condition, it can perform its accurate function. In the wild type the substrate can bind to the phosphatase domain. The exact binding site was constituted by: Ala126, Lys128, Gly129 and Arg130. But in both mutated types the substrate TLA cannot bind to the phosphatase domain.
Table 1. Parameters with conformation information of wild type PTEN.

| Parameter                        | Con 1     | Con 2     | Con 3     | Con 4     | Con 5     | Con 6     | Con 7     | Con 8     | Con 9     | Con 10    |
|----------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Binding energy                    | –4.55     | –4.49     | –4.4      | –4.36     | –4.36     | –4.31     | –4.3      | –4.25     | –4.12     | –3.91     |
| Ligand efficiency                | –0.45     | –0.45     | –0.43     | –0.44     | –0.44     | –0.43     | –0.43     | –0.43     | –0.41     | –0.39     |
| Inhib constant                   | 461.46    | 512.61    | 708.88    | 637.01    | 632.93    | 692.34    | 700.12    | 772.39    | 936.67    | 1.37      |
| Inhib constant units              | uM        | uM        | uM        | uM        | uM        | uM        | uM        | uM        | uM        | uM        |
| Intermol energy                  | –5.45     | –5.38     | –5.19     | –5.25     | –5.26     | –5.21     | –5.2      | –5.14     | –5.03     | –4.8      |
| Vdw_hb_desolv_energy             | –4.85     | –4.85     | –2.53     | –2.99     | –3.03     | –2.47     | –3.49     | –2.67     | –2.79     | –2.53     |
| Electrostatic energy             | –0.59     | –0.54     | –2.66     | –2.77     | –2.73     | –1.71     | –2.47     | –2.24     | 2.27      | 2.27      |
| Total internal                   | 0.77      | 0.72      | 0.7       | 0.65      | 0.63      | 0.69      | 0.59      | 0.65      | 0.6       | 0.6       |
| Torsional energy                 | 0.89      | 0.89      | 0.89      | 0.89      | 0.89      | 0.89      | 0.89      | 0.89      | 0.89      | 0.89      |
| Unbound energy                   | 0.77      | 0.72      | 0.7       | 0.65      | 0.63      | 0.69      | 0.59      | 0.65      | 0.6       | 0.6       |
| Filename                         | a.dlg     | a.dlg     | a.dlg     | a.dlg     | a.dlg     | a.dlg     | a.dlg     | a.dlg     | a.dlg     | a.dlg     |
| cIRMS                            | 43.13     | 43.22     | 44.31     | 54.88     | 54.98     | 44.27     | 48.38     | 44.34     | 49.83     | 44.56     |
| refRMS                           | None      | None      | None      | None      | None      | None      | None      | None      | None      | None      |
| rseed1                           | None      | None      | None      | None      | None      | None      | None      | None      | None      | None      |
| rseed2                           | None      | None      | None      | None      | None      | None      | None      | None      | None      | None      |

Table 2. Parameters with conformation information of Mutated D123 type PTEN.

| Parameter                        | Con 1     | Con 2     | Con 3     | Con 4     | Con 5     | Con 6     | Con 7     | Con 8     | Con 9     | Con 10    |
|----------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Binding energy                    | –4.72     | –4.58     | –4.42     | –4.41     | –4.38     | –4.36     | –4.34     | –4.34     | –4.26     | –4.26     |
| Ligand efficiency                | –0.47     | –0.46     | –0.44     | –0.44     | –0.44     | –0.44     | –0.43     | –0.43     | –0.43     | –0.43     |
| Inhib constant                   | 349.08    | 442.36    | 574.99    | 584.54    | 619.21    | 635.23    | 654.03    | 653.4     | 654.6     | 754.11    |
| Inhib constant units              | uM        | uM        | uM        | uM        | uM        | uM        | uM        | uM        | uM        | uM        |
| Intermol_energy                  | –5.61     | –5.47     | –5.32     | –5.31     | –5.27     | –5.26     | –5.24     | –5.24     | –5.24     | –5.15     |
| Vdw_hb_desolv_energy             | –2.73     | –3.13     | –3.13     | –3.14     | –3.15     | –3.12     | –3.14     | –3.07     | –3.1      | –3.07     |
| Electrostatic energy             | –2.88     | –2.34     | –2.19     | –2.16     | –2.12     | –2.13     | –2.1     | –2.17     | –2.1     | –2.09     |
| Total internal                   | 0.9       | 0.91      | 0.66      | 0.69      | 0.6       | 0.6      | 0.61      | 0.65      | 0.59      | 0.6       |
| Torsional energy                 | 0.89      | 0.89      | 0.89      | 0.89      | 0.89      | 0.89      | 0.89      | 0.89      | 0.89      | 0.89      |
| Unbound energy                   | 0.9       | 0.91      | 0.66      | 0.69      | 0.6       | 0.6      | 0.61      | 0.65      | 0.59      | 0.6       |
| Filename                         | a.dlg     | a.dlg     | a.dlg     | a.dlg     | a.dlg     | a.dlg     | a.dlg     | a.dlg     | a.dlg     | a.dlg     |
| cIRMS                            | 54.14     | 46.96     | 54.11     | 47.49     | 47.52     | 47.49     | 47.52     | 47.26     | 47.46     | 47.51     |
| refRMS                           | None      | None      | None      | None      | None      | None      | None      | None      | None      | None      |
| rseed1                           | None      | None      | None      | None      | None      | None      | None      | None      | None      | None      |
| rseed2                           | None      | None      | None      | None      | None      | None      | None      | None      | None      | None      |

Figure 14. Interacting residues of PTEN (A) Wild type, (B) Mutated by D at 123th position and (C): Mutated by Y at 123th position with TLA displayed through LIGPLOT.
Table 3. Parameters with confirmation information of Mutated Y123 type PTEN.

| Parameter                  | Con 1 | Con 2 | Con 3 | Con 4 | Con 5 | Con 6 | Con 7 | Con 8 | Con 9 | Con 10 |
|----------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------|
| Binding energy             | -4.94 | -4.89 | -4.88 | -4.86 | -4.83 | -4.82 | -4.81 | -4.69 | -4.58 | -4.55  |
| Ligand efficiency          | -0.49 | -0.49 | -0.49 | -0.49 | -0.48 | -0.48 | -0.48 | -0.47 | -0.47 | -0.45  |
| Inhib_constant             | 240.6 | 260.61| 266.16| 273.71| 289.21| 291.93| 297.73| 362.15| 371.25| 460.31 |
| Inhib_constant_units       | uM    | uM    | uM    | uM    | uM    | uM    | uM    | uM    | uM    | uM     |
| Intermol_energy            | -5.83 | -5.78 | -5.77 | -5.76 | -5.72 | -5.71 | -5.71 | -5.39 | -5.57 | -5.45  |
| Vdw_hb_desolv_energy       | -2.89 | -3    | -2.89 | -3.13 | -2.87 | -3.03 | -2.83 | -3.15 | -3.2   | -2.73  |
| Electrostatic energy       | -2.94 | -2.79 | -2.88 | -2.62 | -2.85 | -2.68 | -2.88 | -2.44 | -2.37  | -2.71  |
| Total internal             | 0.83  | 0.63  | 0.67  | 0.76  | 0.66  | 0.61  | 0.7   | 0.65  | 0.65  | 0.63   |
| Torsional energy           | 0.89  | 0.89  | 0.89  | 0.89  | 0.89  | 0.89  | 0.89  | 0.89  | 0.89  | 0.89   |
| Unbound energy             | 0.83  | 0.63  | 0.67  | 0.76  | 0.66  | 0.61  | 0.7   | 0.65  | 0.65  | 0.63   |
| Filename                   | a.dlg | a.dlg | a.dlg | a.dlg | a.dlg | a.dlg | a.dlg | a.dlg | a.dlg | a.dlg  |
| crBMS                      | 0     | 0.76  | 0.97  | 0.77  | 0     | 0.82  | 0     | 0.85  | 0.83  | 0.83   |
| refBMS                     | 50.32 | 50.16 | 50.32 | 50.68 | 59.67 | 49.79 | 44.71 | 50.61 | 43.72 | 44.61  |
| rseed1                     | None  | None  | None  | None  | None  | None  | None  | None  | None  | None   |
| rseed2                     | None  | None  | None  | None  | None  | None  | None  | None  | None  | None   |

at all. The substrate can interact with Lys267 of the mutated D123 containing protein whereas with Lys266 and Lys267 of the mutated Y123 containing PTEN protein.

So, it can be concluded, that though the mutation in H123 leads to some changes in structural conformation but its effect on substrate interaction is very impactful and the phosphatase domain of the mutated protein cannot interact with TLA i.e., the phosphate substrate so the substrate will not be dephosphorylated and this fact leads to the development of the endometrial carcinoma as phosphatase activity of PTEN has been loosed.

Declarations

Author contribution statement

Sunil Kanti Mondal, Madhab Kumar Sen: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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