DOI: 10.7860/JCDR/2023/63221.18000

Review Article

Dentistry Section

Unveiling the Enigma of the Phosphatase and Tensin Gene in Cancer and its Potential Role in Oral Cancer- A Narrative Review

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ABSTRACT

Phosphatase and Tensin Homolog (PTEN) is a tumour suppressor gene that plays a vital role in the normal cell cycle. PTEN acts on the cell via the phosphatidyl-inositol-3-kinase pathway which is involved in the process of cell growth, differentiation, migration, and survival. PTEN is most frequently inactivated in human cancers, because of genetic alterations or transcriptional/post-transcriptional modifications. Literature search was done using the keywords "PTEN in cancer" and "PTEN in Oral Cancer" using Pubmed as the database. This article briefly discusses the multiple features of the PTEN gene and its significance in cancer for improving the understanding of the biology of oral carcinogenesis and the potential for future research in this field.

Keywords: Malignancy, Oral neoplasms, Phosphatidyl-inositol-3-kinase pathway, Tumour supressor gene

INTRODUCTION

Cancer is a significant health issue worldwide and is responsible for a considerable number of deaths. Oral cancer, in particular, is highly prevalent and alarming, especially in India. Despite the vast research conducted on this condition, it remains a major cause of mortality. The incidence and prevalence of oral cancer in the present era have increased from the past due to shifts in lifestyle, thereby changing the environmental factors, the treatment modalities, diagnostic methods, and last but not least demographics. Around 77,000 new cases and 52,000 deaths are reported annually in India, which is approximately one-fourth of global incidences [1]. Oral cancer now occurs in younger individuals as compared to earlier days [2]. Amongst all Oral Squamous cell Carcinoma (OSCC) is the most prevalent type and has multifactorial aetiology encompassing genetic changes and epigenetic factors [3]. It can affect any part of the oral cavity. Chemotherapy, radiotherapy, and surgical management are considered the standard treatments for oral cancer. However, despite the advancements in these treatment modalities, the mortality rate for oral cancer remains high. This could be due to several factors, such as late diagnosis, advanced stage of cancer, metastasis to other parts of the body, and poor response to treatment [4]. Additionally, the side-effects of these treatments can also contribute to the mortality rate, such as weakened immune system, infection, and other complications. Therefore, it is important to continue research and development in the field of oral cancer treatment to improve the outcomes for patients and decrease the mortality rate. Targeted therapy, which is a highlight in many other cancers such as breast cancer, is still ongoing research in OSCC [5].

Oral cancers in human beings have a multitude of genetic changes in every tumour. There are numerous genes involved in the cell kinetics of the human body. Change or mutation in any one of the genes can lead to carcinogenesis. One such gene is a tumour suppressor gene- PTEN. PTEN gene also named Mutated in Multiple Advanced Cancers 1 (MMAC), is the most common "tumour suppressor gene" which is spotted on chromosome '10q23' [6,7]. It tunes the "AKT signaling" pathway which represses apoptosis and advances cell survival. The main function of PTEN is to obstruct this AKT signaling pathway which in turn will suppress cell survival and promote apoptosis. Thus, PTEN will act as a watch guard against the cells which are damaged and need to be removed from the cell cycle [8]. PTEN downregulation is seen in various other cancers such as cancers of breast, prostate, colorectum due to polymorphisms. Gene silencing due to genetic changes and epigenetic modifications of the PTEN gene has also been observed in a group of cancers. Methylation in the promoter region of the PTEN is frequently been observed in cancer of breast, cervix, endometrium, colorectum and brain [9-11].

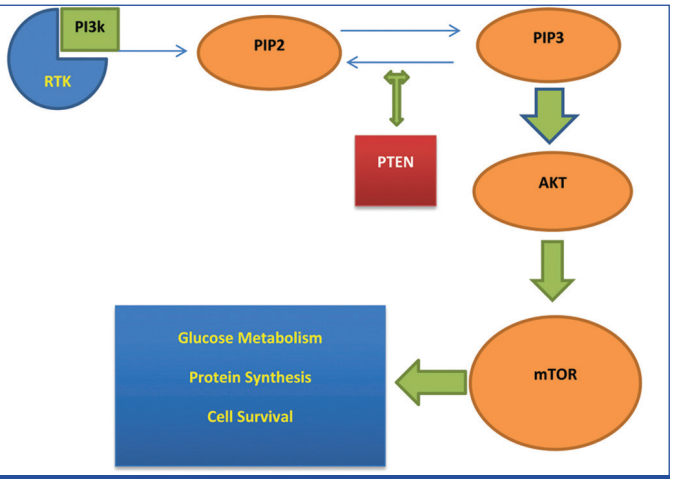
Thus, PTEN methylation may be used as a biomarker for cancer as the loss of PTEN gene is associated with carcinogenesis. PTEN also acts as an essential factor in response to insulin and other growth factors in the cells and is also seen as associated with the process of aging. Somatic PTEN polymorphisms have also been observed to date in many sporadic tumours like breast cancer, prostate cancer and lung cancer [12]. PTEN also has a role in repair mechanism and maintaining the balance of the genome. Studies have witnessed that, PTEN is phosphorylated on Tyrosin (Tyr) 240 in response to De-oxyribonucleic Acid (DNA) damage [13,14]. It then binds to chromatin and enhances the binding of Radiation Absorbed Dose (RAD) 51 to promote DNA repair. This explains the reason why downregulation of PTEN results in resistance to radiotherapy [15].

Pathways of PTEN

PTEN was first detected in 1997 [16]. PTEN deciphers a "dual-specificity protein phosphatase" which is involved in controlling the "phosphatidylinositol 3-kinase (PI3K)/AKT" signaling pathway. PTEN affects cell proliferation by activating G1 arrest in the cell cycle, obstructing cell migration, and persuading cell apoptosis [17]. It is among the three important signaling pathways associated with Receptor Tyrosine Kinase (RTK) activity, along with the protein kinase C and Ras/MAPK pathway. The binding of RTK with the specific receptors activates PI3K pathway and generates an important product-phosphatidylinositol 3,4,5-trisphosphate (PIP3). PTEN is an important regulator of the cellular PI (phosphoinositide) 3-kinase signaling pathway. This AKT pathway regulates the activation of class I "PI 3-kinase" enzymes, activating the second messenger PtdIns P3 (phosphatidylinositol 3,4,5-trisphosphate) from its precursor PtdIns P2 (phosphatidylinositol 4,5-bisphosphate). PtdIns P3 activates downstream signaling by means of a range of effector proteins, including the proto-oncogene product Protein Kinase B (PKB)/Akt, which can identify this lipid and bind it selectively. PTEN antagonises PI 3-kinase signaling by dephosphorylating the 3-position of the inositol ring of PtdIns (3,4,5) P3 and thus inactivating downstream signaling of the pathway [17,18].

The phosphorylation activates serine-threonine PKB, which is also known as AKT, through 3-phosphoinositide-dependent kinase-1. AKT phosphorylation is seen at the T308 position of tyrosine and S473 of serine, causing an immense increase in enzymatic activity. This further activates AKT protein which initiates the transcription of the gene encoding for various proteins such as those involved in glucose metabolism (GLUT4 and hexokinase), protein synthesis (mTOR and ribosomal protein S6), and cell survival (Bcl-2 and Bad), which are involved in many cellular processes.

As a negative regulator of PI3K/Akt/mTOR signaling, and having a tumour-suppressor role, the downregulation of PTEN gene expression can inflict the malignant behaviour of cancer. Increased malignancy of cells after deletion of PTEN is due to unattended activation of the PI3K/Akt signaling pathway. Thus, reduced expression of PTEN can result in carcinogenesis and uncontrolled proliferation and metastasis of cancer cells [Table/Fig-1] [17].



[Table/Fig-1]: Pathway of PTEN function. PTEN blocks the conversion of PIP2 to PIP3 which further prevents the activation of AKT signaling pathway thereby preventing the glucose metabolism, protein synthesis and cell survival.

According to the literature, six important mechanisms are essential for the initiation and progression of cancer. Evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, sustained angiogenesis, tissue invasion and metastasis, and limitless replicative potential [19]. It is noticed that PtdIns(3,4,5)P3 signaling appears to be involved in the regulation of almost all of these mechanisms. One reason for the importance of PTEN in cellular signaling and its tumour suppressor status in many of the tumour types is the lack of functional dissipation. Although other PtdIns(3,4,5)P3 phosphatases have been identified, there are no widely expressed PTEN homologues, and it appears that in many (or most) cell types, PTEN activity has a strong influence on both basal and stimulated PtdIns(3,4,5)P3 levels [13].

With a decrease in PTEN levels, the cancer cells continue to proliferate with more potential to escape the apoptosis. This can be due to the inhibition of glycolysis by PTEN which is involved in the promoted growth of cancer cells [13].

Structure of PTEN

PTEN is a well-known tumour-suppressor gene. There are nine exons on the PTEN gene, and it enciphers a 403-aminoacid protein that has both protein and lipid phosphatase roles and has five functional domains: a) N-terminal phosphatidylinositol 4-5-diphosphate (PIP2)-binding domain; b) phosphatase domain; c) membrane-targeting C2 domain; d) C-terminal tail; and e) a PDZ binding motif. The activities of the gene are controlled by a group of C-terminal phosphorylation (phospho-C-tail) events on Ser380, Thr382, Thr383 and Ser385 by a group of C-terminal phosphorylation (phospho-C-tail) [20,21].

ROLE OF PTEN IN CANCER

PTEN, known as an important tumour suppresser oncogene, involved in the process of cell cycle, growth, and survival of the cells in various tumours, was found by various research teams [21,22]. A decrease in the function of PTEN in cancer can be attributed to decreased synthesis of protein, increased protein breakdown, and post-translational modifications. The function of the most common type i.e., the wild type is regulated by its post-translational modifications. This is due to variation in its localisation at the sub-cellular level, interaction between the proteins, and/or phosphatase activity, irrespective of PTEN accumulation [22,23].

It has been observed that complete absence of the PTEN gene expression is dangerous during development at the embryonic level, and partial suppression results in cancer. PTEN gene has also been studied in the prognosis of cancer. The prognostic significance has been mentioned to be involved in cancer of uterus, breast, prostate, lung, and plasma cells (malignant melanoma) [24-28]. PTEN gene mutation has also been observed in head and neck cancers, especially oral cancers. Shin KH et al., observed point mutation frequency in PTEN gene in approx., 4.65% of cases from which four were due to missense mutations and one due to frame shift mutation in four oral cancers [29].

Shah S et al., on Indian Population has reported that intronic deletions were seen in PTEN gene in three cases, without any statistically significant correlation with gender, tumour size, stage, or grade. In this study, the coding region of the gene did not show any mutations [30]. The survival time was reported to be less in PTEN negative individuals as compared to PTEN positive individuals protein deregulation is more commonly seen in advanced grades and stages of the tumour by Lee JI et al., [7].

PTEN function dysruption is frequently seen in prostate cancer. Many studies have suggested the significant role of PTEN in prostate cancer as a tumour suppressor oncogene [31,32]. It is also significantly correlated with increased expression of B-cell lymphoma-2 (Bcl-2) in glioblastomas [33] and prostate cancer [34]. It has been observed that that loss of PTEN function increases with the stage of the disease and lymph node metastasis. Such patients with loss of PTEN function in cases of prostate cancer show poor prognosis [31]. The simplest way in such cases is to restore the PTEN function. Increasing the dose of PTEN artificially in prostate cancer patients, it is possible to reduce the burden of the tumour by its tumour suppressive activity, thereby drastically improving the prognosis. Therapeutic induction of PTEN in prostate cancer patients is under study. In-vitro studies have been successful wherein nanoparticle-assisted PTEN protein has been introduced in the prostate cancer cell lines which resulted in a decrease in viability of cells [32].

In breast cancer, (primary and secondary tumours), loss of PTEN activity results in limitless transduction of P13K signal. Almost 40%-50% of breast cancer patients have reported a Loss Of Heterozygosity (LOH) at the PTEN loci and about 5%-10% of breast cancer patients reported a loss of PTEN function. The most common type of mutation reported in such cases was the frameshift mutations. Studies have been done in mouse mammary glands which stated that the loss of function of PTEN results in induction of initiation and malignant transformation of breast tumours [20,26]. Polymorphism of PTEN gene at the germline level have also been reported in hereditary syndromes associated with cancer like Cowden's syndrome, thereby increasing the risk for other malignancies like breast cancer, endometrium cancer, thyroid cancer and colorectum cancer. Tumour growth and progression have been reduced by introducing PTEN messenger Ribonucleic Acid (RNA) in tumour models [20].

PTEN IN ORAL CANCER

Though the genetic alteration of PTEN is seldom found in head and neck cancer, it is commonly associated with oral cancer. Gao F et al., reported that the disease-free survival time was more for individuals

who showed a positive PTEN expression in tongue cancer. This implies that the PTEN gene is linked with prognosis of OSCC [35]. Research done on correlation between PTEN gene polymorphism, deleted on chromosome 10 (PTEN) and (OSCC) in the Chinese population showed a positive association between the two [36]. The intronic region of the tyrosine phosphatase domain of the PTEN gene showed 5% somatic mutational frequency. Kurasawa Y et al., conducted a study on correlation of PTEN gene in OSCC individuals as well as in the cell lines, observed statistically significant difference between the expression of OSCC cases and healthy individuals. PTEN expression was decreased in OSCC cases also, mRNA expression using Reverse Trancriptase-Polymerase Chain Reaction (RT-PCR) showed a downregulation in the PTEN gene expression in OSCC cases. But no genetic changes in the PTEN gene in the cell lines could be found. Hence, it was concluded that the decreased expression of PTEN gene could be because of epigenetic factors and is an important factor in carcinogenesis of OSCC [37].

PTEN as a Diagnostic and Prognostic Biomarker for Cancer

Cancer is heterogeneous in nature with varied presentation and progress. Hence, it is essential to identify biomarkers for predictive and diagnostic purposes. PTEN, apart from its prognostic indicator potential, can also help in predicting body's response to various anti-tumour agents. It is also possible that PTEN can also affect tumour micro-environment and immune infiltrate in cancers directly or indirectly along with changing the behaviour of cancer cells [36]. These interactions may result in a permissive or anti-permissive tumour microenvironment. Hence, PTEN plays a vital role to control the overall result of these interactions. Thus, PTEN can be considered as a biomarker for prognostic and diagnostic purposes in various cancers. Though studies have been done concluding the prognostic and diagnostic role as a biomarker, the regulation of this gene is extremely complex, and is difficult to ascertain the absence of the gene or loss of the function of PTEN [36,37].

Immunohistochemistry and immunofluorescence are commonly used to evaluate PTEN protein expression while fluorescent in-situ hybridisation and next generation sequencing) are used to assess the PTEN genomic status [32].

PTEN and Chemotherapy

PTEN deficiency has been reported in chemotherapy-resistant tumours. For example pre-clinical trials have documented the role of PTEN in treatment modules in individual's resistance to the chemotherapeutic drug, Trastuzumab which is frequently used in targeted therapy. This could be attributed to activation of proto-oncogene non-receptor tyrosine protein kinase by de-phosphorylation. It has also been observed that in cases of prostate cancer relapse of the tumour was more common in patients with PTEN loss when compared to those with intact PTEN [38,39].

Studies done on pre-clinical models have suggested that loss of PTEN can cause increased expression of Programmed Cell Death Ligand 1 (PD-L1), which reaffirms the importance of PTEN in modulating the response to immune checkpoint inhibition [40,41]. Artificially increasing PTEN expression by overcoming its transcriptional and post-transcriptional repression is also under investigation and can serve as a remedial avenue for therapeutic intervention to increase PTEN activity. Demethylating agents which are able to restore PTEN expression can also provide a beneficial therapeutic approach for patients with PTEN silencing [40].

PTEN and Immunotherapy

Literature search shows that rearrangement of the immune system of an individual in favour of an anti-cancer microenvironment can show a tremendous improvement in the treatment of various hematological cancers and solid tumours [40,42]. Immunotherapy has been considered a novel method in the treatment of cancer in many cancers showing a remarkable improvement in survival rate. But this success has been observed in research clinical trials, not every patient responds in the same way. This could be due to the reason that various signaling pathways are involved in the process of carcinogenesis [43].

One such pathway is the P13K signaling pathway. This pathway may bring about a difference in the tumour microenvironment which in turn can change the immune response in the treatment of cancer. For a decade a literature has proven the function of PTEN in various cancers in animals [40,44]. A study done by Peng W et al., concluded that loss of PTEN causes an increase in expression of immune-suppression cytokines which in turn results in a decrease in T cell infiltration and apoptosis resulting in decreased T cell-mediated cell death. This reaffirms the association of the role of PTEN in tumour microenvironment and immunity [45]. Thus, changing the level of PTEN in cancer patients will open new potential implications for immunotherapy of cancer [46].

CONCLUSION(S)

Molecular studies have proven the role of PTEN in various cancers and its restoration has a profound effect in the treatment of cancer. More such clinical trials need to be conducted in all types of cancer. PTEN can thus be used as a predictive and prognostic marker. It has good potential in targeted therapy as well. Thus unrevealing the various aspects of PTEN gene suggests that there is immense potential for future research on the therapeutic aspects of this gene.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 04, 2023
- Manual Googling: Apr 12, 2023
- iThenticate Software: Apr 15, 2023 (10%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 02, 2023**
Date of Peer Review: **Mar 25, 2023**
Date of Acceptance: **Apr 17, 2023**
Date of Publishing: **Jun 01, 2023**