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Review

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Role of PTEN Gene in Genetic Alterations in Endometrioid Carcinoma

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Abstract

Endometrioid (type I endometrial) carcinoma is the most prevalent form of endometrial cancer and is strongly associated with genetic alterations, particularly involving phosphatase and tensin homolog (PTEN) gene. PTEN protein is a crucial component of the protein kinase B (PKB)/Akt signaling pathway, which plays a significant role in regulating cell cycle arrest and inducing apoptosis. The loss or mutation of PTEN can disrupt this pathway, contributing to uncontrolled cell proliferation and cancer progression. Recent studies indicate that PTEN genetic alterations are not limited to mutations or loss of expression but also involve complex variations such as gene deletions, structural changes, and diverse regulatory disruptions. Genetic alterations involving PTEN are frequently observed in endometrioid-type endometrial carcinomas, particularly in tumors that develop from premalignant lesions. These alterations, whether mutations, deletions, or reduced expression, significantly disrupt the regulation of cell growth and key signaling pathways, thereby driving tumor initiation and progression. By providing a more integrated understanding of the multifaceted genetic changes in PTEN, this review highlights emerging opportunities for early detection, refined risk stratification, and the advancement of gene-targeted therapeutic strategies specifically for the endometrioid subtype of endometrial cancer.

Keywords carcinogenesis, endometrioid carcinoma, PTEN mutations, targeted therapies, tumor suppressor genes

Introduction

Endometrial carcinoma is a malignancy of the female reproductive system that originates from primary tumors in either the ovary or endometrium (Zheng, 2023). Carcinogenesis of endometrial cancer is closely associated with endometriosis, a benign disorder of the female reproductive system. Endometriosis is defined as the presence of endometrial glands and stroma outside their normal location (the uterus) (Mahdy *et al.*, 2024; Zheng, 2023). Based on the clinical and clinicopathological characteristics, endometrial carcinoma is classified into two types: endometrioid endometrial carcinoma (EEC, type I) and non-endometrioid carcinoma (type II) (Zheng, 2023).

The majority of endometrial cancer cases (75%–80%) are classified as endometroid (type I) endometrial carcinoma (Zheng, 2023). The type I is more commonly diagnosed in premenopausal or perimenopausal women and is influenced by estrogen, which is often associated with endometrial hyperplasia with atypia (Abdol Manap *et al.*, 2022; Burleigh *et al.*, 2015). Histologically, nearly all type I cancers arise from endometrial hyperplasia, exhibit endometrioid differentiation, and are considered to be low-grade tumors (Brooks *et al.*, 2019). Clinically, this type of cancer is well characterized. In contrast, non-endometrioid (type II) endometrial carcinoma, which accounts for 10%–20% of all endometrial cancer cases, is unrelated to the estrogen pathway and originates from the atrophic endometrium. This subtype typically occurs in older women (Ebring *et al.*, 2023).

In Indonesia, endometrioid (type I endometrial) carcinoma is also the most common form of endometrial cancer, making up around 75%–80% of all cases (Hidayati *et al.*, 2021). Reports from several hospitals in the country

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show that this cancer is often diagnosed in relatively young postmenopausal women and is typically detected at early clinical stages, which generally provides a better chance for successful treatment. Many patients also have low-grade tumors, which tend to have a more favorable prognosis (Hutapea *et al.*, 2024). These patterns highlight the importance of early detection and careful clinical assessment to improve patient outcomes of endometrial cancer in Indonesia.

Carcinogenesis of endometrial carcinoma is a complex process involving epigenetic and genetic alterations, including accumulated defects in growth control pathways, abnormalities in oncogenes, tumor suppressor genes, and genes involved in DNA repair (Banno *et al.*, 2014). Mutations affecting tumor suppressor genes, such as PIK3R1, PIK3CA, and PTEN, are among the most common genetic alterations (Urick & Bell, 2019).

PTEN undergoes homozygous deletion mutations in various carcinomas, including nasopharyngeal, prostate, and breast cancers (Carbognin *et al.*, 2019; Y. Chen *et al.*, 2024; Zhou *et al.*, 2019). PTEN mutations are detected in over 77% of endometrial carcinoma cases, particularly in the endometroid carcinoma (Bianco *et al.*, 2020). PTEN is not only the most frequently mutated gene in endometrial carcinoma but also has one of the highest mutation frequencies among primary tumors. Inactivation of the PTEN tumor suppressor gene (formerly known as MMAC1) is observed in up to 83% of tumors originating from distinct premalignant phases. PTEN mutations occur in 20%–33% of atypical endometrial hyperplasia cases and 33%–50% of endometrial cancer cases, indicating PTEN's role in the early stages of carcinogenesis (Manning-Geist *et al.*, 2021; Tashiro *et al.*, 1997).

This review aimed to elucidate the role of PTEN in the genetic alterations involved in the carcinogenesis of endometrioid carcinoma. A deeper understanding of PTEN involvement in carcinogenesis may contribute to the prevention and diagnosis of endometrial cancer, risk assessment, and the development of targeted therapies for mutated genes in type I endometrial carcinoma.

Endometrial carcinoma

Prevalence and risk factors

Endometrial cancer is the 15th most common cancer globally and the 6th most common cancer among women worldwide. In 2019, 435,041 new cases of endometrial cancer and 91,641 related deaths were reported globally (Sung *et al.*, 2021). Endometrial cancer also has a high prevalence in Indonesia. According to GLOBOCAN 2022, 8,384 new cases and 2,454 deaths (18% of total endometrial cases) have been reported in the country (Bray *et al.*, 2024).

Risk factors for this cancer include excessive estrogen exposure, use of tamoxifen-class drugs, age at menarche, late menopause, weight gain, obesity, metabolic syndrome, and family history (PDQ Screening and Prevention Editorial Board, 2023). Although many of these risk factors have been identified, the etiology of endometrial cancer continues to evolve. It is a complex disease that can develop from genetic and epigenetic alterations as well as environmental factors. Recently, various studies have highlighted the critical role of genetic alterations in regulating gene expression during carcinogenesis (Urick & Bell, 2019).

Type of endometrial carcinoma

According to The International Federation of Gynecology and Obstetrics (FIGO) system, this cancer is staged from stage I to IV, reflecting disease severity based on histological type, tumor pattern, and molecular classification (Berek *et al.*, 2023). Early-stage disease is the most common, with a 5-year overall survival (OS) rate of 81%; however, for stage IVA and IVB endometrial cancer, the 5-year OS decreases to only 17% and 15%, respectively (Bartosch *et al.*, 2015). Endometrial cancer can be classified into two types, endometrioid endometrial carcinoma (EEC, type I) and non-endometrioid endometrial carcinoma (type II), based on histological and molecular characteristics, and prognosis (Mahdy *et al.*, 2024; Zheng, 2023).

Endometrioid carcinoma

Endometrioid carcinoma is the most common type of endometrial cancer, accounting for 70%–80% of cases (Berek *et al.*, 2023). Type I tumors are morphologically characterized by high-to-moderate levels of differentiation and superficial myometrial invasion. This subtype is progesterone-sensitive and is generally associated with a better prognosis than type II (Mahdy *et al.*, 2024).

The endometrium is a classical target tissue for ovarian steroid hormones, such as estrogen and progesterone, both of which play crucial roles in the pathogenesis of EEC (Bartosch *et al.*, 2015). Estrogen promotes EEC growth, whereas progesterone inhibits it. These hormones act via their respective receptors located in the cell nucleus. The loss of estrogen and progesterone receptor expression is associated with more aggressive cancer phenotypes and lower survival rates. One of the mechanisms responsible for receptor expression is promoter hypermethylation. Additionally, variations in the expression of estrogen receptor subtypes (ERα and ERβ) as well as differences in progesterone receptor isoforms (PR-A and PR-B) also influence changes in endometrial cell proliferation and differentiation (Odetola *et al.*, 2020).

Carcinogenesis of endometrioid carcinoma

The most common type, endometrioid carcinoma (type I), arises from endometrial hyperplasia caused by excessive estrogen exposure. By contrast, non-

endometrioid/serous endometrial cancer (type II) is not associated with estrogen levels and is thought to originate from atrophic epithelial cells. Some studies have indicated that type II endometrioid carcinoma develops from endometrial intraepithelial carcinoma lesions, resulting from malignant transformation of the endometrial surface epithelium (Banno *et al.*, 2014; Sherman, 2000).

At the molecular level, type I endometrial carcinoma is commonly associated with microsatellite instability (MSI) and mutations in several genes, including PTEN, K-ras, and β-catenin. On the other hand, mutations in type II endometrial carcinoma are more frequently linked to oncogene HER-2/neu and p53 tumor suppressor gene mutations (**Figure 1**). In addition to these gene mutations, retinoblastoma protein (pRb) and cyclins may be involved in endometrial cancer carcinogenesis. Cyclins are proteins that regulate the cell cycle by interacting with cyclin-dependent kinases (CDKs) and are often overexpressed in endometrial cancer (Chen *et al.*, 2020). Unphosphorylated pRb inhibits cell proliferation during the G0 and early G1 phases of the cell cycle. However, when phosphorylated by the cyclin-CDK complex, pRb releases E2F transcription factor, which enhances DNA polymerase activity and promotes cell proliferation (Banno *et al.*, 2014; Sherman, 2000).

Endometrioid carcinoma is often associated with atypical endometrial hyperplasia (AEH). AEH acts as a precursor lesion in most type I endometrial carcinoma cases (Chou *et al.*, 2024). The similarity between the morphology of AEH and type I endometrial carcinoma suggests a pathogenic relationship between these two lesions. Studies have shown that these two lesions share similar immunohistochemical and molecular markers (Kandoth *et al.*, 2013; Sherman, 2000).

The progression of endometrial hyperplasia to endometrial carcinoma is influenced by estrogen exposure, which leads to uncontrolled proliferation (Yang *et al.*, 2019). This proliferation is not only due to increased cellular growth stimulation, but also results from the loss of suppressive factors and regulators of cell proliferation, along with alterations in apoptosis, all of which play significant roles in carcinogenesis (Sherman, 2000). In addition to estrogen exposure, mutations in mismatch repair (MMR) genes have been shown to increase the risk of progression from endometrial hyperplasia to endometrioid carcinoma (Vierkoetter *et al.*, 2016). The proposed diagram of the carcinogenesis pathway of endometrioid carcinoma is shown in **Figure 2**.

Genetic alterations in carcinogenesis of endometroid carcinoma

Research on genetic mutations in endometrial hyperplasia and endometrial cancer has identified several gene mutations that are suspected to play a role in the carcinogenesis of endometrioid carcinoma (**Figure 3**). Genetic mutations found in endometrioid carcinoma include PTEN, β-catenin, and Kirsten rat sarcoma virus (KRAS), which encodes the K-ras protein (Gbelcová *et al.*, 2022; Kilowski *et al.*, 2024; Parrish *et al.*, 2022). PTEN is a tumor suppressor gene located on chromosome 1 and has been identified as a disease-causing gene in three autosomal dominant disorders (Cowden disease, Lhermitte-Duclos disease, and Bannayan-Zonana syndrome). PTEN inactivation has also been observed in malignant melanoma, brain tumors, and various cancers of the endometrium, ovaries, thyroid, breast, and prostate. The PTEN protein induces apoptosis, and in cells with PTEN mutations, carcinogenesis occurs due to impaired apoptosis. PTEN mutations are found in 20%–33% of atypical endometrial hyperplasia cases and 33%–50% of endometrial cancer cases, indicating PTEN's involvement in early carcinogenesis (Banno *et al.*, 2014). However, studies have shown that using PTEN as a biomarker for carcinogenesis via immunohistochemistry is limited in distinguishing between benign and premalignant endometrial hyperplasia (Raffone *et al.*, 2019).

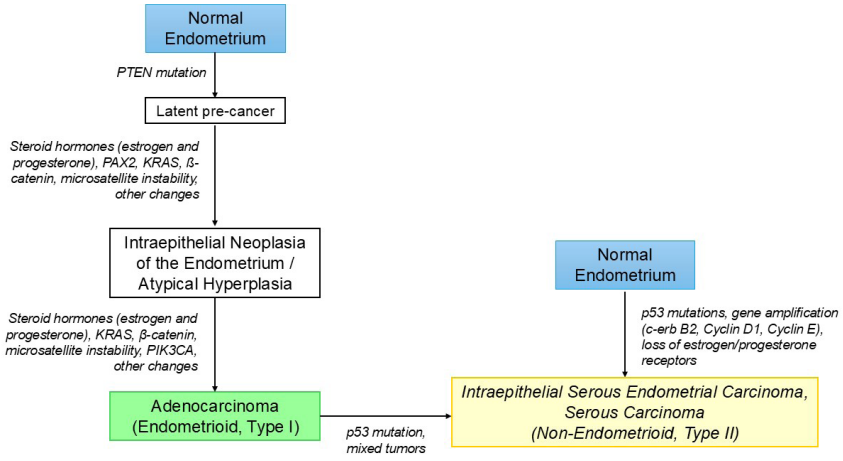

Figure 1 Molecular alterations during endometrial carcinoma carcinogenesis according to their histopathological type.

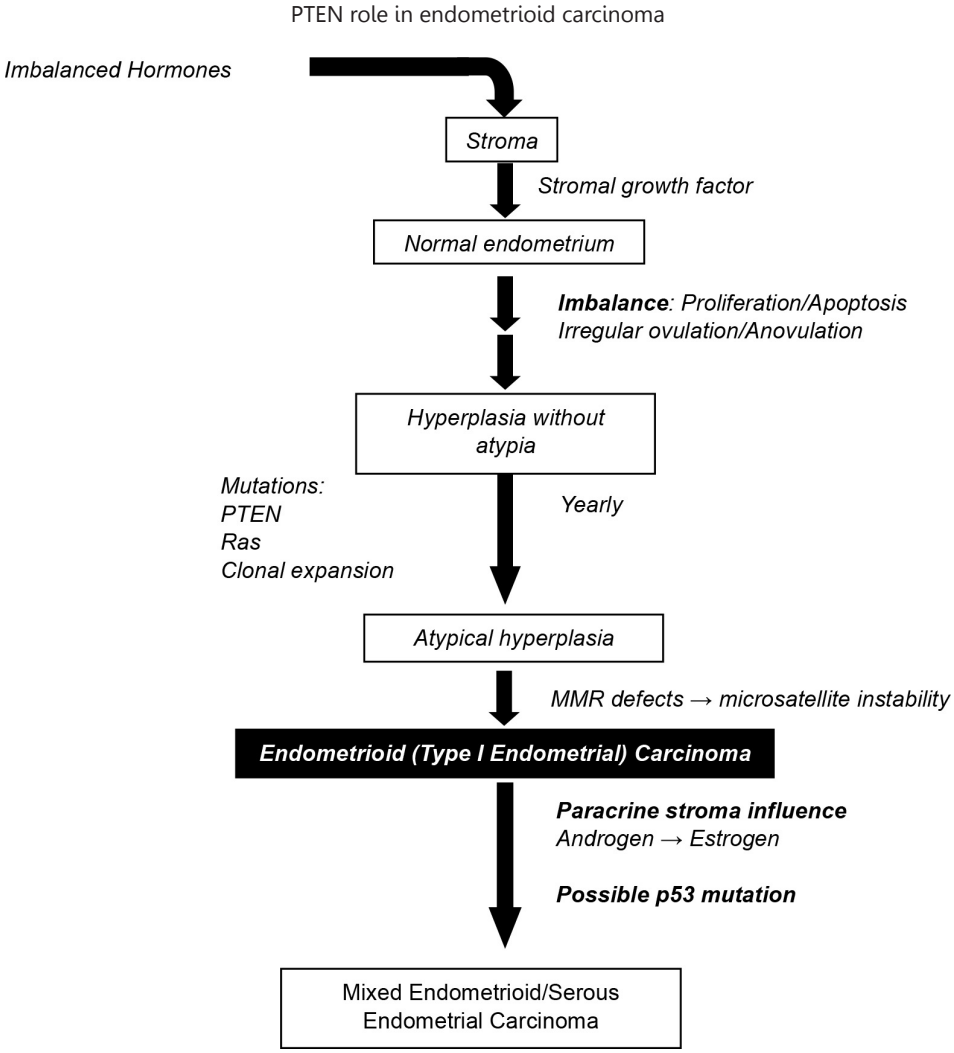

Figure 2 Diagram showing the progression of endometrioid (type I endometrial) carcinoma. Hormonal imbalance and stromal signals trigger abnormal cell growth in the endometrium. Mutations (e.g., PTEN, Ras) and MMR defects lead from hyperplasia to atypical hyperplasia, then to cancer. Late changes may include p53 mutations, resulting in mixed tumor types.

β-catenin (CTNNB1) mutations are also found in 20%–40% of endometrioid carcinoma cases (Parrish *et al.*, 2022; Schlosshauer *et al.*, 2000). β-catenin protein is a component of the E-cadherin/β-catenin complex involved in cell adhesion and the Wnt signaling pathway, which regulates cell proliferation and differentiation. Mutation of β-catenin can prevent its degradation, resulting in the elevated transcription of β-catenin target genes. These mutations are also present in atypical endometrial hyperplasia, indicating that β-catenin mutations occur during the early stages of carcinogenesis (Parrish *et al*., 2022).

The KRAS oncogene encodes a 21-kDa protein involved in signaling from membrane receptors via the MAPK pathway. Mutations in *K-ras* lead to Ras activation, which causes excessive proliferative signaling and promotes carcinogenesis. K-ras mutations are found in 6%–16% of endometrial hyperplasia cases and 10%–31% of endometrial cancer cases (Sideris *et al.*, 2019). A previous study suggested that K-ras plays a role in two stages of carcinogenesis: the transition from endometrial hyperplasia to endometrial cancer and the invasive proliferation of well-differentiated tumor cells (Tsuda *et al.*, 1995).

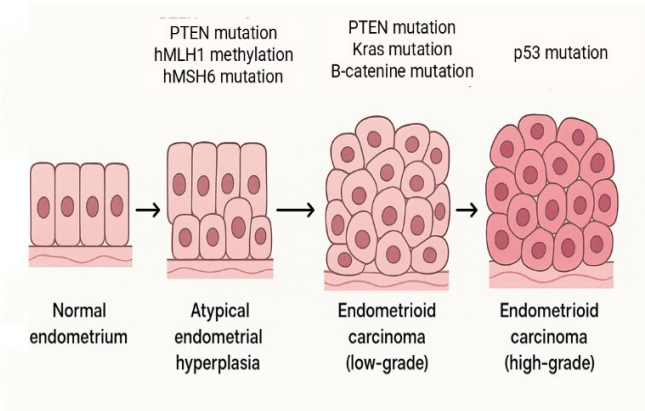

Figure 3. Genetic alterations and histopathological changes in endometrial carcinoma.

PTEN gene

The phosphatase and tensin homolog (PTEN) gene is a well-established tumor suppressor located on chromosome 10q23.31, consisting of 10 exons (Shi *et al.*, 2012). This gene encodes a 53-kDa protein that is homologous to tensin and protein tyrosine phosphatase (PTP) and functions enzymatically as phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase (PI3P). PTEN is broadly expressed in almost all human tissues and plays a critical role in the regulation of cell growth and survival. Its primary function is to negatively regulate the protein kinase B (PKB)/Akt signaling pathway, which is essential for controlling cell cycle arrest and apoptosis (National Center for Biotechnology Information (NCBI), 2024). Disruption of PTEN function can lead to unregulated cell proliferation and contribute to the development of cancer.

The PTEN gene, also known as the "phosphatase and tensin homolog deleted on chromosome ten," contains several important structural regions. Among these, exon 5 holds particular significance, as mutations or alternative splicing events involving this exon have been associated with both neurodevelopmental disorders (NDDs) and increased cancer risk. Isoforms lacking exon 5 are commonly linked to NDD-specific mutations (Jang *et al*., 2023). In addition, PTEN produces several isoforms through alternative translation initiation, including PTENβ, which is translated from an upstream AUU codon, and PTENα, which originates from a CUG codon. These isoforms can influence PTEN localization and specific cellular functions (Zhao *et al.*, 2017).

PTEN itself is composed of several functional domains that contribute to its tumor-suppressive activity (Molinari & Frattini, 2014). The phosphatase domain (PTP) contains a catalytic active site that is critical for its enzymatic function, whereas the C2 domain is essential for membrane binding and maintaining protein stability. PTEN possesses a protein-binding domain (PBD) near its C-terminal region, which mediates interactions with other proteins and supports the regulation of complex cellular processes. Mutations are frequently clustered in the phosphatase domain, potentially disrupting the loop conformation and reducing catalytic activity, whereas alterations in the C2 domain may impair PTEN's ability of PTEN to associate with cellular membranes (Wise *et al.*, 2016). Changes in PBD may interfere with protein-protein interactions, which are essential for proper signaling regulation. PTEN activity is further modulated by post-translational modifications, such as ubiquitination and SUMOylation, which can influence its localization, stability, and functional capacity (Smith & Briggs, 2016). Missense mutations affecting PTEN may compromise its protein stability, alter its electrostatic surface potential, or reduce its catalytic efficiency, all of which can contribute to disease development.

Within the cell, PTEN is predominantly localized in the cytoplasm and plasma membrane, where it dephosphorylates PIP3 and serves as a key antagonist of PI3K/AKT signaling (Jang *et al.*, 2023). Interestingly, some PTEN isoforms, such as PTENβ, display distinct localization patterns that are primarily concentrated in the nucleolus, where they are involved in the regulation of ribosomal DNA transcription and biogenesis (Zhao *et al.*, 2017). PTEN expression and the distribution of its isoforms can vary among tissues, which may contribute to differences in disease characteristics and clinical outcomes across various organ systems.

PTEN gene polymorphisms

PTEN is widely recognized as a critical tumor suppressor involved in regulating essential cellular processes, including proliferation, apoptosis, and genomic stability. Disruptions in PTEN function, through genetic mutations, epigenetic silencing, or protein-level alterations, are frequently implicated in the development of various cancers, including endometrioid-type endometrial carcinoma. Although much of the research has focused on well-characterized PTEN alterations, such as mutations and gene deletions, other forms of genetic variation, including single nucleotide polymorphisms (SNPs) and copy number variations (CNVs), also play a role in disease susceptibility and may influence clinical outcomes.

SNPs of the PTEN gene represent single base-pair changes in the DNA sequence, some of which are missense mutations that can alter the amino acid sequence of the PTEN protein and potentially affect its function. Certain SNPs in PTEN have been associated with an increased cancer risk. For example, rs701848 (CC) and rs2735343 (GG) are associated with a higher risk of various cancers, whereas rs11202586 is specifically associated with testicular germ cell tumors (Brahmaiah *et al.*, 2025; Song *et al.*, 2017). Additionally, rs121909218 (G129E), rs121909229 (R130Q), and rs57374291 (D107N) are associated with breast cancer and are believed to influence PTEN stability (Brahmaiah *et al.*, 2025). Another variant, rs3830675, has been implicated in colorectal carcinomas, particularly in individuals with specific lifestyle factors (Brahmaiah *et al.*, 2025). In silico analyses further suggested that many missense SNPs in PTEN may be deleterious, potentially impairing protein stability and function. However, large-scale studies indicate that common PTEN SNPs may not significantly impact the susceptibility or aggressiveness of certain cancers, such as prostate cancer, suggesting that not all germline SNPs in PTEN are clinically relevant across all tumor types, and the clinical significance can vary depending on the specific SNP and tumor type (Kim *et al.*, 2025; Yehia *et al.*, 2020).

In addition to SNPs, copy number variations (CNVs) involving PTEN are another layer of genetic alterations that may affect disease outcomes. CNVs are structural variations characterized by duplication or deletion of genome segments, which can influence gene dosage and function. In the context of neurodevelopmental disorders, increased CNV burden in individuals with PTEN mutations has been associated with a higher risk of autism

spectrum disorder (ASD) and developmental delay (DD) compared to those with PTEN mutations who present with either cancer or no additional clinical features (Kim *et al.*, 2025). Interestingly, some studies have found no significant association between PTEN CNVs and cancer risk in certain populations such as large prostate cancer cohorts. However, CNVs may serve as genomic modifiers that help explain the variable clinical presentations observed in PTEN hamartoma tumor syndrome (PHTS), influencing whether a PTEN mutation predisposes an individual to neurodevelopmental disorders or cancer (Yehia & Eng, 2021). Clinical genetic testing for PTEN-related syndromes increasingly incorporates both CNV analysis and sequencing to capture a more comprehensive view of the genetic alterations involved.

Role of PTEN in genetic alterations in carcinogenesis of endometrioid carcinoma

PTEN (phosphatase and tensin homolog) is a gene located on chromosome 10q23.31 that encodes the protein PI3P (phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase), which functions as a tumor suppressor. This protein is found in almost all human tissues and plays a role in halting cell division and triggering apoptosis. Additionally, signaling pathways involving PTEN help regulate cell migration, cell adhesion, and angiogenesis and protect genetic information, thus preventing uncontrolled cell growth that could lead to tumors (Massachusetts General Cancer Center, 2023; NCBI, 2024).

PTEN is homologous to dual-specificity phosphatases, meaning that it functions as both a protein and lipid phosphatase (Tu *et al.*, 2020). PTEN dephosphorylates the enzymatic products of phosphoinositide 3-kinase (PI3K), acting as an antagonist of the PI3K/Akt signaling pathway (NCBI, 2024). When activated, PTEN acts as a tumor suppressor via the PI3K/Akt pathway, arresting the cell cycle at the G1 phase in some cell types and inducing apoptosis in others. PTEN protein phosphatase activity inhibits focal adhesion formation, cell spreading and migration, as well as the Mitogen-Activated Protein Kinase (MAPK) signaling pathway triggered by growth factors (Bansal *et al.*, 2009).

Mutations in PTEN that impair its lipid phosphatase activity can disrupt cell cycle arrest or alter PTEN growth-suppressing function. PTEN-induced cell cycle inhibition depends on suppression of the PI3K/Akt pathway. In addition to its main role as a tumor suppressor, PTEN also acts as a metabolic regulator via the insulin/PI3K/AKT signaling axis (Ortega-Molina *et al.*, 2012). The PI3K/PTEN/Akt pathway regulates the cell cycle. Studies have shown that Akt is involved in the regulation of Cyclin D1 and E2F activities (Chen et al., 2020; Jiao et al., 2016). Other studies have found that restoring PTEN expression in PTEN-deficient glioblastoma cells increases Cdk inhibitor p27 and decreases Cdk2 kinase activity (Mamillapalli *et al.*, 2001). These findings suggest that PTEN regulation of p27 may reduce G1-phase kinase activity, which is necessary for S-phase entry (Kurose *et al.*, 2001; Vazquez & Sellers, 2000). These data support PTEN's important role of PTEN in cell cycle regulation through the PI3K/Akt pathway. However, the specific relationship between PTEN, Akt, and p27, and cell cycle kinetics is not yet fully understood.

Several studies have highlighted the critical role of Akt in sustaining cell survival, making the identification of apoptosis-promoting proteins as Akt phosphorylation targets particularly important. Akt inhibits anoikis, a form of apoptosis that occurs when cells detach from the extracellular matrix (Kim *et al.*, 2012). This type of cell death likely plays a key role in preventing the invasion or metastasis of epithelial tumor cells. The anti-apoptotic properties of Akt suggest that the loss of PTEN expression may affect cell survival. Thus, PTEN can inhibit cell growth by regulating apoptosis or cell cycle progression. However, at the molecular level, both actions require suppression of the PI3K/Akt pathway.

Somatic PTEN mutations are the most frequent genetic mutations in cancer. These mutations can produce defective proteins that lose their function as tumor suppressors. Loss of PTEN expression is also one of the mechanisms that reduces PTEN activity, leading to activation of the PI3K/Akt pathway (Molinari & Frattini, 2014). Unlike typical protein tyrosine phosphatases, PTEN primarily catalyzes dephosphorylation reactions on phosphoinositide substrates and functions as a tumor suppressor by inhibiting the PI3K/Akt pathway.

The PI3K/Akt pathway is frequently activated in endometrial cancer owing to mutations. PI3K, Akt, and β-catenin genes are activated when PTEN and p53 genes are inactivated. Activation of the PI3K/Akt pathway can lead to increased cell growth via mTOR, enhanced transcription via β-catenin, and reduced apoptosis owing to p53 inactivation (Chen *et al.*, 2014; Vazquez & Sellers, 2000). Upregulation of pro-apoptotic mechanisms involving Akt-dependent pathways is mediated through PTEN, whereas downregulation of anti-apoptotic mechanisms occurs via B-cell lymphoma 2 (BCL-2) (Kurose *et al.*, 2001).

Further implication of PTEN alterations

PTEN is a tumor suppressor that catalyzes the conversion of PIP3 to PIP2, thereby counteracting PI3K function. PTEN-inactivating mutations are the most common mutations in endometrial cancer. These mutations produce nonfunctional PTEN protein, leading to increased PIP3 and activation of the PI3K/Akt pathway. However, PTEN mutations account for only a small fraction of cases of PTEN protein loss. Loss of PTEN protein (64%) was more frequent in endometrial cancer cases than PTEN sequence abnormalities (43%) (Djordjevic *et al.*, 2012). PTEN sequence abnormalities (51%) and protein loss

(75%) are more common in endometrioid carcinomas than in non-endometrioid carcinomas. Poorly differentiated endometrioid carcinomas have an even higher proportion of PTEN sequence abnormalities (60%) and protein loss (80%) than other non-endometrioid subtypes. Among cases with wild-type PTEN sequences, 44% of patients with endometrial cancer show reduced PTEN protein expression (Chen *et al.*, 2014; Djordjevic *et al.*, 2012).

Loss of PTEN expression increases Akt phosphorylation, alters downstream protein targets, promotes cell proliferation, and inhibiting apoptosis. PTEN deficiency is associated with genomic instability, which is a major cause of carcinogenesis. The causal relationship between PTEN mutations and endometrial cancer has been demonstrated in animal models such as PTEN knockout mice, where this deficiency leads to estrogen-independent endometrial cancer development (Kim *et al.*, 2010a). Inactivation of the tumor suppressor gene PTEN, which is frequently found in endometrioid carcinomas, plays a significant role in carcinogenesis. Heterozygous PTEN inactivation in mice results in abnormal endometrial phenotypes, with 100% of mice developing hyperplastic lesions, of which 20% progress to endometrial carcinoma (Joshi *et al.*, 2012). PTEN inactivation can occur through various mechanisms, including mutations or deletions causing loss of heterozygosity on chromosome 10q23, detected in 37%-61% of all cancer cases and found in 40% of endometrial cancer cases (Li *et al.*, 2005; Pallares *et al.*, 2005).

PTEN mutation patterns differ between microsatellite instability (MSI)-positive and microsatellite-stable tumors. Microsatellites are stable DNA repeat units used as molecular markers, whereas mismatch repair (MMR) gene defects can lead to genomic instability, detectable as changes in microsatellite length (MSI) (Hecht & Mutter, 2006). MSI-positive tumors exhibit a higher frequency of deletions, particularly those involving more than three base pairs, than compared to MSI-negative tumors. Additionally, mutations in MSI tumors typically do not involve polyadenine repeats in exon 8, which is a microsatellite marker (Cohn *et al.*, 2000). However, the exact mechanism underlying MSI changes remains unclear. Thus, the impact of PTEN inactivation is not limited to specific mutations but plays a significant role in overall carcinogenesis.

Further implications of PTEN inactivation become clear when considered along with other common mutations in endometrioid carcinoma. The most frequent PTEN mutation is allelic inactivation, which leads to loss of protein function. Evidence suggests that PTEN inactivation, which causes protein deficiency, may have functional significance, particularly when combined with abnormalities in other downstream genes. PTEN balances phosphatidylinositol-3-kinase (PIK3CA) levels to regulate phosphorylated PKB/Akt levels. PIK3CA mutations are among the most common in endometrioid endometrial carcinoma, with a prevalence of 36%, and are more frequent in tumors with concurrent PTEN mutations (Oda *et al.*, 2005). This suggests a synergistic effect driving the neoplastic transformation.

PTEN mutations exhibit synergistic effects with other genetic mutations in endometrioid carcinoma carcinogenesis. Previous study demonstrated that Mig-6 has a synergistic effect with PTEN deficiency (Kim *et al.*, 2010a). Another epidemiological study found that endometrial cancer patients with both PTEN and TP53 mutations had a poorer prognosis than those with single PTEN or TP53 mutations (Janiec-Jankowska *et al.*, 2010). Additionally, loss of PTEN combined with oncogenic K-Ras mutations accelerates endometrial cancer progression and enhances tumor aggressiveness (Kim *et al.*, 2010b). These findings indicate that PTEN mutations not only interact synergistically with other genetic mutations, but also engage with other proteins in endometrioid carcinoma carcinogenesis, opening avenues for further research into the molecular mechanisms of this disease.

Conclusion

PTEN is a well-known tumor suppressor that regulates cell growth and division by controlling apoptosis and the cell cycle through the PI3K/PTEN/Akt signaling pathway. When PTEN function is impaired through mutations, gene deletions, or decreased expression, this balance is disrupted. Consequently, abnormal signals can encourage uncontrolled cell proliferation and prevent cells from undergoing natural cell death. Loss of PTEN is also closely associated with genomic instability, which plays a major role in the development and progression of cancer. PTEN alterations are frequently found in endometrioid carcinoma and are believed to be one of the primary drivers of the disease. These changes can occur in many forms, all of which contribute to the ability of PTEN to regulate cell growth. Thus, PTEN is a central factor in the early development and continued progression of endometrioid carcinoma. Research and understanding of PTEN gene involvement in carcinogenesis can be applied in endometrial cancer prevention and diagnosis, risk assessment, and the development of treatment strategies targeting other mutated genes in endometrioid carcinoma.

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Author contribution RSF collected the data, described the data, and wrote the article.

Declaration of generative AI in writing process During the preparation of this manuscript, the author used ChatGPT to generate schematic cell images for Figure 3. After using this tool, the author reviewed and edited the content as needed, and took full responsibility for the content of the published article.

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