Biology of PEST-containing nuclear proteins as potential targets in ovarian cancer (Review)

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Abstract. Ovarian cancer (OC) is the deadliest gynecological malignancy, with a 5-year survival rate of 47%, primarily due to late diagnosis and platinum resistance. Although patients with OC often exhibit an initial clinical response to platinum-based chemotherapy, they typically develop resistance to platinum, posing a significant clinical challenge. Therefore, identifying effective biomarkers and potential therapeutic targets is critical. The PEST amino acid sequence, which comprises proline (P), glutamic acid (E), serine (S) and threonine (T), functions as a structural recognition motif for the cellular degradation machinery and modulates post-translational modifications (PTMs) of nuclear proteins (NPs), regulating their activation, localization and stability. PEST sequence-enriched NPs (PEST-NPs) act as oncogenes or tumor suppressors and influence cancer metabolism, immunity and transcription, and are thus potential therapeutic targets. The present review highlighted the multifaceted roles of PEST-NPs in types of OC, focusing on how PTMs of PEST domains mediate the activation, localization and stability of PEST-NPs. PTMs regulate the stability, activation and intracellular localization of PEST-NPs, thereby driving OC initiation, progression and chemoresistance. The present review also highlighted related

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Abbreviations: OC, ovarian cancer; PEST, proline, glutamic acid, serine, threonine; PTMs, post-translational modifications; NPs, nuclear proteins; ROS, reactive oxygen species; PCNP, PEST-containing NP; PUMA, p53 upregulated modulator of apoptosis; MDM2, mouse double minute 2; NLSs, nuclear localization sequences; STAT3, signal transducer and activator of transcription 3; HGSOC, high-grade serous OC; DBD, DNA-binding domain; CTD, carboxyl-terminal domain; WT, wild-type; PI3K, phosphatidylinositol 3-kinase; HTH, helix-turn-helix; EOC, epithelial OC; NSCLC, non-small cell lung cancer

Key words: PEST sequence, nuclear proteins, PCNP, ovarian cancer, therapeutics

hallenges and opportunities, including future research to facilitate the translation of PEST-NP-based OC diagnostics and therapies from the laboratory to the clinic. Future research insights will further support the development of diagnostic and therapeutic approaches for OC based on NPs, facilitating their translation from laboratory settings to applications.

Contents

1. Introduction

OC is associated with the highest mortality rates among female reproductive system malignancies, with a 5-year survival rate of ~47% (1,2). Annually, there are >239,000 new cases of OC worldwide and 152,000 deaths. Only 15% of cases of OC are diagnosed clinically early, and the majority of patients are already diagnosed with metastatic tumors upon receiving an OC diagnosis, thereby exacerbating their unfavorable prognosis and elevated mortality rate. Most cases of OC are treated with surgery and cytoreduction (3); however, in this context, drug resistance arising from repeated therapy may no longer explain the low 5-year survival rates. In particular, OC enhances chemotherapy resistance through its antioxidant capacity by upregulating multiple key antioxidant systems, such as NAD(P)H oxidoreductase 1 (4), the SLC7A11/xCT antiporter (5) and the NRF2 pathway (6), which can prevent the formation of harmful reactive oxygen species (ROS) induced by chemotherapy, particularly platinum-based therapies such as cisplatin. Therefore, investigating new and potent biomarkers of OC tumors, as well as elucidating the molecular mechanisms driving cancer metastasis, is imperative to develop more targeted therapeutic strategies for OC (7).

NPs are known to both contribute to and inhibit the growth of cancer cells by controlling the cell cycle (8), stem cell development (9), exercise metabolism (10), the immune response (11) and DNA damage and repair (12,13). Post-translational modifications (PTMs) of these proteins, including phosphorylation, ubiquitin conjugation, SUMOylation and poly(ADP-ribosyl)ation, are known to control these various biological processes (14,15). Nuclear proteins (NPs) can be altered in different ways, including genomic mutations, transcriptional/splicing variations and PTMs, depending on the expression levels at their target sites. These alterations, acting alone or in concert, allow NPs to exert distinct molecular and biological impacts. For example, when mutated, the nuclear protein p53, normally a tumor suppressor, acquires oncogenic gain-of-function activity at high concentrations, driving metastasis and chemoresistance (16). Similarly, as a core PEST-NP that governs ovarian cancer (OC) progression, especially critical in high-grade serous OC (HGSOC), where ~96% of cases harbor p53 mutations, p53 activation in response to DNA damage induces the expression of ring finger protein 144A (RNF144A) (11). RNF144A exhibits broad cellular distribution, primarily localizing to the plasma membrane and perinuclear region; notably, as an E3 ubiquitin ligase, it is directly involved in regulating the PTM of p53, a key process controlling the stability, degradation and functional output of this PEST-NP. However, the functional importance of the interactions ofRNF144A with DNA-dependent protein kinases, which itself acts as an E3 ubiquitin ligase to mediate p53 degradation during p53 autoubiquitination, remains currently unclear. Therefore, as ubiquitination status of p53 directly dictates its ability to inhibit OC cell proliferation, induce apoptosis or drive chemoresistance, clarifying how DNA-dependent protein kinase (DNA-PK) modulates RNF144A-mediated p53 degradation could uncover novel regulatory mechanisms of PEST-NP function in OC, and potentially identify new therapeutic targets to restore the tumor-suppressive role of p53 in OC. Several NPs, including KU70, PARP1, DNA ligase III and XRCC1, undergo degradation through PAR-dependent alterations (17). PTMs serve key roles in regulating various physiological processes involving these proteins. For instance, ubiquitination controls the stability of PEST-containing NPs (PCNPs) such as p53, while phosphorylation at Ser15/Ser20 disrupts p53-MDM2 interactions to stabilize p53 during DNA damage (18). Such PTM-dependent regulation is often disrupted by p53 mutations in OC, driving chemoresistance (19).

The present review summarized the current research on NP biology and associated potential molecular targets involved in various cellular processes that contribute to the development of OC. Further research may elucidate the precise associations of NPs and mechanisms of cancer progression that hold significant potential for the wider utilization of NPs as diagnostic and therapeutic targets in various types of OC.

2. PEST-NPs and mechanisms of PTM regulation mediated by PEST motifs

The PEST sequence is a peptide sequence rich in P, E, S and T. PEST sequences are commonly found in proteins with a short intracellular half-life, acting as a recognition motif for degradation-related enzymes and thus influencing protein stability and turnover in cellular processes. Further research has demonstrated that PEST sequence-enriched NPs are numerous, widely dispersed and involved in various physiological and cellular processes. Often referred to as 'cell guardians', PEST-NPs regulate pathways such as the ubiquitin-proteasome system, nuclear pore glycosylation and the hexosamine biosynthetic pathway (20). PEST-NPs participate in cell cycle control, cyclic nucleotide signaling, nucleocytoplasmic transport and the nutritional regulation of cellular metabolism and physiology (21). In cancer biology, several PEST-NPs regulate the tumor cell cycle, either directly by binding to DNA or indirectly by ubiquitinating cyclins D1 and E1, leading to G_1 arrest (Fig. 1). PEST-NPs can also modulate the cancer-immune system through apoptosis and autophagy induction and regulate cancer metabolism via the phosphatidylinositol 3-kinase (PI3K), mTOR and MAPK signaling pathways. The biological

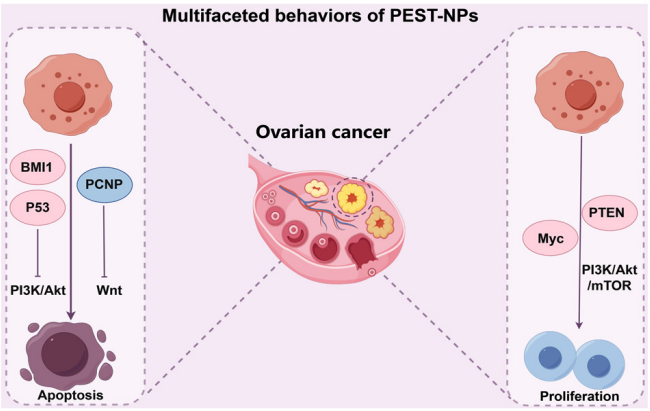

Figure 1. Multifaceted behaviors of the PEST sequence and PEST-NPs. BMI, PCNP and P53 are involved in apoptosis in ovarian cancer via interference with the oncogenic pathways of PI3K/AKT, Wnt, and PI3K/AKT. By contrast, Myc and PTEN are involved in proliferation through the oncogenic PI3K/Akt/mTOR and PI3K/Akt pathways (By FigDraw). PEST, proline, glutamic acid, serine, threonine; NPs, nuclear proteins; PCNP, PEST-containing NP; Bmi1, BMI1 proto-oncogene, polycomb ring finger.

activity of PEST-NPs is influenced by their intracellular distribution and abundance at target sites, with PTMs such as phosphorylation and ubiquitination serving key roles in regulating their localization, activation and expression levels. For instance, the ubiquitination of the PEST-domain of p53 by MDM2 controls its nucleocytoplasmic shuttling and stability, dictating apoptotic vs. pro-survival outcomes in OC (18).

As a structural recognition element, the PEST motif primarily governs substrate degradation primarily through mechanisms such as proteasomal turnover (such as endocytosis of the yeast a-factor receptor STE3) (22) or lysosomal degradation (such as human calcium receptors on the cell surface) (23). For example, Ck2-mediated phosphorylation leads to the degradation of IkB and IKK, whereas cAMP-dependent protein kinase breaks down proteins involved in cyclic nucleotide metabolism. Phosphorylation of the carboxyl terminus of the PEST domain promotes the degradation of substrate proteins such as PCNP and MeCP2, such as PCNP and MeCP2, which are also heavily ubiquitinated (24,25). Additionally, IKK undergoes degradation via calpain-mediated modification of Bcl6 and P300-mediated acetylation of Bcl6 (26,27). The stability and MAPK-induced activation of VEGF2 are mediated by the phosphorylation of serine 1,188 within its PEST sequence (28). Under normal conditions, PEST-NPs maintain short half-lives due to PEST-regulated proteasomal degradation, ubiquitin conjugation and ligase-mediated control of their cellular levels (Fig. 2).

3. PTMs of PEST-NPs: Mechanisms controlling stability/degradation, activation/inhibition and intracellular localization

Two major genetic alterations drive carcinogenesis: The activation of oncogenes and the loss of tumor suppressor activity. In this context, protein modifications mediate transcription, intracellular localization and degradation (29,30). Overproduction or overactivation of transcription factors such as Myc and NF-κB leads to uncontrolled growth and metastasis in various types of cancer (31). For example, PTEN activity, localization and stability are regulated by SUMOylation (mono- or poly-ubiquitination of SUMO1 and SUMO2/3) (32,33). Similarly, in NF-κB signaling, phosphorylation of the PEST motif and subsequent proteolytic degradation of the inhibitor of NF-κB (IκB) kinase initiates NF-κB nuclear translocation, transcriptional activation and DNA damage. Overall, PTMs are responsible for regulating activation and inhibition, maintaining protein stability and degradation, and determining the intracellular localization of PEST-NPs (34,35).

Mechanisms of activation and inhibition by PTMs. p53, a PEST-NP with anticancer properties, induces apoptosis by increasing mitochondrial permeability. Under stress, nuclear p53 interacts with the cytoplasmic Bcl-xl-p53 complex, releasing the p53-upregulated modulator of apoptosis (PUMA) to initiate mitochondria-dependent apoptosis (36,37). Following apoptosis, p53 is rapidly degraded in both the cytoplasm and nucleus: Nuclear p53 is conjugated with ubiquitin, translocates across the nuclear membrane and is degraded by the ubiquitin ligase mouse double minute 2 (MDM2) in the cytoplasm (38,39). This PTM-mediated activation (via stress-induced conformational changes) and inhibition (via MDM2-dependent ubiquitination) exemplify how PTMs control p53 function.

Mechanisms of stability and degradation regulated by PTMs. PEST motif modifications are critical for PEST-NP stability, activation and deactivation. The PEST-containing transcription factor BMI1 proto-oncogene, polycomb ring finger (Bmi1, a PEST-NP) interacts with O-GlcNAcylation transferase at serine 255, increasing its stability and oncogenic activity by suppressing p53, PTEN and CDKN1A/CDKN2A (40). Similarly, tankyrase-mediated ADP-ribosylation of PTEN (a PEST-NP with two PEST sequences) promotes its ubiquitination and degradation by the E3 ligase RNF146, reducing its tumor suppressor activity (33). These examples illustrate how PTMs directly modulate PEST-NP turnover to influence carcinogenesis.

Mechanisms of intracellular localization mediated by PTMs. PTMs of the PEST motif also regulate the localization, a key determinant of their pharmacological and carcinogenic effects, through modifications that impact protein activation, stability and subcellular distribution (35). The nuclear localization sequences (NLSs) and nuclear export sequences (NES) found on cargo proteins are recognized by importins and export proteins, which mediate directional transport across the nuclear envelope (41,42). The imbalanced shuttling of cargo proteins between the nucleus and cytoplasm, often driven by mutations in NLS/NES regions or dysregulation of shuttle determinants like PSPC1, is closely related to tumorigenesis (43,44). Unlike the cytoplasmic form of p53, which induces apoptosis through interactions with mitochondrial Bcl-2 family proteins (such as Bax), the nucleolar form of p53 is activated in response to nucleolar stress and participates in the DNA damage response (45). The antiapoptotic protein Bcl-xL, by contrast, binds to cytoplasmic p53. Unless PUMA releases the protein trapped in p53, the mitochondrial membrane cannot be opened to carry out anticancer actions. Numerous transporter inhibitors are being studied for their

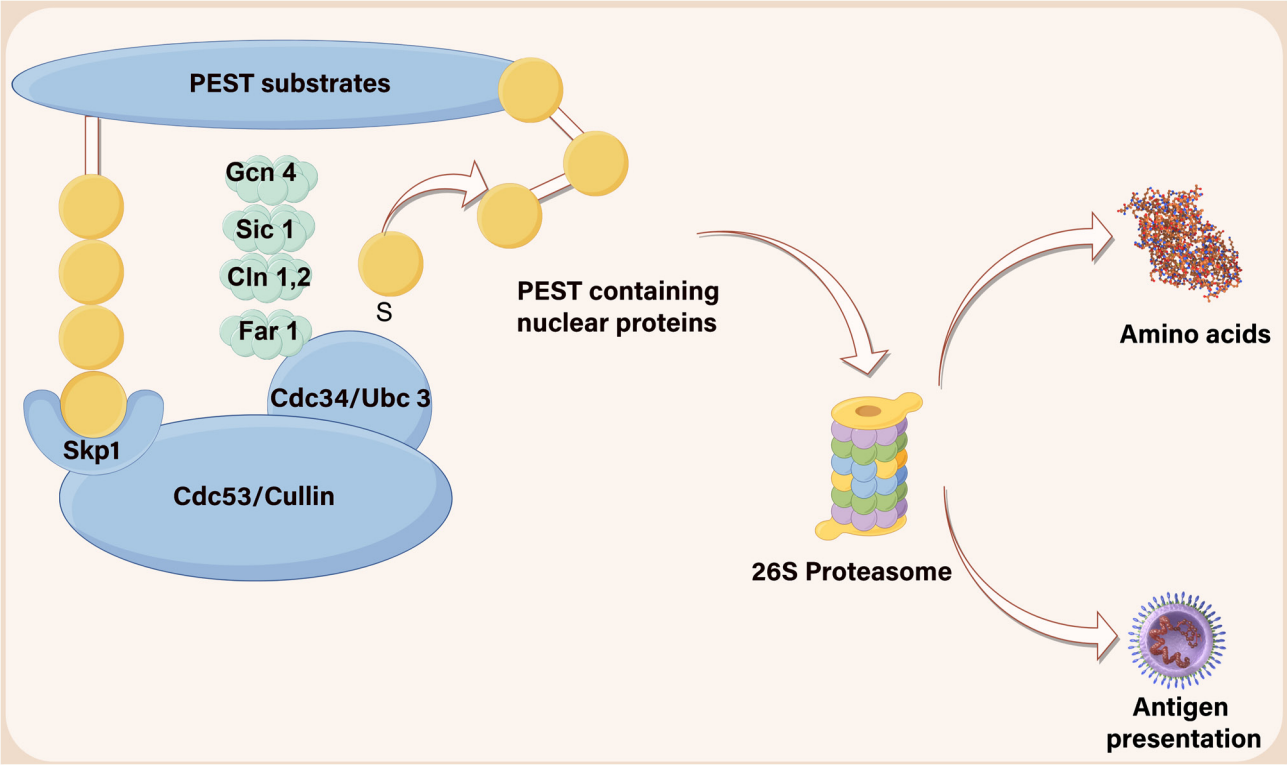

Figure 2. PEST sequence-containing phosphorylated substrates are degraded by a complex of the proteins Cdc34/Ubc3 and SCFs (By FigDraw). Cell division cycle; PEST, proline, glutamic acid, serine and threonine; SCF, Skp1, cullin and F-box protein; Ub, ubiquitin; Ubc, Ub-conjugating enzyme; Cdc, cell division cycle.

potential anticancer properties, such as withacnistin which decreases the levels of antiapoptotic proteins, and prevents signal transducer and activator of STAT3 from being localized in the nucleus (46). As a result, the PEST motif contributes to the diverse properties of NPs, giving PEST-NPs a wide range of molecular and physiological functions.

4. Multidimensional characteristics of PEST-NPs

The present review outlined how PTMs of PEST NPs affect their activation/inhibition, stability/degradation and intracellular localization to induce a tumor-promoting or tumor-suppressive response. The emphasis on molecular-level protein-protein interactions enables supports the understanding of the complex behavior of PEST NPs in cancer biology. Although numerous NPs exist, the most significant model PEST NPs, including p53, PTEN, Bmi1, c-Myc and PCNP, were examined as model PEST-containing proteins. The structural composition of these proteins determines their genesis, mode of action and ultimate fate. The computer-aided application 'PEST Discover' defines authentic PEST domains by calculating a 'PEST score', a metric combining residue composition (P, E, S and T) and hydrophobicity to predict proteolytic signals. This score [PEST-FIND=0.5 x (mole percent of P/E/D/S/T)-0.5 x (hydrophobicity index)] discriminates degradation-prone regions (score >0.5) and enables structural comparisons of PEST-containing proteins. The computational framework aligns with tools like PESTfind (http://emb1.bcc.univie.ac.at/embnet/tools/bio/PESTfind), which implements this algorithm (Table I).

p53. A number of malignancies (50%) have a mutation in the p53 gene, which can result in either loss of function or carcinogenicity (47). Loss-of-function mutations in the p53 tumor suppressor have the potential to cause chromosomal instability, loss of cell cycle arrest, loss of apoptosis, loss of senescent growth arrest and ineffective DNA base excision repair (48). These modifications enable the avoidance of key cell cycle pathways, promoting cancer growth. By contrast, p53 oncogenic mutations with gain-of-function effects can accelerate tumor metastasis, alter the transcriptional activity of target genes, inhibit apoptosis and increase chemotherapeutic resistance (49). A large proportion (96%) of patients with HGSOC have p53 mutations that span both gain-of-function (oncogenic) and loss-of-function (loss of p53 activity) events (50-52).

Human p53 functions as an active homotetramer, with each subunit consisting of 393 amino acids. This protein has a complex domain structure, including an N-terminal region with a ubiquitin ligase (MDM2) binding site, an amino-terminal transactivation domain (TAD; comprising TAD1 and TAD2), a DNA-binding domain (DBD), a tetramerization domain, a linker region, a proline-rich domain and a carboxyl-terminal domain (CTD) (41,53). The N-terminal segment features five repeats of proline-XX-proline sequences, where 'X' represents an amino acid that varies across species, as do several phosphorylation sites between residues 62 and 94 (53). The MDM2 binding site overlaps with the TAD, specifically TAD1 (residues 1-39) and TAD2 (residues 40-61). The N-terminal region, particularly TAD2, contains PEST motifs, which can interact with the DBD,

Table I. Comprehensive overview of key PEST-NPs and corresponding roles in cancer metabolism and transcription.

Protein	No. of amino acids	Signaling pathways	PEST score[a]	No. of transcripts	Cytoband	Chromosome no.	Chromosome location, bp	(Refs.)
p53	393	MAPK	-3.7-1.7	25	p13.1	17	7,661,779-7,687,550	(161-166)
PTEN	403	PI3K/Akt/mTOR	19.41-20.49	2	q23.31	10	87,863,113-87,971,930	(167-169)
Bmi1	326	Notch and Wnt, INK4A/ARF, MAPK, APK3, PI3K/AKT	ND	4	p12.2	10	22,321,211-22,331,484	(114,115,117, 120,165, 170-175)
Myc	439	PI3K/AKT/mTOR	2.3-11.8	9	q24.21	8	127,735,434-127,741,434	(165,166)
PCNP	178	MAPK, mTOR, PI3K, AKT, STAT3, P-STAT5	ND	3	q12.3	3	101,574,095-101,594,437	(151,156,165, 166,176)

[a]The PEST score combines the mole percent of 4 amino acids with a hydrophobicity value, Ho, derived from the sequence via the following equation: PEST-FIND=0.5(MP)-0.5(Ho). This score, which can range from negative values (indicating a lower likelihood of degradation) to positive values (indicating a higher likelihood of degradation), helps to predict the stability and degradation rate of proteins within the cell. Higher PEST scores typically indicate regions that are more likely to be targeted for rapid degradation. 'FIND' is part of the name of the classic PEST sequence prediction tool PEST-FIND, a computational algorithm used to identify PEST motifs (proline, glutamic acid, serine and threonine-rich regions) in proteins and calculate their PEST scores. PEST, proline, glutamic acid, serine, threonine; NPs, nuclear proteins; PCNP, PEST-containing NP; PTMs, post-translational modifications; Bmi1, BMI1 proto-oncogene, polycomb ring finger; ND, no data.

potentially inhibiting DNA binding. The DBD regulates the nuclear and cytoplasmic functions of p53, as it is critical for mediating DNA-dependent nuclear activities and indirectly influencing cytoplasmic processes through its structural role in maintaining p53 functional integrity (54). Missense mutations in the DBD (R175, Y220, G245, R248, R249, R273 or R282) account for 62% of all p53 mutations that are associated with cancer (82% of HGSOC cases). These mutations eliminate DNA-binding capabilities either directly or indirectly (53-55). According to a previous study, the amino acid arginine at position 273 (R273) in the DBD is the most frequently altered, with histidine (R273H) accounting for 46.6% of the R273 mutations and cysteine (R273C) accounting for 39.1% (19). It has been proposed that these DBD mutations lead to a structural shift that affects p53 stability, making the protein structure stiffer compared with wild-type (WT) p53 (56). These important DBD mutations interfere with the ability of p53 ability to regulate apoptosis, causing malignant cells to proliferate unrestrained. The CTD carries three nuclear localization signals that allow p53 to localize to the nucleus (57).

As a transcription factor, p53 interacts with thousands of genes and is essential for preserving cellular homeostasis (58,59). In normal cells, p53 is maintained at a tightly regulated, physiological level; this strict control is necessary because p53 acts as a potent inducer of apoptosis, and unregulated p53 activity would trigger excessive cell death that disrupts normal tissue homeostasis (60). Under normal circumstances, the cellular expression level of the p53 protein, similar to that of other PEST-NPs, is very low because of its short half-life of ~620 min. PEST motifs, which are attached to the COOH terminus of residual proteins, act as signals for PTMs of p53 (phosphorylation and ubiquitination) and regulate not only proteasomal degradation (57). The PEST motifs attached to the CTD of p53 function as signals for its PTMs, including phosphorylation and ubiquitination; these motifs not only regulate the proteasomal degradation of p53 but also modulate its intracellular localization (53). The protein p53 mediates distinct responses depending on its subcellular localization: Cytoplasmic accumulation of p53 promotes mitochondrial outer membrane permeability and initiates mitochondria-dependent apoptosis (61), whereas nuclear localization enables p53 to trigger the DNA damage response and transcribe target genes involved in cell cycle regulation (54,62). Upon cellular stress, p53 is activated via phosphorylation and other PTMs; this activation enhances its stability and DNA-binding capacity, thereby increasing the expression of target genes associated with cell cycle arrest and DNA repair (62). In the cytoplasm and mitochondria, monomeric or homodimeric p53 interacts with Bcl-xL (antiapoptotic) and Bak (apoptotic regulator) to control autophagy and apoptosis (60). In the cytoplasm and mitochondria, monomeric or homodimeric p53 interacts with Bcl-xL (antiapoptotic) and Bak (apoptotic regulator) to control autophagy and apoptosis (61-63).

Inactivation of p53 activity can occur directly through mutation or indirectly through the aggregation or disruption of regulatory proteins (64). The E3 ubiquitin ligase MDM2 typically maintains low levels of p53 through ubiquitin-mediated proteasomal degradation, a process facilitated by the PEST motifs located in the CTD of p53 (65). Overall, two

basic pathways for p53 inactivation have been proposed: p53 mutation and WT p53 degradation through negative regulatory proteins, such as MDM2 or MDM4 (41). The ubiquitin ligases MDM2 and MDM4 facilitate the targeting of p53 for proteasomal degradation (65). In malignancies such as epithelial (EOC) and HGSOC, the most aggressive and common subtypes of OC (52), the upregulation of MDM2 and MDM4 (inhibitors of p53) can lead to the downregulation of p53, in addition to p53 mutations (57,65). The upregulation of MDM2 and MDM4 inhibitors can lead to the downregulation of p53, in addition to p53 mutations. Thus, a primary focus of treatment strategies for malignancies with wild-type p53 has been the development of antagonists for MDM2 and MDM4 (65).

The overexpression of the PI3K pathway occurs in 40-70% of OCs and is thus another significant mechanism for p53 regulation (66). The suppression of PI3K has been shown to lead to the regression of OC both *in vivo* and *in vitro* (67). Additionally, PTEN, a negative regulator of PI3K, is often found to be absent in OC. Furthermore, owing to the exposure of a structural 'sticky' region, typical p53 mutations can lead to protein aggregation (57). These distinct yet related pathways highlight the complexity of p53 regulation, several mechanisms of which are currently poorly understood. Cancer cells have developed the capacity to modify and inactivate p53, dubbed 'the guardian of the genome' for its role in maintaining genomic integrity (60), to evade tumor suppression and promote proliferation; p53 mutations are nearly ubiquitous in HGSOC, with reported frequencies exceeding 90% in clinical cohorts (53). Notably, however, there are currently no Food and Drug administration approved p53-based therapeutics for HGSOC. While WT p53 and p53-based therapeutics, which may be administered via drug delivery systems such as nanoparticles, viruses, polymers and liposomes, have been a focus of extensive study (68-73), these innovative therapeutic approaches have yet to be fully developed and optimized.

In response to active accumulation in specific subcellular compartments, the p53 protein mediates distinct cytoplasmic and nuclear responses. Cytoplasmic accumulation of p53 induces mitochondrial outer membrane permeability and apoptosis through direct interactions with anti-apoptotic Bcl-2 family proteins (60,61), whereas nuclear localization enables p53 to initiate the DNA damage response and transcription of target genes involved in cell cycle regulation and genome maintenance (53,54). A p53 mutation, however, can suddenly disrupt the normal processes of tightly regulated nucleocytoplasmic shuttling. PTMs include phosphorylation at threonine 155, which mediates nuclear export (74); phosphorylation at serine 392, which mediates mitochondrial localization (75); and kinase inhibitors, which suppress nuclear export and are responsible for p53 nuclear export (57). Another alteration of p53 that results in activation, DNA binding and nuclear localization is acetylation at lysine residues (76).

PTEN. PTEN is a tumor suppressor nuclear protein initially discovered in a mutant form in glioblastoma, prostate and breast cancer cell lines and xenografts (77). PEST-NP PTEN (or MMACI/TEP1) has 9 exons, 1,212 nucleotides and 403 amino acids and has a molecular mass of 47 kDa (78-80). The N-terminal phosphatase and C-terminal domains, along with a short N-terminal tail, constitute the major portion of the PDZ-binding C2 domain, which is responsible for binding the phospholipid membrane and serves a key role in the proper positioning of PTEN at the plasma membrane in the C-terminal region. The protein also contains two PEST sequences, which regulate its tumor-suppressive function (81,82).

The tail of the C-terminus comprises ~50 amino acids and is responsible for active phosphorylation. The primary cause of the anticancer activity of PTEN is its lipid phosphatase activity. Loss of function is characterized by the inhibition of the enzymatic activity of PTEN. Invasion and gene expression are correlated with phosphatase activity. In addition to being responsible for the ubiquitin-mediated proteasomal degradation of proteins, the PEST region of PTEN also contributes to increased protein stability, and its loss significantly decreases the expression of the PTEN protein. The nuclear import, tumor-suppressing properties and degradation of PTEN are controlled by ubiquitination, specifically ubiquitination of its PEST motifs (81-83). PTEN contains two PEST sequences in its carboxyl-terminal region; these motifs not only contribute to maintaining PTEN protein stability (81,82) but also serve as key targets for ubiquitin ligases. This PEST motif-specific ubiquitination directly modulates PTEN's nuclear translocation, abrogates its tumor-suppressive activity and promotes its proteasomal degradation (83).

KRAS, BRAF, PTEN and β-catenin mutations are present in type I tumors, which are considered to be genetically stable (84-86). KRAS and BRAF mutations, in particular, are mutually exclusive, affect two-thirds of type I OCs, and cause early neoplastic transformation by constitutively activating the mitogen-activated protein kinase signal transduction pathway (87). PTEN mutations can coexist with KRAS mutations in the ovary, which has been found to cause invasive and broadly metastatic EOC (86,87). PTEN mutations can also occur independently, leading to aberrant activation of the PI3K/Akt/mTOR pathway (88). According to several preclinical models, one of several genetic modifications affecting the fallopian tube is the deletion of PTEN (89-91).

The conditional homozygous PTEN deletion mediated by PAX8-cre recombinase was sufficient to cause borderline serous OC and endometrioid tumors in mouse models (92). Research suggests that HGSOC has a unique etiology; the current HGSOC formation paradigm suggests that it originates in the fallopian tube, which is supported by genomic, transcriptomic and proteomic investigations demonstrating shared molecular signatures between fallopian tube precursor lesions and invasive HGSOC (93-95). Mutations in the p53 gene that cause protein stabilization in the fallopian tube are crucial in this process. Following the loss of other tumor suppressors or the amplification of oncogenes (such as PTEN and KRAS), a serous tubal intraepithelial carcinoma develops, which later metastasizes to the ovary and peritoneum (94).

Research has shown that four out of twelve (33%) serous intratubal carcinoma samples had PTEN deletion (95). These findings, in line with those of endometrioid carcinomas of the uterus, where progressive loss of PTEN and PAX2 expression characterizes early precancerous lesions and carcinogenesis (96,97), led to the suggestion that variations in PTEN and PAX2 expression may be involved in the early stages of serous carcinogenesis. As observed in the

endometrial model, it is unknown whether these modifications occur before malignancy or concurrently with its onset. Additionally, it has been demonstrated that the loss of PTEN enables the formation of multicellular tumor spheroids in the fallopian tube epithelium. These spheroids colonize the ovary by adhering to the extracellular matrix that is exposed after ovulation and may have seeded the ovary in patients with HGSOC (96). PTEN loss has been associated with increased cell transformation and proliferation both *in vitro* and *in vivo*, as well as with the stimulation of MUC1 expression, which is known to serve key roles in cancer cell migration and metastasis (97).

Bmi1. Bmi1, a polycomb group protein (also known as PRC1), is essential for the epigenetic regulation of several cellular processes, including proliferation, differentiation, stem cell self-renewal and chemoresistance to various cancer drugs. In EOC, Bmi1 contributes to resistance against platinum-based chemotherapeutic agents (such as cisplatin), Bmi1 encodes 326 amino acids with a molecular weight of 44-46 kDa. The protein has two domains: Bmi1, which associates with and partially encloses Ring1b, and the tail of Ring1b, which wraps around Bmi1. The oncogene Bmi1 binds to the substrate protein and ubiquitinates the lysine of the substrate protein, via the E3 ligase Ring1b, (97,98). For example, Bmi1 reduces the stability of p53 by ubiquitinating it via Ring Finger Protein 2/Ring1b (99,100).

Two NLSs, NLS1 and NLS2, are located in the protein Bmi1 and are responsible for the nuclear localization of Bmi1. NLS2 is a key signal for the nuclear localization of Bmi1 (98). Bmi1 is split into three parts on the basis of its function: An N-terminal conserved ring domain, a central helix-turn-helix (HTH) domain and a carboxyl-terminal area with a PEST-like domain. The ring domain of Bmi1 focuses on DNA strand breaks in response to DNA damage, which helps cells escape senescence due to the synergistic action between the N-terminal ring domain and central HTH domain Bmi1 (101,102). As a result, it lengthens the time that cells can replicate, leading to the accumulation of more cells in the G_2/M phase and thereby increasing cell proliferation (103).

Bmi1 also increases the length of time that a tumor cell can survive because by activating N-Myc, as it blocks the transcription of tumor suppressor genes such as p16, p19, p53 and PTEN; thus, Bmi1 has an oncogenic function (104,105). Bmi1 overexpression has been documented in lymphomas (106), prostate cancer (107), non-small cell lung cancer (NSCLC) (108), nasopharyngeal carcinoma (109) and breast cancer. Specifically, in prostate cancer, Bmi1 upregulation correlates with downregulated p16(INK4A) and p14(ARF). In NSCLC, high Bmi1 expression is associated with reduced p16 and p14ARF levels. In colon cancer, Bmi1 overexpression coincides with decreased p16INK4a/p14ARF expression. Through the suppression of the p21CIP1 gene and the INK4A/ARF locus, Bmi1 is essential for tumor cell growth and survival in brain cells (110).

The progression of neuroblastoma caused by Bmi1 is facilitated by the upregulation of cyclin E (111). In prostate cancer cells and mammary epithelial cells, Bmi1 also increases telomerase activity (112,113). Bmi1 PTMs at various serine residues control its INK4A/ARF-dependent and INK4A/ARF-independent functions (114). Through an INK4A/ARF-independent mechanism, phosphorylation of Bmi1 by AKT promotes glioma and hepatic carcinogenesis (115,116) and reduces tumor growth through an INK4A/ARF-dependent pathway. In accordance with the type of residual substrate, alterations in the AKT kinase activity of Bmi1 alter its oncogenic characteristics (117).

MAPKAPK3, a MAPK-activated protein kinase, also phosphorylates Bmi1. The activation or upregulation of MAPKAPK3 leads to the phosphorylation of Bmi1 and other Polycomb proteins, the recruitment of substrate proteins from chromatin, the activation of the INKA4/ARF locus induce cell cycle arrest and senescence to inhibit cancer progression (118,119). Bmi1 is positively regulated by numerous transcriptional and posttranscriptional regulators, including N-Myc, C-Myc, specialized protein 1, twist-related protein 1, forkhead box protein M1, E2F1 and sal-like protein 4. By contrast, Bmi1 is suppressed at the transcriptional level by Mel-18, Kruppel-like factor 4 and histone deacetylase inhibitors. The expression of Bmi1 is also regulated by the Notch and Wnt pathways (120).

In PTEN-null prostate cancer, elevated Bmi1 expression and its role in neoplasia progression are supported by studies showing that Bmi1 upregulation correlates with PTEN loss and promotes tumor aggressiveness, while Bmi1 depletion inhibits progression. Regarding Bmi1 degradation, it is regulated by βTrCP-mediated ubiquitination: βTrCP recognizes a specific motif in Bmi1, promoting its proteasomal turnover via the ubiquitin-proteasome system (121). βTrCP mediates the ubiquitination of Bmi1 at tyrosine 18 within its N-terminal RING finger domain; subsequently, the ubiquitinated Bmi1 is shuttled into proteasomes for degradation (121,122). The degradation of Bmi1 is increased in MCF10A cells when TrCP is overexpressed, whereas the opposite occurs in these MCF10A cells with no TrCP overexpression (122).

In a previous study, compared with original ovarian carcinomas, metastatic lymph nodes and recurring tumors significantly overexpressed Bmi1 (123). Furthermore, Bmi1 is highly expressed in metastatic and recurrent tumors, and was found to be predictive of both survival and relapse (124). A number of studies have investigated the role of Bmi1 as a pathway regulator in both stem cells and cancer cells, validating its oncogenic activation in various human malignancies Examples include EOC, where Bmi1 overexpression in metastatic/recurrent tumors correlates with disease progression and platinum resistance (125), NSCLC, where it links EMT to cancer stem cell properties (126), as well as lymphomas, prostate cancer, nasopharyngeal carcinoma and breast cancer, where elevated Bmi1 expression is associated with tumor aggressiveness and suppressed tumor suppressor genes (125,126). Upon suppression of Bmi1, cell proliferation was significantly reduced and a greater proportion of EOC cells remained in the G_1 phase. Previous research demonstrated that ER-coupled Bmi1 signature activity influences the status of p16INK4a and cyclin D1, which correlates with tumor molecular subtypes and biological behavior in breast cancer (127).

Furthermore, Bmi1 knockout decreased the ability of EOC cells to migrate and invade; additional studies demonstrated that Bmi1 is responsible for triggering the EMT, which leads to tumor invasion and metastasis (128). Additionally, the overexpression of Bmi1 in EOC cells increased the expression

of cyclin D1, CDK4 and Bcl-2, thereby increasing cell proliferation and inhibiting cell death (129). By contrast, a previous study demonstrated that silencing Bmi1 had the opposite effect on controlling the cell cycle and apoptosis; it was also shown that Bmi1 knockout increased the susceptibility of EOC cells to platinum (123). Similarly, Wang *et al* (130) reported that downregulating Bmi1 increased ROS, triggered the DNA damage repair pathway and ultimately promoted cisplatin-induced apoptosis. Together, these data provided insight into chemoresistance, an ongoing and complex problem in the management of EOC.

Myc. The Myc gene, which may be located at chromosome 8q24.21, encodes the super-transcription factor Myc (131). Myc oncoproteins (c-Myc, N-Myc and L-Myc) regulate the transcription of >15% of expressed genes (132). The PEST-NP Myc, as the prototypical nuclear transcription factor, dimerizes with MAX to drive proliferation and repress differentiation via E-box binding (133). However, Myc requires cooperative genetic events, such as loss of p53/p16 checkpoints, to overcome apoptosis/senescence and induce oncogenesis, as demonstrated in Myc-Ras transgenic models (134). In ovarian cancer, c-Myc overexpression is detected in 65.9% of epithelial tumors, correlating with aggressive phenotypes, consistent with its PEST-mediated instability and oncogenic plasticity.

The wide, unstructured amino-terminal region in Myc proteins, which is considered critical for transcriptional activation, contains conserved boxes known as Myc boxes (MBI and MBII) (135). The PEST sequences, meanwhile, are responsible for ubiquitination, with two conserved Myc boxes (MBIII and MBIV) and one NLS for nuclear accumulation comprising the middle portion of Myc proteins (136). The basic helix-loop-helix leucine zipper domain is made up of 100 amino acids, which is necessary for the DNA-protein interactions that start transcription (133,136). Human cancer cells frequently overexpress the protein Myc; specific examples include EOC, where c-Myc overexpression correlates with aggressive tumor phenotypes (133), as well as lymphomas and prostate cancer, where Myc overexpression has been linked to malignant transformation processes (133). Protein translation, cell cycle progression and differentiation, tumor metabolism and ribosome biogenesis are important downstream effects of Myc. Numerous biological processes, including cell differentiation, growth, survival, immune surveillance and apoptosis, are coordinated with the regulatory process mediated by the downstream effects of Myc (137). Myc-associated cell cycle abnormalities occur after SUMOylation, leading to the enzymatic activation of Myc (135).

The protein expression of c-Myc has previously been identified in OC and stromal cells via immunohistochemical techniques (138). In 76% of cases of early-stage EOC, Skírnisdóttir *et al* (139) reported positive staining for c-Myc via the same method. Tumor grade and positivity status are related; the c-Myc protein was discovered to be overexpressed in 65.9% of EOC cases compared with that of normal ovary cancer cases, according to research by Chen *et al* (140). However, no discernible distinction in histological subtypes was observed.

In addition, Plisiecka-Hałasa *et al* (141) reported that endometrioid and clear-cell carcinomas frequently overexpress c-Myc. Van Dam *et al* (142) reported that 35% of ovarian epithelial carcinomas overexpress the c-Myc protein, using flow cytometry. A related study by Watson *et al* (143) reported that serous papillary ovarian carcinomas express considerably higher levels nuclear c-Myc protein when compared with that of normal ovaries. Sasano *et al* (144) reported that there was no connection between the intracellular distribution of c-Myc and the nuclear grade, histological grade or mitotic activity in OC (144). Nevertheless, research on ovarian mucinous tumors has demonstrated a clear correlation between the distribution and expression of the c-Myc protein and the size and subtype of the tumor (145,146).

However, retrospective clinical data analysis has indicated that standard histological indicators are more reliable predictors of tumor behavior than an evaluation of the c-Myc expression pattern solely by immunostaining. Ning *et al* (147) observed that, following treatment with platinum-based regimens for ovarian carcinomas, c-Myc upregulation was associated with improved tumor differentiation, increased p27 levels and decreased Ki-67 expression. Furthermore, Ning *et al* (147) reported an association between shorter overall survival and elevated nuclear c-Myc expression in early-stage OC.

Curling *et al* (148), by contrast, did not identify a relationship between the c-Myc protein and the prognosis of OC. Similar findings were reported by Jung *et al* (149), who reported no connection between endometrioid tumor patient outcomes and high levels of c-Myc protein expression levels. Yamamoto *et al* (150) reported that c-Myc protein expression in early-stage EOC did not significantly affect the survival rate. Nevertheless, a clear correlation was found between the expression of proliferation markers such as Ki-67 and the level of phosphorylated c-Myc (Ser62). Additionally, high levels of phosphorylated c-Myc have been associated with a worse prognosis (151). With respect to c-Myc amplification and mRNA expression, it remains unclear how c-Myc protein expression levels are related to specific clinical indicators in OC. Therefore, it is important to conduct further research to determine the clinical significance of phosphorylated c-Myc in OC. Therefore, it is important to conduct further research to determine the clinical significance of phosphorylated c-Myc in OC.

PCNP. A PEST-NP member currently under investigation is PCNP, a PEST-containing nuclear protein first identified in the early 2000s, which consists of 178 amino acids and exhibits consistent colocalization with the RING finger protein NIRF in the perinuclear region (152,153). PCNP mRNA has been detected in several cell types, including normal fibroblasts (WI-38 and TIG-7), fibrosarcoma (HT-1080) and hepatocellular carcinoma (HepG2) cells (151). Further evidence, such as PCNP overexpression in ovarian cancer driving Wnt/β-catenin-mediated cell proliferation, migration and epithelial-mesenchymal transition (154), and its interaction with NIRF to regulate cell cycle-related stability (151). PCNP and NIRF have been demonstrated to interact with each other both *in vitro* and *in vivo*. The presence of the ubiquitin domain in the N-terminus and the ring finger catalytic domain in the C-terminus of NIRF suggests that the PCNP has catalytic activity. The ubiquitination of PCNP by NIRF is highlighted by the interaction of PCNP with NIRF *in vitro* and *in vivo*, which in turn controls the stability and regulation of PCNP.

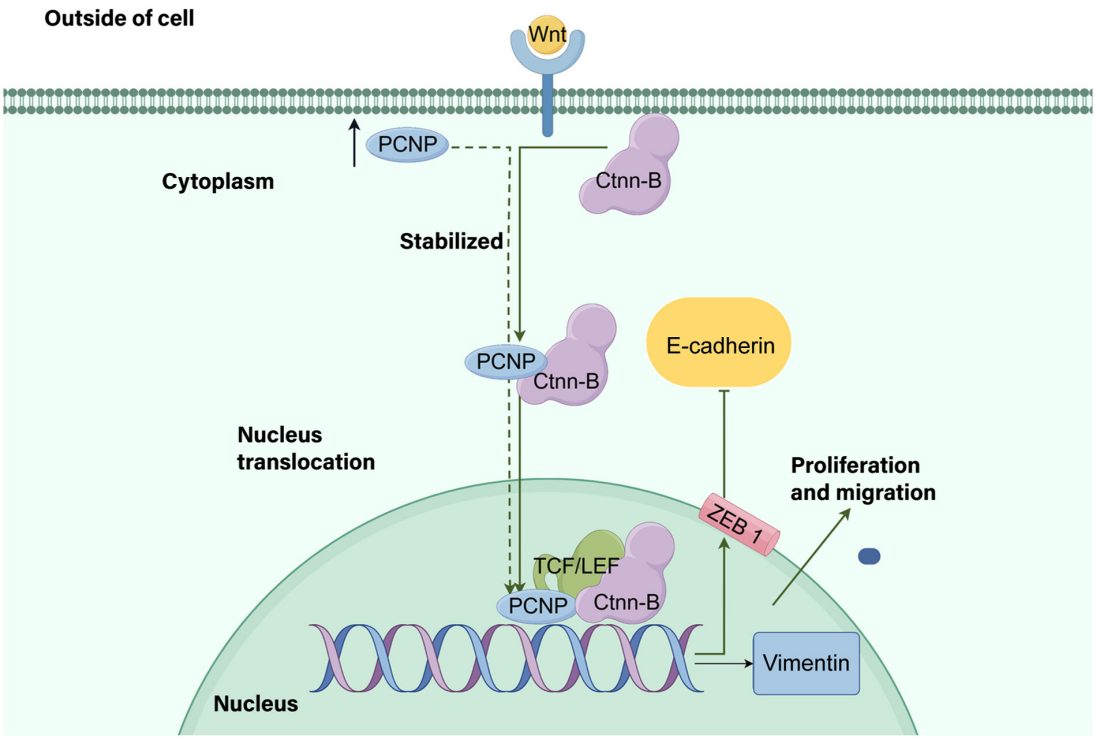

Figure 3. Wnt signaling pathway activation and the progression of ovarian cancer is facilitated by the interaction of PCNP with β-catenin, which stabilizes PCNP and enhances the expression of β-catenin in the nucleus (By FigDraw). PCNP, PEST-containing nuclear protein; Ctnn-B, β-catenin; TCF/LEF, T-cell factor/lymphoid enhancer factor; ZEB1, zinc finger E-box binding homeobox 1; E-cadherin, epithelial cadherin.

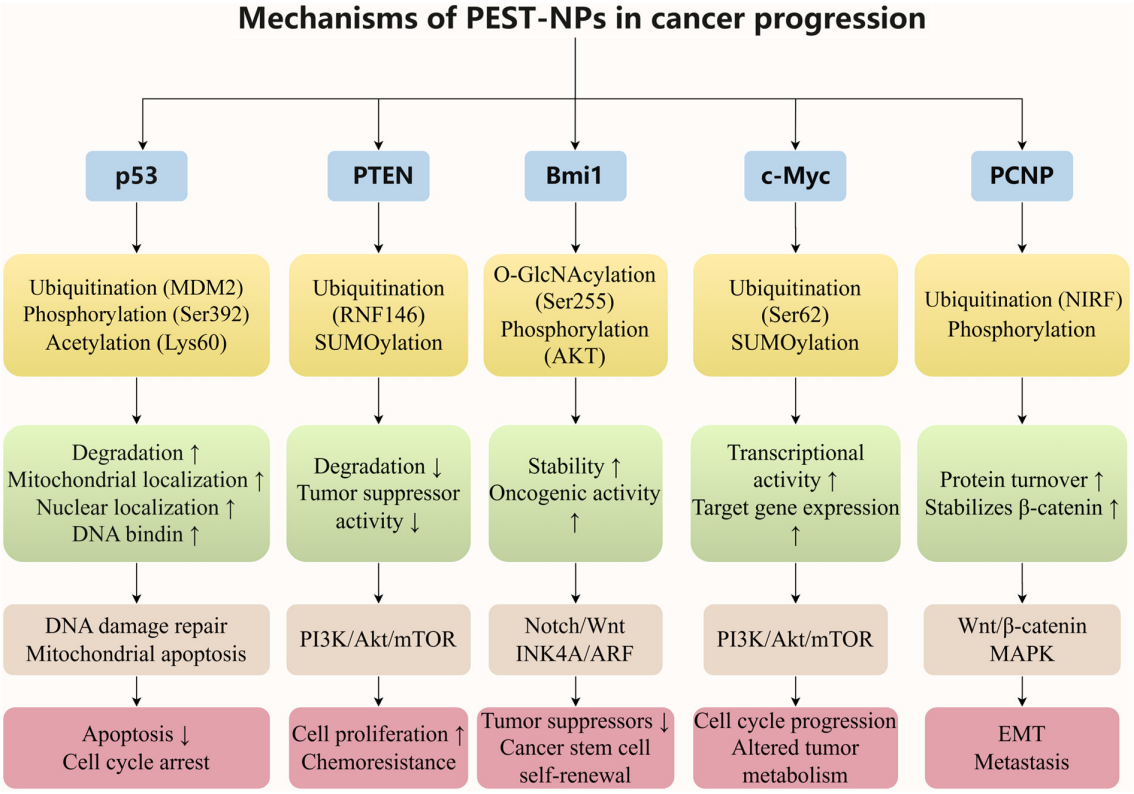

Figure 4. Mechanisms of PEST-NPs in cancer progression via PTMs and key signaling pathways. Summarization of the interactions between PEST-NPs (p53, PTEN, Bmi1, c-Myc and PCNP) and their key post-translational modifications (ubiquitination, phosphorylation, acetylation, SUMOylation and O-GlcNAcylation), which regulate protein stability, activation or subcellular localization. These modifications further modulate downstream signaling pathways (such as PI3K/Akt/mTOR, Wnt/β-catenin, Notch and mitochondrial apoptosis) and contribute to cancer progression phenotypes, including altered cell proliferation, apoptosis, stem cell self-renewal, metabolism, epithelial-mesenchymal transition and metastasis (By FigDraw). PEST, proline, glutamic acid, serine, threonine; NPs, nuclear proteins; PCNP, PEST-containing NP; PTMs, post-translational modifications; Bmi1, BMI1 proto-oncogene, polycomb ring finger; EMT, epithelial-mesenchymal transition.

Table II. PTMs of PEST-NPs control stability/degradation, activation/inhibition and intracellular localization.

Protein	PTM	Effect on stability/degradation	Effect on activation/inhibition	Effect on intracellular localization	(Refs.)
p53	Ubiquitination by MDM2	Promotes degradation via proteasomal pathways	Inhibits tumor suppressor function	Nuclear export after ubiquitination, leading to cytoplasmic degradation	(47)
Bmi1	O-GlcNAcylation	Increases stability and oncogenic activity	Inhibits p53, PTEN and CDKN1A/CDKN2A activity	Localized to nucleus where it exerts oncogenic effects	(48)
PTEN	Ubiquitination by RNF146	Promotes degradation via proteasomal pathways	Inhibits tumor suppressor activity	Shuttles between nucleus and cytoplasm, affecting its tumor suppressor role	(40)
PCNP	Ubiquitination and phosphorylation	Promotes degradation	Regulates cellular proliferation, and invasion	Localized in the nucleus, influencing cellular functions	(23,48)

PEST, proline, glutamic acid, serine, threonine; NPs, nuclear proteins; PCNP, PEST-containing NP; PTM, post-translational modification; Bmi1, BMI1 proto-oncogene, polycomb ring finger.

The ring finger proteins MDM2 and p53 share a similar interaction (20,154). Additionally, NIRF is expressed at a markedly high level in several malignancies, including EOC, hepatocellular carcinoma and NSCLC (154,155).

According to previous studies, the MAPK and PI3K/AKT/mTOR signaling pathways serve pivotal roles together with PCNP in the proliferation, migration and invasion of OC, neuroblastoma and lung adenocarcinoma (154,156). Mechanistically, PCNP binds to β-catenin, accelerates its nuclear translocation and activates Wnt/β-catenin signaling, suggesting that PCNP is an upstream regulator of Wnt-mediated OC progression and a potential therapeutic target (Fig. 3). The Wnt signaling pathway, which regulates cell proliferation, apoptosis and EMT, is critical for tumor initiation and development, and aberrations in this pathway significantly contribute to OC progression (157-159). Dong *et al* (154) identified a direct link between PCNP and the Wnt pathway: PCNP is overexpressed in OC tissues and cells (compared with that of paracancerous and IOSE80 cells), and this overexpression promotes OC cell proliferation, migration and invasion while suppressing apoptosis (validated in SK-OV-3/A2780 cells and xenograft models). High expression levels of PCNP can reduce apoptosis by increasing the expression levels of the transcription factor (STAT) activators of phosphor signal transducers (153). In addition to TNF-inducible protein 8-like 2, PCNP is also involved in the immune response in rheumatoid arthritis (160). Although PCNP is known to mediate caspase activities, upregulating cleaved caspase-3, -8, and -9 *in vitro* and *in vivo*, it remains unclear how PCNP specifically activates these caspases to induce apoptosis (156). The induction of autophagy and apoptosis in distinct cell lines, however, implies that alternative nuclear transporters are involved in the dual behavior of the protein (156). Overall, however, further research is needed on the nuclear transportation of PCNP (Fig. 4; Table II and III).

5. Conclusion

As analyzed in the present review, OC progression is driven by dysregulated transcription factors and signaling pathways, with PEST-NPs emerging as key regulators through their PTMs. PTMs such as phosphorylation, ubiquitination and SUMOylation control the stability, activation and intracellular localization of core PEST-NPs, thereby modulating oncogenic pathways such as the PI3K/Akt/mTOR and Wnt/β-catenin pathways to influence OC growth, metastasis and chemoresistance.

Notably, PCNP and Bmi1, as key PEST-NPs, may hold translational potential for OC therapy based on their characterized roles. The direct interaction of PCNP with β-catenin accelerates nuclear translocation and activates Wnt/β-catenin signaling, a pathway critical for OC proliferation, migration and invasion. Targeting PCNP could therefore involve strategies to block its binding to β-catenin or inhibit its phosphorylation, which modulates its oncogenic activity in regulating the MAPK and PI3K/Akt/mTOR pathways. Given that PCNP is overexpressed in OC tissues and cells compared with that of their normal counterparts, such interventions may specifically disrupt tumor-promoting

Table III. Mechanisms of PEST-NPs in cancer progression via PTMs and key signaling pathways.

PEST-NPs	Key PTMs and regulators	Effects on protein (stability/activation/localization)	Downstream signaling pathways	Cancer progression phenotypes	(Refs.)
p53	Ubiquitination (by MDM2) Phosphorylation (Ser392) Acetylation (Lys60)	Ubiquitination: Promotes proteasomal degradation; inhibits tumor suppression Phosphorylation: Enhances mitochondrial localization Acetylation: Promotes nuclear localization and DNA binding	DNA damage repair pathway Mitochondrial apoptosis pathway	Reduced apoptosis (via degradation) Cell cycle arrest (via activation)	(47,53, 60,75)
PTEN	Ubiquitination (by RNF146) SUMOylation	Ubiquitination: Induces degradation; reduces tumor suppressor activity SUMOylation: Regulates nucleocyto-plasmic shuttling	PI3K/Akt/mTOR pathway	Enhanced cell proliferation (via pathway activation) Chemoresistance	(32,33, 83)
Bmi1	O-GlcNAcylation (Ser255) Phosphorylation (by AKT)	O-GlcNAcylation: Increases stability and oncogenic activity Phosphorylation: Activates downstream signaling	Notch/Wnt pathway INK4A/ARF pathway	Suppression of tumor suppressors (p53/PTEN) Cancer stem cell self-renewal	(40,99, 115)
c-Myc	Phosphorylation (Ser62) SUMOylation	Phosphorylation: Enhances transcriptional activity SUMOylation: Activates target gene expression	PI3K/Akt/mTOR pathway	Cell cycle progression Altered tumor metabolism	(135,140)
PCNP	Ubiquitination (by NIRF) Phosphorylation	Ubiquitination: Regulates protein turnover Phosphorylation: Stabilizes β-catenin	Wnt/β-catenin pathway MAPK pathway	EMT Metastasis	(154,156)

PEST, proline, glutamic acid, serine, threonine; NPs, nuclear proteins; PCNP, PEST-containing NP; PTMs, post-translational modifications; Bmi1, BMI1 proto-oncogene, polycomb ring finger; MDM2, mouse double minute 2.

signaling without affecting normal cells. The ability of Bmi1 to be overexpressed in metastatic and recurrent OC supports its utility as a therapeutic target. Inhibiting Bmi1 could reduce its stabilization via O-GlcNAcylation or block its phosphorylation by AKT, thereby reversing its oncogenic effects on cell cycle progression and stemness. This may sensitize OC cells to platinum-based therapies, as Bmi1 silencing has been shown to increase platinum susceptibility in preclinical models.

These insights deepen the current understanding of OC pathogenesis by linking PEST motif-mediated protein dynamics to tumor behavior, thus underscoring PEST-NPs as valuable diagnostic biomarkers and therapeutic targets. To advance clinical translation, future research should focus on elucidating the intricate interactions of PCNP with cancer-related genes and pathways, validating PEST-NP-targeted strategies in preclinical models and exploring PEST-NP expression/PTM profiles as predictors of treatment response, which will serve to bridge the gap between laboratory research and clinical applications.

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Availability of data and materials

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Author contributions

HL, ZLJ, YL, YHZ, MUA and ZDL conceived the study and drafted the manuscript. MBK, SK and UAKS prepared the figures, participated in manuscript content revision and table legend editing. YZ and XYJ provided funding and supervision, reviewed the manuscript framework, revised key sections and ensured academic consistency. ZLJ and YL participated in the extensive review, revision, and figure/table production of the review. Data authentication is not applicable. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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