

REVIEW

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Sex hormone receptor signaling networks drive pancreatic solid-pseudopapillary neoplasm pathogenesis and therapy

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Abstract

Solid-pseudopapillary neoplasm of the pancreas (SPN) represents a rare pancreatic tumor with a low malignant potential, predominantly affecting young women. This suggests a potential involvement of sex hormones in the development of the tumor. Research has demonstrated the expression of progesterone receptor (PR), estrogen receptor β (ER β), and androgen receptor (AR) in certain SPN tumor cells, with the activation of these receptors potentially contributing to tumor growth and proliferation. Sex hormones and their receptors modulate these multiple signaling pathways, influencing the progression of SPN at various levels. Notably, the CTNNB1 mutation serves as a pivotal driver of SPN, leading to the inhibition of β -catenin degradation and its nuclear translocation, as well as the abnormal activation of the Wnt signaling pathway. Furthermore, the Notch signaling pathway, the Hedgehog signaling pathway, and the epithelial-mesenchymal transition may also play significant roles. With the deepening understanding of the molecular mechanisms of SPN, especially the revelation of the interactions between sex hormone receptors and signaling pathways, potential targets for endocrine and targeted combination therapy have been identified. It is anticipated that precise combinations of endocrine and targeted therapies will improve the survival rate and quality of life for patients with unresectable or malignant SPN, bringing about a new breakthrough in the treatment of SPN.

Keywords Solid-pseudopapillary neoplasm, Pancreas, Sex hormones, Sex hormone receptors, Signaling pathways

Solid-pseudopapillary neoplasm (SPN) of the pancreas is a rare neoplasm characterized by low-grade malignancy. Initially described by Frantz in 1959 as a “Pancreatic papillary cystic tumor,” it is also referred to as Frantz’s tumor [1]. The WHO designated it as SPN in 1996, categorizing it as an exocrine neoplasm of the pancreas [2]. In 2010, the WHO reclassified SPN as a low-grade malignant neoplasm. The CiteSpace timeline analysis reveals that research on SPN has undergone three stages: the early focus on diagnosis and case reports (e.g., “case report,” “diagnosis”), the mid-term shift towards molecular mechanisms (e.g., “e-cadherin,” “androgen receptor”), and the recent concentration on signal-



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ing pathways and targeted therapies (e.g., “progesterone,” “Wnt pathway”). This trend aligns closely with the keyword emergence map (Fig. 1) – after 2011, there was a sudden increase in research intensity on “solid-pseudopapillary neoplasm” (with an emergence strength of 2.76), and its co-occurrence with markers such as “beta-catenin,” indicating that molecular mechanisms have become the core of research.

SPN constitutes approximately 1%-2.7% of all pancreatic exocrine tumors [3]. The exact origin of SPN within the pancreatic tissue remains speculative, with hypotheses ranging from the pancreatic ductal epithelium, acinar cells, endocrine glands, totipotent stem cells, primitive cells, the neural crest, to the gonadal ridge [4–10]. Epidemiological data indicate that over 90% of SPN cases occur in young females, with a male-to-female incidence ratio of approximately 1:9 [11]. The age distribution of SPN in females exhibits a bimodal pattern, with peaks at 28 and 62 years, whereas in males, it shows a unimodal

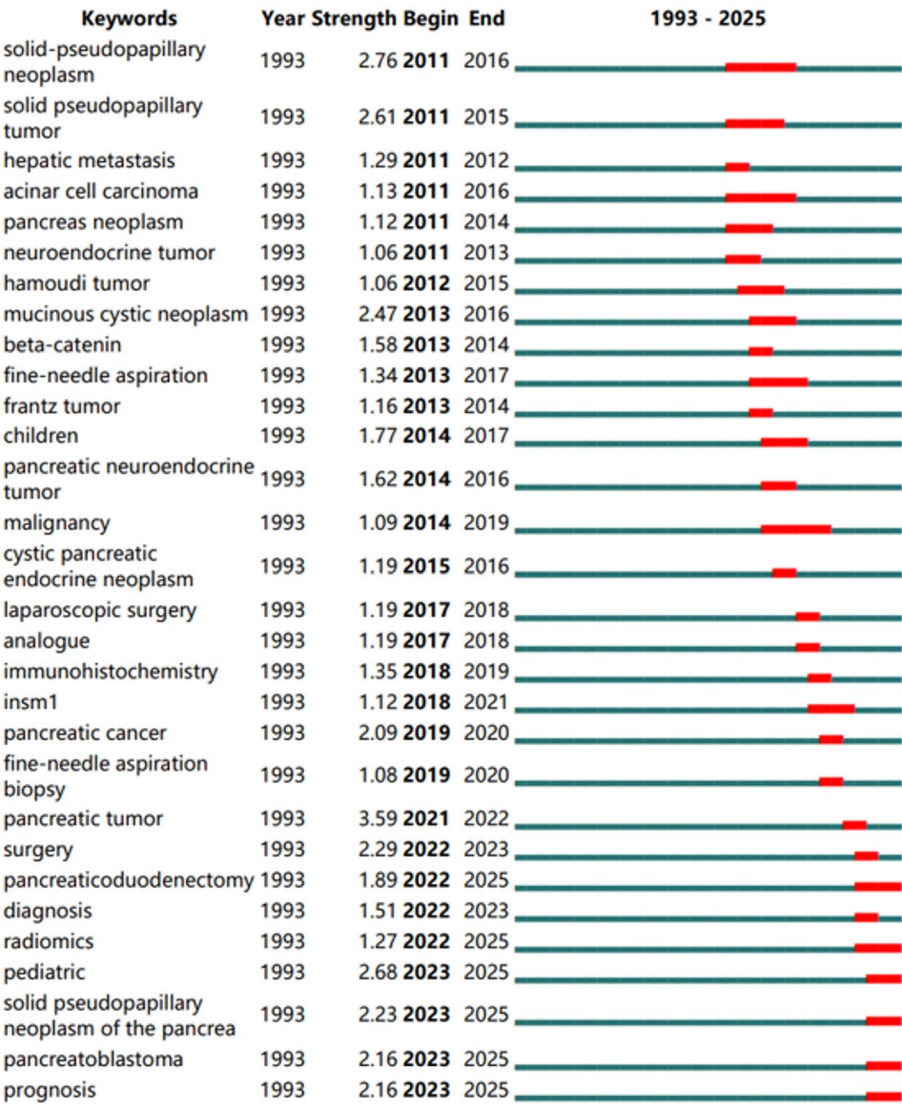


Fig. 1 Solid-pseudopapillary neoplasm of the pancreas (SPN) related research keyword emergence analysis map. Red bars: Indicate the time range of keyword emergence, with bar length corresponding to the duration of the emergence period. Strength: The value reflects the attention given to the keyword during the emergence period; higher values indicate greater research interest

pattern with a peak at approximately 64 years [12]. The keyword clustering analysis further reveals a strong association in cluster #12 among “progesterone,” “females,” and “androgen receptor” (cluster #11), as well as the co-occurrence of “mutation” and “neuroendocrine” in cluster #3 (Fig. 2). This suggests that the potential mechanism driving SPN may involve the synergistic action of sex hormone receptor regulation and genetic mutations.

In adults, the tail of the pancreas is the most frequent location for SPN, with the head and body being less commonly affected [13]. Conversely, in pediatric patients, the head of the pancreas is the predominant site for SPN [14, 15]. Despite advancements in imaging techniques that have improved diagnostic rates, a definitive diagnosis still relies on pathology and immunohistochemistry (such as the emerging marker INSM1). Based on the aforementioned research trends, this article primarily explores how sex hormones and their receptors regulate the onset and progression of SPN, providing a theoretical framework for endocrine and targeted therapies (Fig. 3).

1 Overview of SPN

1.1 Pathological features of SPN

SPN commonly arises in either the tail or head of the pancreas. The average size of SPN at the time of detection is 7.5 cm [16]. The tumor is primarily composed of cystic, solid, and pseudopapillary elements. Substantial variability in the extent of cystic degeneration is noted among different cases. Typically, SPNs in female patients are larger in diameter compared to those in male patients, with most tumors exceeding 5 cm in diameter. These tumors frequently exhibit classic features such as cystic degeneration, necrosis, hemorrhage, and calcification [17]. Hence, it is imperative to exercise utmost vigilance concerning the likelihood of solid pseudopapillary neoplasm (SPN) when young female patients present with pancreatic masses exhibiting both cystic and solid components. Conversely, SPNs encountered in male patients are more prone to exhibit predominantly solid characteristics, devoid of discernible pseudopapillary or pseudo-glandular structures, and marked degenerative alterations, thereby heightening the risk of misdiagnosis

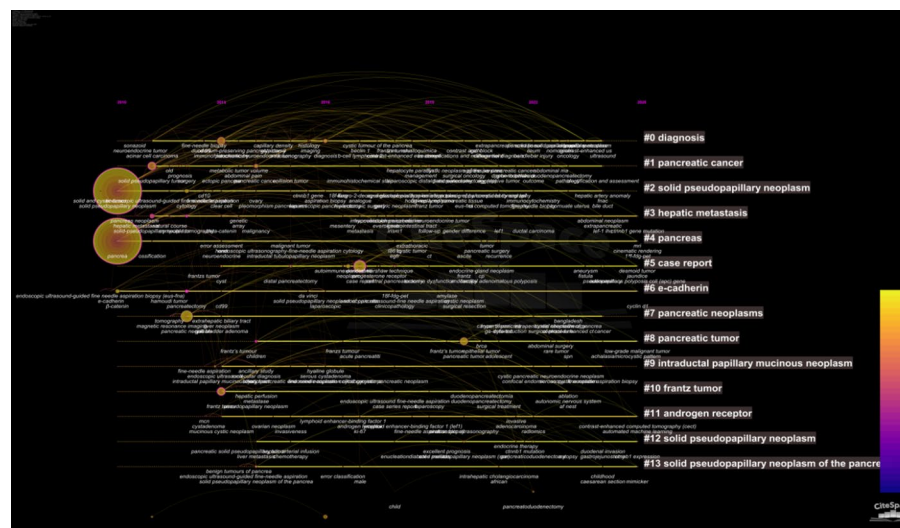


Fig. 2 Research timeline distribution of Solid-pseudopapillary neoplasm of the pancreas (SPN). Keywords and clustering: Keywords are grouped by research themes, with the timeline showing their first appearance. Temporal distribution: The horizontal axis represents years, and the vertical position indicates the keyword cluster

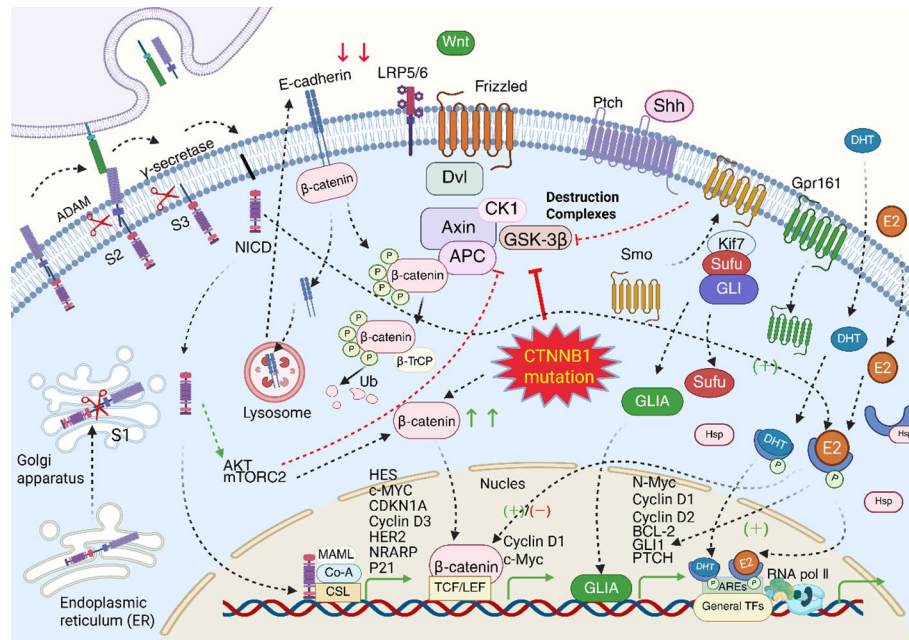


Fig. 3 Signaling Network in Solid-pseudopapillary neoplasm of the pancreas (SPN). This schematic illustrates the interplay of key signaling pathways dysregulated in SPN, highlighting the central role of Wnt/ β -catenin pathway activation. The network includes nuclear receptor (AR, ER), NOTCH, and Hedgehog pathways, showing key molecules and potential cross-talk. (See Supplementary Data for detailed pathway description). Key to Symbols: Solid Black Arrows: Direct molecular interactions or sequential steps. Green Arrows: Activation or increased gene transcription. Red Blunt-Ended Lines: Inhibition or decreased expression. (+): Promotion. (-): Inhibition. Dashed Arrows: Translocation (e.g., NICD, β -cat to nucleus) or indirect regulation. "P" in Green Circles: Phosphorylation. "Ub" Symbol: Ubiquitination. Scissors Symbol: Proteolytic cleavage (e.g., NOTCH, GLI processing)

as malignant tumors [18]. The solid region of the SPN, microscopically composed of cellular cables separated by small vessels, showing varying degrees of perivascular collagen deposition, forming a unique pseudorosette pattern similar to islet cell tumors [19]. The tumor cells within the parenchymal region exhibit a relatively uniform size and morphology, characterized by medium-sized, polygonal shapes, distinct cell boundaries, and lightly stained or translucent cytoplasm. The nuclei are round to ovoid in shape, with occasional nuclear grooves and nuclear division discernible [20]. The characteristic features of SPN are the pseudopapillary structures formed by the loose monomorphic tumor cells surrounding the fibrous vascular stalk, mucoid changes in the stroma around the small vessels, and eosinophilic bodies among some tumor cells [20].

1.2 Molecular biological markers of SPN

Due to atypical clinical and pathological manifestations, immunohistochemistry plays a vital role in identifying SPN, helping to distinguish other pancreatic tumors such as pancreatic neuroendocrine tumors, pancreatic ductal adenocarcinoma, and pancreatic acinar cell carcinoma. However, due to the rarity of SPN, large-scale clinical research is difficult to carry out, and a set of optimal immune marker combinations that can accurately diagnose SPN have not yet been determined. Numerous publications indicate that SPN cells commonly express β -catenin [21], vimentin [22], α -1-antitrypsin [22], progesterone receptor [23], CD10 [22], CD99 (perinuclear spotting) [24], and E-cadherin (missing) [25, 26]. However, the expression of other diagnostic markers such as galectin-3 [27], synaptophysin [28], estrogen receptor [29, 30], and androgen receptor [21,

31] varies in different studies (Table 1). Several studies have pointed out that CTNNB1 mutation, β -catenin nuclear accumulation, and the resulting activation of Wnt signaling pathway constitute the main molecular characteristics of SPN [32–35]. Although the combination of morphological characteristics and the nuclear positivity of β -catenin immunohistochemistry has always been the gold standard for the diagnosis of SPN, the high degree of overlap with the morphological and immunohistochemical findings of other pancreatic tumors still poses difficulties in the diagnosis of SPN. Lymphatic enhancer binding factor 1 (LEF1) serves as a pivotal molecule in the Wnt signaling pathway, and its diagnostic effectiveness in SPN has been validated in recent scholarly works. The findings of Kim et al. [21] substantiate β -catenin as the marker exhibiting the highest sensitivity (98.9%) and specificity (97%) for SPN detection. Additionally, lymphatic enhancer binding factor 1 (LEF1), transcription factor 3 (TFE3), and androgen receptor (AR) also display remarkable sensitivity and specificity. Notably, when β -catenin, LEF1,

Table 1 Summary of key immunohistochemical markers in SPN

Marker	Expression Pattern in SPN	Diagnostic Utility & Notes	Category
β -Catenin	Abnormal nuclear/cytoplasmic accumulation (loss of membranous expression)	Cornerstone for diagnosis. Caused by CTNNB1 mutation. Exceptionally high sensitivity and specificity.	Classic
E-Cadherin	Loss of membranous expression	Key negative marker, crucial for distinguishing from pancreatic neuroendocrine tumors (PanNETs).	Classic
Progesterone Receptor(PR)	Nuclear positivity (vast majority of cases)	Important ancillary marker with very high frequency of expression, reflecting female predominance.	Classic
CD10	Membranous/cytoplasmic positivity	Commonly used ancillary positive marker with high sensitivity.	Classic
Vimentin	Strong cytoplasmic positivity	Ancillary marker supporting mesenchymal differentiation. High sensitivity.	Classic
CD99	Paranuclear dot-like positivity	A relatively unique staining pattern that is suggestive of the diagnosis.	Classic
α -1-antitrypsin	Cytoplasmic positivity	Ancillary positive marker.	Classic
Androgen Receptor(AR)	Nuclear positivity (variable reported rates)	Expression may be more prominent in male patients; has diagnostic and pathogenetic implications.	Emerging/Supplementary
Lymphoid Enhancer-Binding Factor 1	Nuclear positivity	Downstream effector of the Wnt pathway; high sensitivity and specificity. Improves diagnostic accuracy in combination.	Emerging/Supplementary
Transcription Factor E3	Nuclear positivity	A recently proposed useful marker that aids in diagnosis.	Emerging/Supplementary
Galectin-3	Cytoplasmic positivity (may be decreased in metastases)	Investigational marker; expression may correlate with tumor behavior.	Investigational
Synaptophysin	Typically negative or only focal/weakly positive	Important negative marker used to rule out PanNETs (which are typically diffusely and strongly positive).	Negative Marker
Estrogen Receptor- α	Nuclear negative (vast majority of studies)	An important negative feature, forming a stark contrast with high PR expression.	Negative Marker
INSM1	Typically negative or only focally positive	Important negative marker used to rule out PanNETs (which are typically diffusely positive).	Negative Marker
Chromogranin A	Typically negative	Important negative marker used to rule out PanNETs.	Negative Marker

and TFE3 are utilized in concert, they achieve a sensitivity of 100% and a specificity of 91.9%, respectively.

1.3 Biological behavior of SPN

The vast majority of SPNs exhibit low-grade malignancy and have relatively inert biological behavior. They can usually be cured by surgical resection, and the five-year survival rate after surgery is 94–97% [11, 36]. While a minority of SPNs demonstrate aggressive behavior, metastasis, and recurrence, the mortality rate associated with these cases remains exceptionally low. The reported metastasis rate lies within the range of 10–15%, with the liver, peritoneum, and duodenum being the common sites of metastasis [28]. Kim et al. have suggested that the Ki-67 proliferation index, when exceeding 5%, serves as an effective marker for predicting the metastasis of SPN [21]. Furthermore, a separate study has demonstrated that the Fudan prognostic index, which incorporates both the Ki-67 index and tumor size exceeding 10 centimeters, exhibits a superior capacity in predicting recurrence-free survival (RFS). This index proves to be more precise than the Ki-67 index alone and outperforms existing staging systems such as the AJCC and ENETS TNM [37]. However, despite the occurrence of recurrence or metastasis, patients undergoing reoperation are still capable of attaining prolonged survival [38]. For those surgically inaccessible and more aggressive SPN, a comprehensive approach incorporating various treatment options may necessitate consideration.

1.4 SPN and other pancreatic tumors

SPN exhibits a distinct spectrum of features from other pancreatic tumors at both clinicopathological and molecular biological levels. Table 2 systematically compares the key characteristics of SPN with seven major pancreatic tumors: pancreatic ductal adenocarcinoma (PDAC), pancreatic neuroendocrine tumors (Pan-NETs), intraductal papillary mucinous neoplasms (IPMNs), acinar cell carcinoma (ACC), adenosquamous carcinoma (ASC), serous cystadenoma (SCN), and mucinous cystadenoma (MCN). Histologically, SPN is characterized by monomorphic polygonal cells forming pseudopapillary structures around delicate fibrovascular cores [20]; PDAC exhibits infiltrative glandular patterns with dense desmoplastic stroma; Pan-NETs display organoid nesting with “salt-and-pepper” chromatin [39]; IPMNs consist of intraductal papillary mucinous epithelial proliferation, which may be accompanied by invasive components; ACC is composed of acinar units with eosinophilic granular cytoplasm; ASC shows both glandular and squamous differentiation; SCN typically forms a honeycomb-like microcystic pattern lined by glycogen-rich simple cuboidal epithelium, often with a central fibrous scar [40]; MCN is characterized by tall columnar mucinous epithelium with distinctive ovarian-type stroma [41]. At the molecular level, >90% of SPNs harbor CTNNB1 exon 3 missense mutations, leading to nuclear accumulation of β -catenin and sustained activation of Wnt signaling [42]; PDAC is primarily driven by KRAS mutations, with frequent co-mutations in TP53/CDKN2A/SMAD4 [43]; Pan-NETs commonly exhibit inactivation of MEN1/DAXX/ATRX and activation of the mTOR pathway [44]; ACC may present with BRAF fusions or SMAD4 mutations; SCN often shows VHL inactivation; MCN, similar to PDAC, is predominantly characterized by KRAS and TP53 mutations [41], which are markedly distinct from the driver events in SPN. In terms of therapeutic strategies, SPN is considered a low-grade malignancy, and the majority of cases can be cured by

Table 2 Comparative overview of SPN versus major pancreatic tumor subtypes

Feature	SPN	PDAC	Pan-NET	IPMN	ACC	ASC	SCN	MCN
High-risk population	Young women (average age 28)	Elderly male	Middle-aged and elderly people	Elderly male	Middle-aged and elderly males	Elderly male	middle-aged and elderly women	Middle-aged woman
Site of predilection	Pancreatic body and tail	Pancreatic head	Any part of the pancreas	Pancreatic heads	Any part of the pancreas	Pancreatic head	Any part of the pancreas	Pancreatic body and tail
Histomorphology	Polygonal cells with a single shape form a pseudopapillary structure around the thin vascular axis	Adenomatous structure disorder, obvious cellular atypia, infiltrative growth, often accompanied by fibroconnective tissue hyperplasia	solid nested or trabecular architecture, uniform cell morphology, "salt-and-pepper" chromatin pattern	Intraductal papillary proliferation with mucin secretion and epithelial dysplasia	Tumor composed of acinar-like structures, cells are eosinophilic with abundant cytoplasm and marked nuclear atypia	Contains both adenocarcinoma and squamous cell carcinoma components	Composed of thin-walled cysts lined by a single layer of cuboidal epithelium with clear cytoplasm; central fibrous scar or stellate structure may be seen	Tall columnar mucinous epithelium with clear lumen with ovarian-type stroma
Immunohistochemical signature	β-catenin nuclear(+), CD10(+), PR/ERβ/AR(+), E-cadherin (-)	CA19-9 (+), MUC1(+), SMAD4(-)	CgA/Syn (+), INSM1(+), Ki-67 grading	MUC2(+),MUC5AC(+), CDX2(+)	Trypsin(+), chymotrypsin (+), lipase (+), α-1-antitrypsin(+)	P63(+), p40(+),CK5, (+), CK6(+)	α-inhibin(+), MUC1(+), MUC6(+)	MUC5AC(+), ER/PR(+)
Driver mutation	CTNNB1 exon-3	KRAS, TP53, CDKN2A, SMAD4	MEN1, DAXX/ATRX, mTOR pathway genes	KRAS, RNF43, CDKN2A	BRAF, SMAD4, KRAS, APC	KRAS, P53, SMAD4	VHL, VEGF, HIF1-α, CAIX	KRAS, TP53
Malignant potential	Low-grade malignant, metastasizable	Highly malignant, highly metastatic	G1-G3, metastasizable	Low to high grade, with potential for invasion	Moderately malignant	Highly malignant	Minimal malignant potential	Low-grade malignant
First-line therapy	Surgery	Surgical resection (for resectable cases), combined chemotherapy (such as FOL-FIRINOX or gemcitabine + albumin-bound paclitaxel)	Surgery	Surveillance or surgery	Surgery combined with chemotherapy	Surgery combined with chemotherapy	Surveillance or surgery	Surgery

SPN solid pseudopapillary neoplasm, PDAC pancreatic ductal adenocarcinoma, Pan-NET pancreatic neuroendocrine tumor, IPMN intraductal papillary mucinous neoplasm, ACC acinar cell carcinoma, ASC adenosquamous carcinoma, SCN serous cystic neoplasm, MCN mucinous cystic neoplasm

radical surgery alone; in contrast, PDAC and ASC require surgical resection combined with adjuvant chemotherapy such as FOLFIRINOX or gemcitabine-albumin paclitaxel; Pan-NET, IPMNs, and MCN are primarily treated with surgical intervention; SCN has an extremely low malignant potential and may be managed conservatively or with local resection. This comprehensive comparison not only establishes SPN as a distinct disease entity but also provides a theoretical foundation for its precise differential diagnosis and exploration of Wnt-targeted therapies.

2 The role of sex hormones and their receptors in SPN

2.1 Correlation between sex hormone levels and risk of developing SPN

Female patients constitute the predominant population affected by SPN, and some researchers speculate that the gender characteristics of SPN may be attributed to women's exposure to progesterone and/or estrogen during their reproductive years [12]. The delayed onset in certain female individuals could potentially stem from a lifelong accrual of environmental exposures. There have been documented instances of rapid progression of SPN during pregnancy [45, 46]. Notably, tumors identified in postmenopausal women exhibit significantly reduced dimensions in comparison to those found in premenopausal women. Nonetheless, no discernible variation in tumor size has been observed between postmenopausal women and male individuals [12, 47]. These findings indicate that female hormones, particularly estrogen and progesterone, may encourage the multiplication of SPN, whereas the reduced secretion of these hormones post-menopause might account for the regression of tumors. Nonetheless, the incidence of SPN in males implies that these hormones may play a contributory role in their progression, yet they are not the sole determinants. Additionally, it is plausible that the estrogen-rich tumor microenvironment exerts an influence on SPN, particularly given the pancreas's aromatase activity, which transforms androgens into estrogens [48], and its capability to convert weaker estrogens (estrone) into more potent forms (estradiol) through the 17 hydroxysteroid dehydrogenase pathway [49]. Although there are no definitive conclusions regarding the impact of estrogen and progesterone on the biological behavior of SPN, this topic necessitates that researchers delve into the possible involvement of sex hormones in the emergence and progression of SPN via laboratory investigations and hormone level evaluations. A case study conducted by Singh et al. on a primary ovarian SPN revealed analogous mutations in the CTNNB1 gene to those observed in pancreatic SPN [50], hypothesizing that SPN might have originated from the genital crest [51]. This hypothesis offers a credible rationale for the prevalence of SPN in females.

2.2 Expression of sex hormone receptors and related signaling pathways

2.2.1 Progesterone receptor (PR) and SPN

PR, a member of the nuclear receptor family, is tasked with responding to progesterone signals and modulating the expression of certain genes, thereby influencing cell growth, differentiation, and metabolic pathways [52]. Notably, PR exists in two primary isoforms, PRA and PRB, each with distinct functional implications. PRA is potentially linked to the suppression of gene transcription, contributing to the inhibition of cell proliferation in certain contexts. Conversely, PRB is often associated with enhancing gene transcription and playing a pivotal role in both cell proliferation and differentiation [53]. In SPN, the expression of PR is widespread and significant, with diffuse strong positive

expression in over 70% of SPN cases, particularly the PRB subtype. As an active receptor, PRB can activate downstream proliferative pathways by binding to progesterone, which may be related to the rapid tumor growth observed in SPN patients during pregnancy. Additionally, several studies have indicated that PR loss is associated with poor prognosis in various tumors, including SPN [20, 26, 54]. Le et al. proposed that progesterone can inhibit the growth of pancreatic tumor cells in a PR-dependent manner, and progesterone therapy can induce apoptosis in human pancreatic cancer cells and delay tumor growth [54]. These studies suggest that high PR expression may be associated with the lower malignancy of SPN. In summary, the roles of progestogens and progesterone receptors (PRs) in tumor occurrence and development are multifaceted. They may influence tumor growth and metastasis by promoting or inhibiting tumor cell proliferation, inhibiting apoptosis, and affecting the tumor microenvironment. Future research needs to clarify how the spatiotemporal expression patterns of different PR subtypes dynamically regulate SPN progression and whether progestogen therapy has potential for clinical translation.

2.2.2 Estrogen receptor (ER) and SPN

There are inconsistencies in the existing literature regarding the expression of ER in SPN. Some literature reports negative ER expression in SPN, which may be due to the fact that the monoclonal antibodies used in performing immunohistochemistry are directed only against ER α . However, following the discovery of human ER β and the advancement in the development of commercial immunohistochemistry kits [55], recent investigations have revealed that ER β exhibits positive expression in SPN [56]. Geers et al. [27] disclosed that the expression of nuclear ER α was absent in both primary and metastatic SPN tumor cells, whereas immunostaining for nuclear ER β protein demonstrated robust positivity. Notably, Tognarini et al. [57] discovered that the levels of ER β were significantly diminished in tumor tissues compared to those in normal pancreatic tissues, whereas ER α levels were augmented as revealed by both protein and mRNA analyses. A consistently elevated ER α /ER β ratio in tumors versus non-tumor tissues represents a hallmark of estrogen-dependent cancers [58, 59]. Furthermore, as previously demonstrated, SPN exhibits a higher ER α /ER β ratio in tumor tissues than in healthy tissues, potentially indicating an estrogen-dependent tumor nature. However, due to the conflicting findings present in the literature, further comprehensive studies are imperative to ascertain the precise pattern of ER expression in SPN. Meanwhile, it is advisable not to solely rely on immunohistochemical methods for analyzing ER expression, as this approach may not provide a comprehensive understanding of the phenomenon.

Estrogen receptor belongs to the esteemed nuclear receptor super family [60]. It is a transcription factor activated by ligands, possessing the archetypal structural attributes of nuclear receptors. It comprises an NH-terminal domain (NTD), a DNA-binding domain (DBD), and a COOH-terminal ligand-binding domain (LBD). The NTD is the smallest of these conserved domains, and there is only 15% homology between ER α and ER β in this region, whereas the DBDs of the two are identical, with 97% homology. In addition, the LBD with only 59% homology is essential for the two isoforms of ER α and ER β to fulfill their distinct roles, leading to differences in their regulatory gene transcriptional activities and consequently triggering different biological effects [61, 62]. ER α exerts a pivotal role in facilitating cell proliferation across a diverse range of tumor cells,

encompassing breast cancer, endometrial cancer, and ovarian cancer. It undergoes conformational changes upon binding to estrogen, translocating from the cytoplasm to the nucleus, binding to estrogen-responsive elements, and subsequently regulating the transcription of target genes. This ultimately influences crucial processes like cell cycle progression, apoptosis, and angiogenesis. Recent research has demonstrated that patients exhibiting positive nuclear ER α expression face a less favorable prognosis, and that this positive ER α expression is correlated with heightened levels of the tumor-promoting factor, G-protein-coupled cysteinyl leukotriene receptor 1 (CysLT1R), as well as nuclear β -catenin proteins [63]. This observation underscores a positive stimulatory role of ER α in tumor cytogenesis. ER β modulates the transcriptional activity of ER α via the formation of heterodimers with ER α or by engaging with target gene promoters independently of ligand availability, thereby influencing the stimulatory or inhibitory effects of ligands on cell proliferation [64]. In an in vitro examination of breast cancer cells, Geers et al. [27] discovered that ER β , in the presence of estrogen, triggered the expression of p21. P21, also known as CDKN1A, is an essential cell cycle regulatory protein. It inhibits tumor formation and development through various mechanisms, including cell cycle arrest, response to DNA damage, induction of cellular senescence, regulation of apoptosis, and suppression of tumor cell invasion and metastasis [65–68]. ER β , as a nuclear receptor, can bind to the estrogen response elements (EREs) in the promoter region of the p21 gene, directly promoting p21 transcription and thereby increasing p21 protein expression. Additionally, ER β can reduce p21 protein degradation by inhibiting the ubiquitin-proteasome system, such as blocking the activity of E3 ubiquitin ligases like Skp2. The multifaceted molecular interactions between P21 and ER β collectively construct a synergistic network that effectively inhibits tumor cell proliferation, promotes cellular senescence, maintains genomic stability, and blocks tumor metastasis [68]. However, a contrasting study presented a divergent viewpoint, contending that the preponderance of research investigating antiproliferative capacity has relied predominantly on transient transfection or induction methodologies. Furthermore, it was asserted that in the context of breast cancer cells, where ER β is consistently expressed, it fails to exhibit antiproliferative attributes, but rather, ER β possesses the capability to amplify, rather than counteract, ER α signaling [69]. The study further underscores that it does not preclude the possibility that ER β may exhibit its antiproliferative capability in alternative cellular contexts or under different circumstances [69]. This discrepancy may arise from the specificity of cell types, differences in experimental systems, and the complexity of the ligand microenvironment. Therefore, there is an urgent need to construct models specific to SPN to elucidate the regulatory mechanisms of the ER subtype network.

2.2.3 Androgen receptor (AR) and SPN

AR is a ligand-dependent nuclear transcription factor (TF) belonging to the steroid hormone receptor superfamily, encoded by the NR3C4 gene [70]. As with all other members of the family, AR comprises the LBD, DBD, and NTD, with a short amino acid sequence, referred to as the “hinge region”, intervening between the LBD and DBD. This hinge region also incorporates a portion of the nuclear localization signal (NLS), which is essential for the nuclear translocation of AR. The 5 α -reductase enzyme possesses the capability to transform intracellular testosterone into 5 α -dihydrotestosterone (DHT). Under physiological circumstances, both testosterone and DHT are capable of

binding to and activating the AR, with DHT exhibiting a greater affinity for the AR. In the absence of ligands, the AR primarily resides within the cytoplasm, where it binds to heat shock proteins (HSPs) including HSP-90, HSP-70, HSP-56, cytoskeletal proteins, and other chaperone proteins [71]. In the presence of testosterone or DHT, their interaction with the AR triggers the dissociation of the AR from the heat shock proteins. Subsequently, this enables the AR to translocate into the nucleus, where it binds to androgen response elements (AREs). These AREs then facilitate the recruitment of coactivators, ultimately leading to the activation of target gene expression. AR can also impact downstream transcriptional activity via interactions with co-regulatory factors, such as Forkheadbox Protein A1 (FOXA1) [72]. This process of gene transcription is commonly known as “classical transactivation” or “ligand-mediated transactivation” [73]. Furthermore, it has been established that the androgen receptor (AR) signaling pathway engages in crosstalk with numerous other pathways. Specifically, AR possesses the capability to stimulate the mammalian target of rapamycin (mTOR) via the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) cascade, thereby exerting anti-apoptotic effects [74]. Additionally, AR is capable of initiating the activation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway, which has been identified as a pivotal element in the development and activation of the AR pathway itself [75]. Concurrently, numerous downstream effectors within the MAPK signaling cascade offer a vast array of potential modulators of AR function. These modulators, via the process of phosphorylation, exert their influence by either augmenting or suppressing the transcriptional activity of AR, thereby having a profound impact on the growth, proliferation, and differentiation of tumor cells. It has also been discovered that the androgen receptor signaling pathway contributes to the development of SPN, with the upregulation of specific genes within this pathway, notably MED30, MED17, DAXX, and THRAP3. This upregulation may lead to an abnormal activation of the androgen receptor pathway [76]. The androgen receptor signaling pathway has been discovered to be intricately associated with the Wnt/ β -catenin pathway. In this interaction, the androgen receptor binds specifically to the armadillo repeat structural domain found within linker proteins [77]. Consequently, this binding process has the potential to amplify AR-mediated transcription, thereby enhancing its overall functionality.

A study by Zou et al. [78] noted that among the many markers of SPN, only the androgen receptor (AR) differed in expression between the sexes. Despite the prevalence of over 80% of tumors being AR-positive, the expression of AR in male tumors is notably more robust than in female tumors, potentially offering insights into the fundamental mechanisms underpinning gender disparities. Takahashi et al. [18] discovered that despite comparable tumor sizes between genders, a preponderance of male SPNs manifested a solid composition devoid of pronounced degenerative alterations. A rigorous and comprehensive comparison of the clinicopathological features of SPN across genders has been undertaken by a group of scholars. Drawing upon a substantial literature review conducted by Lin et al. [79], which encompassed 1014 SPN patients, comprising 877 females and 137 males, the study revealed several noteworthy findings. Firstly, the average age of male SPN patients was observed to be five years older than their female counterparts, with males averaging 33.4 years and females 28.3 years. Secondly, the incidence of metastasis among male patients was significantly elevated, exhibiting a two-fold increase compared to females (10.2% vs. 4.3%). Furthermore, males demonstrated a

higher prevalence of invasive malignant tumors, with a notable trend towards increased occurrence (24.4% vs. 12.4%). Lastly, and perhaps most strikingly, the mortality rate among male SPN patients was three times higher than that of females (11.4% vs. 3.6%). In a comprehensive analysis of 34 individuals diagnosed with SPN, comprising 27 females and 7 males, Machado et al. [80] discovered a noteworthy trend: the average age of male patients suffering from SPN was markedly older than that of their female counterparts (37 years as opposed to 25 years). Additionally, the study revealed a heightened prevalence of portal infiltration among male patients, despite the absence of statistically significant gender disparities in terms of the location of occurrence, incidental discoveries, and tumor recurrence. However, based on an analysis of clinical data from 285 previously reported SPN patients (21 males and 264 females) and 15 of them by Tien et al. [80], there were no significant differences in patient age, tumor size or location, or incidence of malignancy. Given the current limited number of male patient samples and the insufficient investigation into the correlation between AR expression levels and clinical stages, future research needs to delve into various aspects such as AR subcellular localization and coactivator expression.

2.2.4 Sex hormone receptor profile in SPN

Studies have shown that SPNs exhibit a unique sex hormone receptor expression profile: PR is frequently expressed, ER α is almost consistently absent, and AR shows variable expression (Table 3). Although the sex hormone microenvironment is believed to be involved in their pathogenesis and progression, the expression levels of these receptors show no significant correlation with most conventional clinicopathological prognostic indicators. Their potential value is mainly reflected in two aspects: First, case reports suggest that endocrine therapy, such as tamoxifen, may yield clinical benefits for patients with advanced, unresectable SPNs that are ER/PR-positive, providing a preliminary basis for targeted intervention. Second, despite the absence of ER α protein, existing evidence (such as ER β expression or functional experiments) still indicates that the estrogen signaling pathway may be active, highlighting the complexity of its regulatory mechanisms and warranting further investigation. In summary, this unique receptor expression profile not only serves as an important diagnostic marker for SPNs but also opens up a potential therapeutic exploration path for patients with advanced disease.

3 Molecular mechanisms and the regulatory roles of sex hormones and their receptors

3.1 Wnt/ β -catenin (CTNNB1) signaling pathway and SPN

Wnt signaling represents an intercellular evolutionary coordination mechanism that holds paramount importance in orchestrating diverse physiological processes within organisms. These encompass stem cell regeneration, proliferation, division, migration, as well as cell polarity, fate determination, and the specification of neural crest, neural symmetry, and morphogenesis [92]. Research has indicated that an abnormal activation of the Wnt/ β -catenin signaling pathway is intimately associated with the escalating prevalence, malignant progression of the disease, unfavorable prognosis development, and even a heightened cancer-related mortality rate [93].

Table 3 Summary of studies on sex hormone receptor expression in SPN

First Author (Year)	Case Size (n)	Detection Method	Antibody/Clone (Company)	Subcellular Localization	Positive Criteria	Positive Rate (%)	Correlation with Clinicopathological Features/ Prognosis
Jørgensen [81]	2	IHC	Not specified	Nucleus	Count 500 cells, 80 positive	ER: 16% (80/500)	Suggested ER presence might benefit anti-estrogen therapy (e.g., Tamoxifen) for inoperable cases.
Miksmahl [51]	59	IHC	PR: DAKO; ER: DAKO	Nucleus (PR)	Semi-quantitative (-, 1+, 2+, 3+)	PR: 100% (57/57); ER: 0% (0/57)	High PR expression supports hypothesis of origin from embryonic gonadal/ovarian primordial related cells.
Yeh [46]	10	IHC	PR: pgR636 (DAKO); ER: ID5 (DAKO)	Nucleus (PR)	Reiner's criteria (Negative/Positive)	PR: 100% (10/10); ER: 0% (0/10)	Unique PR expression in SPT, absence of ER, reflects female predominance.
Choi [82]	12	IHC	PR: PgR 636 (DAKO); ER: 1D5 (DAKO)	Not specified	Intensity and distribution (Diffuse >50% or Focal < 50%)	PR: 33.3% (4/12); ER: 0% (0/12)	Hormone receptor expression not reliable for differential diagnosis (vs. NFICT). SPN has lower Ki-67.
Ohiwa [83]	1 (Male)	EIA	Monoclonal Ab (Dainabot)	Not mentioned	< 5.0 fmol/mg protein negative	PR: Negative; ER: Negative; AR: Not tested	Suggested estrogen/progesterone not involved in pathogenesis in this male case.
Tien [19]	15	IHC	PR/ER/AR: NeoMarkers	Nucleus (PR)	Not specified	PR: 100% (15/15); ER: 0% (0/15); AR: 0% (0/15)	No difference in PR expression or clinical features between males and females.
Geers [27]	5	IHC	ERα: 1D5 (Neomarkers); ERβ: PPG5/10 (Serotec) or Polyclonal (Biogenex); PR: 1A6 (Neomarkers)	Nucleus	Not explicitly described	ERα: 0%; ERβ: 100%; PR: >80% strong (primary); weaker in metastasis	Weaker PR expression in metastasis may correlate with aggressive behavior.
Liu [84]	3	IHC	ER: 6F11; PR: 1A6 (Ventana)	Nucleus	Not detailed	ERα: 0% (0/3); PR: 100% (3/3)	The single male patient showed PR positivity (90% of cells).
Tognarini [57]	1 (SPNC cell line)	IHC/mRNA	ERα: 6F11 (Ventana); ERβ: EMR02 (Novocastra); PR: 1E2 (Ventana)	Tissue: Nucleus (ERα, PR); Cell line: Negative by IHC	Not specified	Tissue: ERα(+), PR(+), ERβ(-/+); Cell line: Negative by IHC, mRNA positive	Functional evidence: 17β-estradiol promoted SPNC proliferation, Tamoxifen inhibited it.
Park [76]	14	Microarray/IHC/WB	AR: Not specified (Roche)	Nucleus (IHC)	Gene level: Microarray; Protein: IHC/WB validation	mRNA(AR): Significantly upregulated (9.89-fold); Protein(AR): 100% (14/14)	AR signaling pathway is activated, potential diagnostic marker. Clinical significance needs study.
Regi [85]	9 (Males)	Serum Hormone Assay	Not tested on tissue	Not applicable	Assessed serum levels and sexual function	Estrogen/Progesterone: Normal in all patients	Male occurrence might be related to long-term exposure to normal female hormone levels.

Table 3 (continued)

First Author (Year)	Case Size (n)	Detection Method	Antibody/Clone (Company)	Subcellular Localization	Positive Criteria	Positive Rate (%)	Correlation with Clinicopathological Features/ Prognosis
Bellarbi [86]	2 (1 F, 1 M)	IHC	Not specified	Not specified	Not specified	PR: Positive (1/1 F); ER: Negative (0/1 F); AR: Not tested	PR expression and female predominance suggest possible hormone dependence.
Hirabayashi [87]	22 (16 F, 6 M)	IHC	ER: SP1 (Ventana); PR: 1E2 (Ventana)	Nucleus	Semi-quantitative (-, +, ++, +++)	ER: 0% (0/22); PR: 95.5% (21/22)	No significant correlation between PR expression and gender, age, tumor size, etc.
Uppin [88]	33 (IHC:31)	IHC	ER: IDS; PR: PR88 (BioGenex)	Nucleus	Not detailed	ERα: 0% (0/31); PR: 64.5% (20/31)	Correlation with clinicopathological features not discussed.
Kim [21]	91	IHC (TMA)	AR: Not specified	Nucleus	TMA scoring	AR: 81.3% (74/91)	AR expression more frequent in males ($p = 0.035$). No correlation with malignant behavior.
Calvani [21]	14	IHC	ERα: SP1 (Roche); PR: 1E2 (Roche)	Nucleus	Positive: ≥1% tumor cells stained	ERα: 0% (0/13); PR: 100% (13/13)	No difference in IHC profiles between males and females.
McHugh [31]	19 Cytology/15 Surgical	IHC	AR: AR441 (Dako/Agilent)	Nucleus	Any nuclear staining in tumor cells	AR(Cytology): 25.0% (4/16); AR(Surgical): 26.7% (4/15)	No significant gender difference in AR positivity ($p = 0.097$). No correlation with malignancy.
Yasuda [89]	1 (Case Report)	IHC	PR/ERα: Not specified	Not described	Not described	PR: Negative; ERα: Negative	Tumor regression with negative receptors supports hypothesis that hormonal changes influence SPN growth.
Korrietskaya [90]	1 (Case Report)	IHC	ER/PR: Not specified (Allred)	Nucleus	Allred Score = 7	ER: Positive; PR: Positive	Durable stable response to endocrine therapy (Tamoxifen).
Ghabra [91]	1 (Case Report)	IHC	Not mentioned	Nucleus	Not detailed	ER: Positive; PR: Positive	Used for diagnostic confirmation. Correlation not discussed.

SPN Solid Pseudopapillary Neoplasm, IHC Immunohistochemistry, WB Western Blot, EIA Enzyme Immunoassay, mRNA Messenger RNA, ER Estrogen Receptor, AR Androgen Receptor, SPT Solid Pseudopapillary Tumor, NFICT Non-Functioning Islet Cell Tumor, TMA Tissue Microarray, SERM Selective Estrogen Receptor Modulator, F female, M male

Numerous studies point out that the abnormal accumulation of β -catenin in the nucleus and the loss of E-cadherin are the most characteristic immunohistochemical manifestations of SPN [25, 26, 78, 94]. As β -catenin serves as a pivotal regulatory molecule within the archetypal Wnt signaling cascade, it holds immense significance in maintaining tissue homeostasis and orchestrating cell proliferation, differentiation, and function. Consequently, this canonical Wnt signaling pathway is frequently referred to as the Wnt/ β -catenin signaling pathway. The vast majority of studies confirm that CTNNB1 exon 3 mutation is the core molecular event of SPN, with mutation frequencies ranging from 74% to 100%. The types of mutations are mostly missense mutations, and they are highly concentrated in the 32nd, 33rd, and 37th codons, and the 34th and 41st codons are also relatively common (Table 4). Among them, D32 site mutations (especially D32N/Y/H) may be more common in metastatic SPN, while S37 mutations are more frequent in primary SPN [95]. In addition to CTNNB1, some cases, especially SPN with aggressive or metastatic characteristics, may be accompanied by co-occurring mutations or chromosomal instability such as APC, TP53, PTEN, PIK3CA, KDM6A, BAP1, and TET1 [35, 95–101]. These additional genetic alterations are associated with higher proliferative activity (Ki-67 index) and poor clinical behavior.

β -catenin, as a downstream transcriptional activator of the Wnt signaling pathway, binds to E-cadherin on the cytosolic side in the absence of Wnt ligands and is tightly regulated by a destruction complex (DC) composed of scaffold protein Axin, adenomatous polyposis protein (APC), glycogen synthase kinase 3 β (GSK3 β), and casein kinase 1 (CK1) [109]. DC mediates β -catenin phosphorylation at Ser45/Thr41/Ser37/Ser33 sites, and the phosphorylated β -catenin is ubiquitinated and degraded by the β -TrCP/Skp pathway in the cytoplasm, through β -transducin repeat protein (β -TrCP), to maintain low levels of free β -catenin in the cytoplasm [110]. The Wnt signaling pathway typically involves extracellular ligands, with receptors consisting of the frizzled (Fzd) receptor and the Lrp co-receptor. Activation of the Wnt pathway occurs upon binding of the Wnt ligand to the receptor, which neutralizes the inhibitory effect of the DC. Subsequently, the intracellular β -catenin protein accumulates and translocates to the nucleus, where it forms a complex with the T cell factor/lymphoid enhancer factor (TCF/LEF) family of DNA-binding proteins. This complexation subsequently influences the transcription of downstream target genes, such as the cell cyclin D and c-MYC [100, 111].

In SPN, the CTNNB1 mutation results in the loss of the binding site for GSK-3 β phosphorylation, which hinders the normal degradation of β -catenin, resulting in its accumulation in the cytosol, which in turn triggers aberrant activation of the Wnt/ β -catenin pathway [112]. Apart from the CTNNB1 mutation, the disruption of other constituents within the complex similarly results in the irregular accumulation of β -catenin, encompassing genetic alterations in APC and Axin-1. Mutational inactivation of APC in the colorectum leads to aberrant stabilization of β -linker proteins and persistence of β -catenin protein-Tcf4 complexes, which contribute to the transformation of epithelial cells into crypt progenitor cells, resulting in the formation of adenomas [113]. It was additionally observed that tumors in patients with SPN carrying APC codon mutations displayed aggressive clinical characteristics [100]. Several cases have also been reported in the literature suggesting a potential correlation between familial adenomatous polyposis (FAP) and SPN [114, 115]. Axin is a multi-domain protein that interacts with

Table 4 Summary of key genomic studies on CTNNB1 mutations in solid pseudopapillary neoplasms of the pancreas

First Au- thor (Year)	Study Type	Sample Size	CTNNB1 Mutation Frequency	Hotspot Codons	Co-occurring Alterations	Clinico- pathological Associations
Kim [102]	Cohort	20	16/20 (80.0%)	D32 (5), S33 (7), S37 (4)	LOH at APC locus (5q22.1) in 55.5% (10/18) of cases.	1. S33 mutation correlated with male sex ($P < 0.019$). 2. Nuclear β -catenin accumulation seen in all cases.
Rund [103]	Retrospective Cohort	12	Not tested	Not tested	Chromosomal gains (e.g., 13q, 17q, 1q, 8q) identified by aCGH.	Number of chromosomal alterations associated with aggressive histological features ($P = 0.024$).
Huang [104]	Cohort	27	27/27 (100%)	D32 (14), S33 (3), G34 (4), S37 (5), T41 (1)	No AXIN1 mutations; loss of/reduced cytoplasmic Axin-1 expression in all cases.	1. S37 mutation associated with weak Axin-1 expression ($P = 0.018$). 2. The single T41-mutant case showed extensive necrosis.
Ko- bayashi [105]	Case Report/Review	Case: 1 Review: 123	Case: 1/1 (100%) Review: 111/123 (90.2%)	Case: S37F Review: D32 (32.5%), S33 (15.4%), G34 (17.9%), S37 (22.0%), T41 (1.6%)	Case: Not mentioned.	Review: Summarized mutation distribution; no specific clinical correlations reported.
Kubota [33]	Cohort	7	7/7 (100%)	D32 (3), S37 (2), T41 (2)	Unexpected CTNNB1 mutation (D32N) found in one pancreatic neuroendocrine tumor.	Not analyzed.
Spring- er [99]	Retrospective Cohort	10	10/10 (100%)	Not specified	TP53 (1 case, 10%); PIK3CA (2 cases, 20%).	CTNNB1 mutation was 100% specific for distinguishing SPN from other cystic lesions.
Guo [106]	Cohort (WES)	9	9/9 (100%)	D32 (3), S37 (3), S33 (2), G34 (1)	Other SNPs/Indels present (e.g., USP9X); no recurrent co-driver mutations.	High SNP burden correlated with metastasis and large tumor size (>100 mm) ($p < 0.01$).
Wang [100]	Prospective (Panel)	6	4/6 (66.7%)	S37A (2), D32N (2)	APC frameshift mutation identified in one CTNNB1-wild-type aggressive tumor.	The APC-mutant case showed aggressive histology and fatal liver metastasis.

Table 4 (continued)

First Au- thor (Year)	Study Type	Sample Size	CTNNB1 Mutation Frequency	Hotspot Codons	Co-occurring Alterations	Clinico-pathological Associations
Sele- nica [107]	Basic (Multi-omics)	14	14/14 (100%)	D32, S33, S37, T41 (by illustration)	Genomically simple; recur- rent mutations only in THADA, TPRXL; one TP53 mutation.	Low genomic complex- ity consistent with indolent behavior.
Amato [96]	Cohort (Metastasis)	Primary: 10 Pairs: 5	15/15 (100%)	D32 (3), S33 (2), S37 (3), T41 (2) (WES-based)	Inactivating mutations in epigen- etic regulators (KDM6A, BAP1, TET1) in meta- static SPNs.	1. Epigenetic mutations as- sociated with metastasis. 2. Increased CNVs in meta- static SPNs.
Rodri- guez- Matta [35]	Large Retrospective Cohort	31	29/31 (93.5%)	D32 (14, 45.2%); S37 (9, 29.0%); G34 (3, 9.6%)	TP53 (3, 9.6%); LRP1B (2, 6.4%); others (e.g., BRCA2, PTEN).	Cohort enriched for metastatic/ recurrent cases (64%); more concomitant mutations in metastases.
Zou [78]	Retrospective Comparative	30 (M:9, F:21)	30/30 (100%)	Shared: D32, S33, S37 Female-specific: G34, T41, C62	Not specifically reported.	Male SPNs had distinct features (solid growth, fibrous stroma, clear cells, strong AR expression).
Wang [101]	Case Report	1	1/1 (100%)	S33C	PTEN (p.G127R), ATM (p.S1878L), germline FANCD2 mutation.	Everolimus (mTOR inhibitor) based on PTEN mutation led to stable liver metastases for >22 months.
Flem- ing [95]	Retrospective Cohort	28 (Pri- mary:17, Met:11)	24/28 (85.7%)	Primary: S37F/C (37.5%) Metastatic: D32N/Y/H (54.5%)	Rare alterations (e.g., NTRK1, PTCH1, ERCC5, BAP1).	D32N/Y/H mutations more common in metastatic SPNs ($p = 0.0161$), suggesting association with aggressiveness.
Zhao [108]	Retrospective Cohort	179	133/179 (74.3%)	D32 (26%), S33 (23%), S37 (21%), G34 (14%), T41 (11%)	No consistent non-CTNNB1 mutations found by NGS in three atyp- ical cases.	Pediatric group (< 18 y) had larger tumors, higher Ki-67, higher Syn nega- tivity, and loss of nuclear CTNNB1 expression.

Table 4 (continued)

First Au- thor (Year)	Study Type	Sample Size	CTNNB1 Mutation Frequency	Hotspot Codons	Co-occurring Alterations	Clinico-pathological Associations
Li [98]	Cohort (cfDNA)	14 (Metastatic)	2/14 (14.3%) (in cfDNA)	D32Y (2 cases)	BRAF mutations (4 cases) more frequent than CTNNB1; others (KRAS, PIK3CA).	Detection of somatic mutations in cfDNA was associated with metastatic potential.
Cheng [97]	Case Report	1 (Metastatic)	0/1 (0%)	Wild-type	APC homozygous loss-of-function mutation (primary & metastasis).	Showcased an aggressive, APC-driven SPN (Ki-67 30%, widespread metastases).

SPN Solid-pseudopapillary neoplasm of the pancreas, LOH loss of heterozygosity, aCGH array comparative genomic hybridization, WES whole-exome sequencing, SNP single nucleotide polymorphism, Indel insertion/deletion, CNV copy number variation, cfDNA cell-free DNA, AR androgen receptor

a variety of proteins and acts as a scaffold protein to promote β -catenin degradation. Huang et al. [104] discovered that Axin-1 is underexpressed in SPN, and it was hypothesized that the reduced expression of Axin-1 in the cytosol could potentially contribute to the abnormal distribution of β -catenin within SPN.

A rigorous study conducted by Abraham et al. [116] on 19 patients with SPN revealed that 74% of the cases exhibited an elevated expression of cyclin D1. This protein functions as a downstream effector of nuclear connexin, with its transcription facilitated by the connexin complex through binding to specific sequences present on the promoter region of cyclin D1. Consequently, the overexpression of cyclin D1 can be considered as a potential downstream consequence of β -connexin dysregulation. Additionally, Singhi et al. [117] observed a diffuse overexpression of LEF1 in SPN, suggesting a potential involvement of the CTNNB1/LEF1 transcriptional complex in tumor development, albeit the precise mechanism underlying LEF1 overexpression remains unclear.

Despite the observation of aberrant activation of the Wnt/ β -catenin pathway and overexpression of cyclin D1, which are typically associated with aggressive malignancies, SPN unexpectedly exhibited an unusually benign clinical course. Scholars have offered diverse interpretations for this phenomenon. Selenica et al. [107] conducted gene expression analysis on SPN and postulated that the lack of somatic genetic alterations and low-level genomic complexity in addition to the CTNNB1 mutation could offer an explanation for the inert behavior of SPN. In contrast, Hallas et al. [118] posited that despite the overexpression of cyclin D1 in SPN, its functionality is at least partially constrained owing to the presence of p21 and p27, inhibitors of cyclin D1 expressed in SPN. These inhibitors disrupt the Wnt signaling pathway by blocking the hyperphosphorylation of Rb proteins, ultimately resulting in a diminished proliferation rate within SPN [119]. They also discovered that the expression of the β -catenin stabilizing gene BCL9L in SPN was notably diminished, potentially accelerating β -catenin degradation and impairing its nuclear function, thereby hindering β -catenin's ability to perform its transcription-promoting duties [118]. This finding also sheds light on the underlying mechanism behind the excessively benign characteristics of SPN. Interestingly, Geers et al. [27] discovered elevated concentrations of galectin-3 within the regions of typical SPN tumors. However, the expression of galectin-3 was notably diminished in invasive

nodules and areas characterized by diffuse growth, nuclear anisotropy, pleomorphism, and a heightened rate of nuclear division. Galectin-3 is a β -galactoside-binding protein that possesses numerous biological functions, encompassing cell-cell interactions, cell-matrix adhesion, cell proliferation, cell differentiation, as well as apoptosis [120]. It safeguards cells from apoptosis through the secondary down-regulation of cell cycle proteins E and A levels, coupled with the up-regulation of cell cycle inhibitor proteins p21 and p27. Whereas galectin-3 expression was lower in metastatic nodules, Shimamura et al. suggested that this could be the result of decreased galectin-3 expression leading to low cell adhesion and promoting tumor progression [121].

The interaction mechanism between SPN neutrogen receptors and the Wnt/ β -catenin pathway has not been fully elucidated, and the existing understanding mainly stems from mechanistic inferences from other tumor models. Studies have shown that estrogen receptors can regulate Wnt pathway activity through various pathways: ER α can transcriptionally inhibit the expression of key components such as AXIN1, directly promoting the stabilization and activation of β -catenin [122, 123]. At the same time, ER β activation can upregulate the level of non-phosphorylated β -catenin through the PI3K/AKT signaling pathway, driving cell proliferation [124, 125]. At the level of pharmacological intervention, selective estrogen receptor modulators (such as Ormeloxifene) can directly bind to β -catenin and GSK3 β and inhibit their transcriptional activity, which provides an experimental basis for the direct regulation of the Wnt pathway by sex hormone-related ligands [126]. These mechanisms collectively suggest that in SPN, the structural activation of the Wnt pathway driven by CTNNB1 mutations may synergize with sex hormone signaling through similar pathways, thereby providing a reasonable biological explanation for the epidemiological feature of this tumor's high incidence in young women. However, the validation of these inferences still requires in-depth functional studies in SPN-specific models.

3.2 Notch signaling pathway and SPN

Apart from the aberrant activation of the Wnt/ β -catenin signaling cascade, certain research endeavors have unearthed that the constituents of the Notch pathway exhibit abnormal expression patterns within SPN. Specifically, there is a notable upregulation of Notch target genes, including HEY1 and HEY2, as well as Notch ligand genes such as JAG1 and receptor genes like NOTCH2. Conversely, the expression of SEL1L, the gene responsible for encoding the Notch repressor protein, is observed to be diminished. These findings collectively suggest that the Notch pathway may potentially contribute to the initiation and progression of SPN [5]. Classical research has revealed that Notch signaling constitutes an evolutionarily conserved pathway. The Notch receptor undergoes three distinct cleavages, transforming into the active effector form known as the Notch intracellular domain (NICD). This NICD can subsequently be degraded within the cytoplasm or transported into the nucleus, where it regulates the transcription of specific target genes [127]. In the non-canonical Notch signaling pathway, NICD may be translocated to the nucleus or remain sequestered within the cytoplasm, engaging in intricate interactions with additional signaling cascades, including NF κ B, mTORC2, AKT, and Wnt pathways [128–130]. And a potential close correlation between the Notch and Wnt/ β -catenin signaling pathways has been observed [76, 130].

Considering the sex distribution characteristics of SPN and the expression of sex hormone receptors detected in some cases, the possible crosstalk between sex hormone signaling and the Notch pathway is of concern. Currently, this interaction is not directly supported by evidence in SPN, but its biological plausibility mainly stems from findings in other tumor models. For example, in breast cancer and other models, estrogen and progesterone can regulate the stability of NOTCH ligands and enhance their transcriptional activity through their receptors [131, 132]. In turn, NOTCH signaling regulates the transcriptional function of sex hormone receptors and activates their downstream target genes even in the absence of ligands [133]. This bidirectional interaction has important clinical implications, for example, in hormone-sensitive tumors, treatment targeting a single pathway may lead to drug resistance due to compensatory activation of the other pathway, while combined inhibition strategies show better anti-tumor effects [134]. In addition, a variety of sex hormone receptors have been shown to be involved in the regulation of the NOTCH pathway, suggesting that this may be a relatively conserved molecular mechanism [135, 136]. If similar crosstalk mechanisms exist in SPNs, they may jointly affect tumor cell proliferation, survival, and their unique low metastatic potential. The confirmation of this theoretical possibility requires future systematic evaluation of functional experiments using the SPN preclinical model for parallel intervention of hormone receptors and Notch signaling.

3.3 Hedgehog (Hh) signaling pathway and SPN

The findings of Park et al. demonstrate notable activation of the Hedgehog signaling pathway in SPN, which is concurrent with the upregulation of genes including BMP7, ZIC2, GLI2, GLI3, and Sufu [76]. The Hedgehog pathway comprises pivotal elements, namely ligand Hh proteins (Shh, Ihh, Dhh), receptor proteins (Ptch and Smo), GIL proteins (GLI1, GLI2, GLI3), and fusion protein inhibitors (Sufu) [137]. The function of the GLI repressor (GLIR) is predominantly derived from GLI3, whereas the function of the GLI activator (GLIA) is primarily attributed to GLI2. Furthermore, GLI1 serves as a direct transcriptional target of the Hh signaling pathway, augmenting the function of GLIA via a positive feedback mechanism [138]. In the absence of Hh ligands, Ptch localizes to the primary cilia and inhibits its activity by inhibiting Smo translocation into the primary cilia tip, resulting in the cleavage of the full-length glioma-associated oncogene (GLIFL) to GLIR by phosphorylation by protein kinase A (PKA), glycogen synthase kinase-3 (GSK3), and casein kinase 1 (CK1), thereby inhibiting the expression of the target gene [139–141]. However, upon activation of Hh signaling, Hh binds to Ptch proteins, leading to the internalization and degradation of the Hh-Ptch complex within the lysosome. Consequently, Ptch ceases to inhibit Smo, enabling it to relocate to the primary cilium's tip. Here, Smo signals Sufu to release GLIA, which subsequently translocates to the nucleus, thereby activating the transcription of downstream target genes [142, 143]. As an important negative regulator of the Hh pathway, Sufu is between Smo and GLI and directly binds to GLI protein and inhibits the onboarding of Hh signaling pathway by preventing GLI protein translocation to the nucleus [144, 145]. Abnormal activation of the Hh signaling pathway in tumor development is associated with mutations and amplification of relevant genes in the pathway as well as ligand overexpression. The aberrant activation of the Hh pathway includes ligand-dependent activation and ligand-independent activation, in which ligand-dependent pathway activation is

associated with tumors such as gastrointestinal tumors, prostate cancer and pancreatic cancer [146], and ligand-independent pathway activation is associated with basal cell carcinoma and medulloblastoma [147]. In the pancreas, pancreatic ductal adenocarcinoma (PDAC) has been observed to correlate with the upregulation of Shh, while the development of pancreatic intraepithelial neoplasia is intimately linked to the activation of GLI2 [148]. Nevertheless, the precise function of the Hh signaling pathway in SPN remains an area of ongoing research and exploration.

At present, there is no experimental confirmation of the mechanism of direct interaction between sex hormone receptors and the Hh pathway in SPN. Existing indirect evidence suggests that sex hormone receptors can cross-talk with the core components of the Hh pathway through multiple molecular mechanisms. For example, in breast cancer, ER has been shown to directly initiate gene transcription of Gli1 [149] or maintain its stability and activity by directly binding to the Gli3 protein [150]. In addition, the antiestrogen drug tamoxifen has also been shown to affect GLI1 expression and nuclear localization through ER [151]. Similarly, in prostate cancer models, AR can directly bind to the Gli2 protein to jointly regulate downstream target genes [152]. These findings systematically suggest that sex hormone receptors can deeply regulate the Hh signaling pathway by regulating gene transcription and direct binding at the protein level. Studies in other tumors have revealed that crosstalk of the sex hormone-Hh pathway often synergistically promotes malignant phenotypes such as stem cell properties, epithelial-mesenchymal transition (EMT), and treatment resistance. Given the reported expression of sex hormone receptors in SPN, it is speculated that similar crosstalk mechanisms may also exist in SPN, but this is still an important scientific hypothesis to be verified by future studies.

3.4 Epithelial-mesenchymal transition (EMT) and SPN

In comparison to normal pancreas and alternative pancreatic tumors, the epithelial indicator E-cadherin exhibits a notable downregulation, concurrently with a substantial upregulation in the expression of mesenchymal markers, vimentin and N-cadherin, within SPN. Furthermore, the enhanced expression of EMT regulatory genes, TWIST2 and ZEB2 [76], hints at the potential occurrence of EMT in SPN. Dong et al. [153] have suggested that EMT could potentially be a contributing factor to the recurrence of SPN. EMT is a pivotal biological process in cellular biology, characterized by the loss of polarity in epithelial cells and the subsequent acquisition of mesenchymal cell attributes. This intricate mechanism not only contributes significantly to embryonic development and tissue repair, but it is also intimately linked to the metastasis of cancer, underscoring its importance in various biological contexts [154]. As a crucial cell adhesion molecule, E-cadherin functions in the maintenance of tight junctions within epithelial cells. The downregulation of E-cadherin serves as a significant indicator of EMT initiation, and its absence of expression has been firmly established as a contributory factor in cancer progression. This loss is frequently linked to an aggressive tumor phenotype and a poor clinical prognosis [155, 156].

Furthermore, alterations in the ZEB factor, the miR-200 family, and TGF β significantly contribute to the intricate EMT process. MicroRNAs encompass a diverse category of 18–24 nucleotide-long non-coding RNAs that selectively bind to and either cleave mRNAs or suppress the translation of their corresponding genes [157]. The

microRNA-200 family encompasses five distinct members: miR-200a, miR-200b, miR-200c, miR-141, and miR-429. This family contributes to the enhancement of the epithelial phenotype by means of post-transcriptional inhibition of ZEB1/ZEB2 (ZEB) and TGF β 2. Conversely, the absence of the miR-200 family may signify an advanced stage in the progression of epithelial tumors [158]. TGF β is the main inducer of EMT in embryogenesis and cancer metastasis, and the expression of ZEB transcription factors is upregulated by TGF β , resulting in their binding to E-box elements and inhibition of E-cadherin and polarity factor genes, ultimately leading to EMT alterations in some cells [158]. The study revealed that subsequent to TGF β -mediated EMT, the expression levels of all five members belonging to the miR-200 family underwent a decrease at both genomic loci [159]. On the other hand, the EMT mesenchymal phenotype is maintained by the high expression of ZEB, thanks to its interaction with the miR-200 family (double negative feedback loop) and autocrine TGF β signaling (inhibition of TGF β 2 alleviated by the deletion of the miR-200 family) [158]. As aforementioned, by analyzing the expression levels of the ZEB factor, miR-200 family, and TGF β within SPN, we can gain insights into the potential role of EMT in the initiation and progression of SPN (Fig. 4).

The functional association between neutral hormone receptors and EMT in SPN has not been clearly elucidated, and the understanding of this issue currently relies on indirect evidence from other tumor models. Studies have confirmed that in different types of cancer, sex hormone signaling is an effective inducer of EMT. For example, the estrogen receptor GPER1 in breast cancer and gastric cancer can upregulate EMT transcription factors such as Snail and Slug by activating the PI3K/AKT pathway, thereby inhibiting E-cadherin and enhancing cell migration and invasion [160], and androgen receptors can also drive the occurrence of EMT in prostate cancer cells and promote metastasis [161]. Notably, the mucinous cystic neoplasms, which belong to the same pancreatic cystic tumors as SPN, also express PR and ER in their stroma and show an association between changes in EMT markers and invasive behavior [162]. In addition, basic research indicates that steroid nuclear receptors are potential direct regulators of core EMT transcription factors (such as ZEB1/2, Twist) [163], and their signals can interact with the EMT network through pathways such as TGF- β , PI3K/AKT [164]. The expression of related hormone receptors in SPN may interfere with EMT through similar pathways, providing a potential explanation for its local invasive behavior. However, this hypothesis still lacks specific functional and mechanistic data for SPN and urgently requires experimental validation.

3.5 Experimental framework for verifying cross-talk between sex hormone receptors-signaling pathways

In order to explore the potential crosstalk between the above sex hormone receptors and Wnt, Notch and Hedgehog pathways in SPN, the following integrated experimental strategies may be considered in future studies. At the functional level, the expression of relevant hormone receptors can be specifically knocked down by shRNA or CRISPR technology in preclinical models of SPN (such as patient-derived organoids), and then the TCF/LEF luciferase reporter system can be used to evaluate pathway activity changes, and the transcription level of related target genes can be detected by quantitative PCR to quantify their impact on the activity of different signaling pathways. At the mechanistic level, protein immunoprecipitation and chromatin immunoprecipitation can

be used to detect whether there is a direct molecular interaction between sex hormone receptors and the core components of the pathway. In addition, SPN organoids were exposed to a combination of hormone receptor modulators and pathway inhibitors, and cell phenotypes were analyzed by high-throughput imaging, combined with RNA sequencing and proteomic analysis, to reveal the global signaling network of hormone receptor regulation. This experimental pathway aims to provide a validable theoretical framework for elucidating the functional crosstalk of hormone receptors and signaling pathways in SPN.

4 The real-world dilemma in SPN research: from experimental models to clinical exploration

Although mutations in the CTNNB1 gene have been elucidated as the core driver event in SPN, functional research into the heterogeneity of its biological behavior, the regulatory details of its signaling pathways, and its mechanisms of malignant transformation remains severely lagging. This lag is primarily attributable to the rarity of the tumor, which simultaneously leads to a paucity of research models and difficulties in conducting high-quality clinical studies.

At the basic research level, it has been established that SPN possesses a relatively simple genomic alteration profile, in which CTNNB1 point mutations are observed in over 90% of cases [35]. Furthermore, a whole-exome sequencing study found this mutation to be present in all tumor samples, with its mutational burden correlating with tumor size and metastatic potential [106]. Furthermore, transcriptomic studies have also revealed aberrant expression of several key genes in SPN, including EGFR, FYN, MYC, and CD44, suggesting that signaling pathways such as ErbB and GnRH may be cooperatively involved in disease pathogenesis [165]. This has begun to outline the complex landscape of molecular pathways in SPN. In recent years, with the introduction of new technological platforms, significant progress has been made in SPN research. A 2023 single-cell RNA sequencing study constructed the first single-cell transcriptomic atlas of SPN, proposing that it may originate from pancreatic endocrine progenitor cells. The study also identified primary marker genes such as NOV and DCN, as well as recurrence-associated genes like S100A10 and MGP, suggesting the activation of the Wnt/ β -catenin pathway and the roles of EMT and MYC pathways in tumor recurrence [153]. A multi-omics study published in 2025, integrating methylation, transcriptome, cfDNA, and tumor microenvironment analyses, systematically elucidated the molecular basis of malignant transformation in SPN. The study identified aberrant expression of genes such as LY96, IFI16, and GLUD1 in invasive SPN, and detected mutations in CTNNB1, BRAF, and others in circulating cell-free DNA (cfDNA), thereby providing new clues for prognostic biomarkers and therapeutic targets [98]. Meanwhile, a 2025 case report identified a case of metastatic SPN driven by a homozygous mutation in the APC gene, which demonstrated an early response to mFOLFIRINOX chemotherapy, offering new insights into atypical driver mechanisms and personalized treatment for SPN [97]. Collectively, these studies underscore the need to enhance the diagnosis and treatment of SPN through multi-omics integration and novel biomarkers in the future [166].

However, the in-depth study of SPN continues to face the severe challenge of a scarcity of model systems. Well-characterized SPN cell lines are exceedingly rare, and genetically engineered mouse models that can accurately recapitulate the features of human

SPN remain nonexistent. Patient-derived xenograft (PDX) models, on the other hand, are challenged by low engraftment rates and long latency periods due to the slow growth of SPN. In recent years, technological advances in organoid models have brought significant breakthroughs to pancreatic cancer research. Notably, a recent study successfully established a biobank of 260 pancreatic tumor organoids that explicitly included SPN models [167]. This provides direct evidence for the application of this technology to SPN research, which can better retain tumor characteristics and provide a better platform for drug testing and mechanism research of SPN. However, the scarcity of these models directly leads to the limitations of research methodology: the current understanding of the molecular mechanisms of SPN, whether it is the core Wnt/ β -catenin pathway or the high-frequency expression of PR and the significance of ER β , is mostly derived from retrospective analysis of clinical specimens. The lack of effective models makes it difficult to verify whether these hormone receptors are synergistic in tumorigenesis and development and their specific mechanisms at the functional level, which constitutes a significant gap in current research. At the same time, the rarity of tumors also hinders prospective clinical trials or multi-omics integrated analyses that require large samples.

At the clinical level, the lack of models combined with the scarcity of cases leads to the absence of high-level clinical evidence. Current treatment decisions for SPN, especially systematic treatment options for advanced patients, are mostly based on small retrospective studies or personal experience, and there is a lack of standardized evidence-based guidelines. Future research breakthroughs depend on collaborative efforts: short-term focus should be on using novel models such as organoids for high-throughput drug screening and functional genomics studies such as CRISPR-Cas9 to prioritize the validation of key pathogenic pathways; Using these novel platforms to deeply explore the functions of hormone receptors such as PR and ER β and their potential interactions with CTNNB1 mutations will provide a solid experimental basis for understanding the unique biology of SPN and exploring endocrine therapy strategies. In the long term, it is necessary to promote multi-center collaboration to explore international registry studies and “basket trials” based on molecular characteristics to develop more effective treatment strategies for this rare tumor.

5 Advances and prospects for the treatment of SPN

Given the relatively benign nature of SPN, surgical resection is typically regarded as the preferred mode of treatment [168]. Multiple clinical series have confirmed that surgical resection is the key to achieving a cure for SPN. Even for cases with large tumor volumes or local invasion, extremely high R0 resection rates and excellent long-term survival rates can still be attained [169–171]. Traditional surgical procedures encompass pancreaticoduodenectomy and distal pancreatectomy accompanied by splenectomy. Nevertheless, these methodologies are often accompanied by substantial deterioration of both pancreatic exocrine and endocrine functions [172]. Consequently, a number of experts advocate for the adoption of organ-preserving resection techniques, including midpancreatic resection, localized tumor enucleation, duodenum-preserving pancreatic head resection, and spleen-preserving distal pancreatic resection [173]. With the advancements in minimally invasive surgical techniques, laparoscopic and robotic-assisted pancreatectomy have emerged as safe and effective therapeutic options [36]. Surgical excision is still considered the best treatment for SPN with metastases [174]. It is recommended that

for patients diagnosed with SPN accompanied by liver metastases, a metastatic resection with a margin of at least 1 cm should be deemed sufficient [175]. For male patients, Machado et al. [80] advocated for that a more aggressive surgical approach would be preferable to male patients and that closer follow-up would be required because of the potential for more aggressive and malignant potential. There exists no definitive chemoradiotherapy protocol for unresectable SPN, and only a limited number of studies have documented notable tumor regression following treatment with gemcitabine in conjunction with radiotherapy [176, 177]. In addition to gemcitabine, chemotherapy drugs commonly used in SPN include 5-fluorouracil, cisplatin, and paclitaxel [178, 179]. With neoadjuvant chemoradiotherapy, it is expected that the tumor will shrink, thus creating the possibility of surgical resection.

Furthermore, given that SPN is more common in young women and some patients' tumor tissues express PR and ER β , endocrine therapy has been proposed as a biologically reasonable but exploratory direction for the treatment of unresectable or metastatic SPN. Currently available evidence is largely restricted to isolated case reports, representing a very low level of evidence (Table 5). For example, there are scattered reports describing that the anti-estrogen drug tamoxifen may provide clinical benefits in the treatment of advanced SPN [90, 180]. Only one in vitro study using primary SPN cell cultures found that estrogen could stimulate tumor cell proliferation, while the selective estrogen receptor modulator tamoxifen significantly inhibited its growth [57]. In addition to tamoxifen, other endocrine drugs such as aromatase inhibitors and gonadotropin-releasing hormone (GnRH) antagonists are theoretically chosen based on the

Table 5 Summary of case reports on endocrine therapy for Solid-pseudopapillary neoplasm of the pancreas (SPN)

First Author (Year)	Patient Profile	Agent	Regimen	Outcome	Time to Response	Follow-up	Adverse Events
Ko-rniet-skaya [90]	32-year-old female with metastatic SPN, progressed after multiple surgeries & chemotherapy lines	Tamoxifen	20 mg/day, ongoing for $\geq$ 12 months	Stable Disease (SD)	Assessed at $\sim$ 12 months	$\geq$ 12 months	Well-tolerated, no significant AEs reported
Soloni [178]	20-year-old female with unresectable SPN at diagnosis	Tamoxifen	Not reported	Stable Disease (SD)	Not reported	2 years	Not reported
	18-year-old female with unresectable SPN at diagnosis	Tamoxifen	Not reported	No Response (NR)	Not reported	12 years	Not reported
Shorter [180]	20-year-old female with liver metastases at diagnosis, not resected	Tamoxifen	"Brief course", details unspecified	Stable Disease (SD)	Not reported	12 years	Developed diabetes mellitus (causality unclear)
Sclafani [181]	20-year-old female with extensive liver metastases at diagnosis, unresectable	Tamoxifen	Not reported	Stable Disease (SD)	Not reported	22 months	Not reported

epidemiology and molecular characteristics of the disease, but their clinical efficacy has not been confirmed. It must be recognized that the current evidence is primarily based on summaries of treatment experiences with individual cases, lacking prospective or controlled trial data to strongly support the efficacy of endocrine therapy in SPN. Therefore, these methods are not currently recommended as standard treatment. Converting these exploratory concepts into clinical practice faces significant challenges. The rarity of SPN makes conducting prospective clinical trials exceptionally difficult, including patient recruitment, trial design, defining clear endpoints for unresectable/metastatic disease, determining the timing of treatment, and managing potential side effects. Thus, the key for future research lies in identifying biomarkers that can predict treatment efficacy. For example, quantitative detection of PR/ER in tumor tissue or molecular profiling combined with the CTNNB1 mutation spectrum may help identify patient populations most likely to benefit from endocrine therapy, thereby enabling precision treatment.

Moreover, apart from endocrine therapy, it is equally crucial to delve into the potential of targeted therapy, premised on a deeper comprehension of the molecular mechanisms underlying SPN (Table 6). For instance, the preponderance of patients afflicted with SPN exhibit a mutation in the CTNNB1 gene, resulting in the aberrant activation of the Wnt/ β -catenin signaling cascade (Fig. 3). But given the significant challenges in directly inhibiting the transcriptional activity of nuclear β -catenin, the current research strategies for the Wnt pathway mainly focus on developing targeted therapies for its upstream and downstream nodes and synergistic pathways. There have been many explorations, including targeting the transcriptional coactivator complex of β -catenin, such as using small molecule inhibitors like PRI-724, E7386, or Tegavivint to disrupt its interaction with key proteins such as CBP or TBL1 [95]. These therapies have entered the early clinical trial stage and have shown preliminary potential. In addition, for the degradation complex upstream of the Wnt pathway, some studies have proposed that Wnt pathway activation driven by APC inactivation can also be a therapeutic target, such as by stabilizing AXIN with Tankyrase inhibitors to promote β -catenin degradation, which provides a new direction for future research [97]. Intervention on other signaling pathways that are synergistic with the Wnt pathway is another promising direction. The mTOR inhibitor everolimus has also been studied for the treatment of metastatic SPN and has shown good drug tolerability [101, 182]. Additionally, strategies targeting other synergistic nodes, such as epigenetic regulation, are also receiving attention from the academic community [96].

However, the clinical translation of these emerging strategies still faces significant obstacles. Since the Wnt pathway is crucial for maintaining the normal renewal and stability of various tissues (such as the intestine and bones) in adult individuals, systemic inhibition can lead to severe off-target toxicity, thereby limiting the therapeutic window of the drug and making the range of safe and effective dosages extremely narrow. Therefore, developing highly selective and low-toxicity drugs still poses major challenges. Meanwhile, β -catenin itself lacks a typical drug-binding pocket, and its protein-protein interaction interface is difficult to be efficiently targeted by small molecules, constituting a core bottleneck in drug design. At the clinical development level, SPN as a rare tumor has few aggressive cases, which not only leads to difficulties in patient recruitment and

Table 6 SPN-related molecular mechanisms and targeted drugs

Molecular mechanism	Signaling molecule	Function	Drug
Wnt/ β -catenin signaling pathway	WNT	Complex interaction with the FZD/LRP receptor initiates and activates the Wnt/ β -catenin signaling pathway.	
	FZD	WNT receptor	OMP-18R5 (FZD1/2/5/7/8) OTSA-101 (FZD10) OMP-54F28 (FZD8) Niclosamide (FZD1)
	LRP5/6	Auxiliary receptor	DKK1
	DVL	A crucial aspect of transducing WNT signaling into the intracellular compartment.	Sulindac
	GSK-3 β	Phosphorylate β -catenin (Thr41, Ser33, Ser37); a component of the destructive complex	NSAIDS
	AXIN	Scaffold protein; a component of the destructive complex	E7449
	APC	A component of the destructive complex	
	CK1	Phosphorylate β -catenin (Ser45); a component of the destructive complex	Pyruvium SSTC3
	β -catenin	The central molecule of the Wnt/ β -catenin signaling pathway	Vitamin D3 (β -catenin/TCF-4) PRI-724(β -catenin/CBP)
	TCF/LEF	Transcriptional activators; engage with β -catenin to stimulate the transcription of target genes	Vitamin D3(β -catenin/TCF-4)
	PORCN	Lipid modification through palmitoylation in the hydrophobic domain of the WNT protein.	LGK974 RXC004 ETC-159
NOTCH signaling pathway	DSL protein (DLL1, DLL3, DLL4, Jag1, Jag2)	NOTCH ligands; binds to receptors to activate the NOTCH signaling pathway	Jagged1 siRNA-CH (Jag1) Rova-T (DLL3) Demiczumab (DLL4)
	NOTCH1, NOTCH2, NOTCH3, NOTCH4	NOTCH receptors: NOTCH1 (high expression in pancreas and lungs) NOTCH2 and NOTCH3 (high expression in skin and bone) NOTCH4 (high expression in hair follicles)	Brontictuzumab (NOTCH 1) NAS (NOTCH 1) NAC (NOTCH 2) OMP-59R5 (NOTCH 2, NOTCH 3)
	SERCAS	Endoplasmic reticulum Ca ²⁺ -ATPase; an important co-factor for S1 cleavage	Bepiridil
	ADAM	Enzyme involved in S2 cleavage; contains structural domains of catabolites and metalloproteases	ZLDI-8 miR-3163 GI254023X
	γ -Secretase	Enzyme involved in S3 cleavage	DAPT NMK-T-057 MRK-560
	NICD	NOTCH intracellular structural domain that enters the nucleus to regulate gene expression; a critical signaling molecule in the NOTCH signaling pathway	
	MAML	Co-activator; forms ternary complex with NICD and CSL	IMR-1
	CSL	DNA-binding proteins; constitutes a transcriptional activator	RIN1
Hedgehog signaling pathway	Hh protein(Shh, Ihh, Dhh)	Hh ligand; activates the Hedgehog signaling pathway	RU-SKI 43 Robotnikinin (Shh)
	Ptch	Receptor of Hh protein; a negative regulator of Hedgehog signaling pathway	

Table 6 (continued)

Molecular mechanism	Signaling molecule	Function	Drug
	Smo	Key signal transduction proteins in the Hedgehog signaling pathway	Cyclopamine GDC-0449 LDE-225 PF-04449913 IPI-926 LY2940680 BMS-833,923 LEQ-506 TAK-441 MRT-92
	Gpr161	Belongs to the GPCR family; negatively regulates the Hedgehog signaling pathway by modulating cAMP signaling	
	PKA	Phosphorylates the Sufu/GLI complex and finally cleaves GLI into GLIR	
	CK1		
	Sufu		BH3 mimetics
	GLI(GLI1, GLI2, GLI3)	GLI1 and GLI2 are transcription activators GLI3 is a transcription activator	GANT 61 GANT58 HPI Arsenic trioxide Arcyriaflavin C Glabrescione B Physalin F Bicyclic imidazolium
	EMT		
	TGF-β	One of the most important factors in the induction of EMT; involved in the EMT process through multiple signaling pathways	Fresolimumab Trabedersen
	Snail	Major inducer of EMT; inhibits expression of epithelial markers and promotes mesenchymal markers	Snail/HDAC-IN-1
	ZEB(ZEB1, ZEB2)	Inhibits the miRNA-200 family and induces EMT	Biochanin A (ZEB1)
	miRNA-200	Targeting ZEB; Inhibits EMT	
	Twist(Twist1, Twist2)	Induces EMT	Harmine (Twist1)
	FOXC2	Promotes EMT by inhibiting the expression of the miR-34 family	MC-1-F2
	E-cadherin	Epithelial cell marker; its absence is an important feature of EMT	Salinomycin
	N-cadherin	Mesenchymal cell marker; upregulation of its expression is a key marker of EMT	AHD-1

the absence of large-scale clinical trials but also results in a lack of reliable preclinical models, severely hindering systematic drug validation and clinical translation [107, 166].

In summary, although the current evidence for drug treatment of SPN is very weak and still in the exploratory stage, the authors believe that future breakthroughs will depend on deepening the understanding of molecular mechanisms, overcoming the challenges of clinical translation, and validating the potential of new strategies such as combined endocrine-targeted therapy through multicenter, prospective clinical trials, ultimately bringing definite survival improvements to patients with advanced SPN.

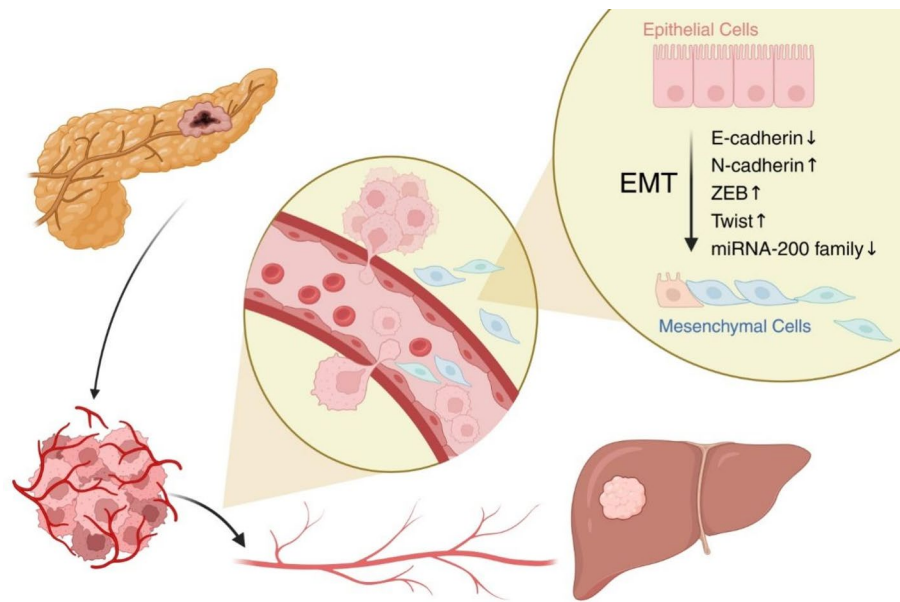


Fig. 4 Epithelial-mesenchymal transition (EMT). EMT is closely associated with tumor progression and metastasis. During EMT, TGF- β is a key inducer. TGF- β binds to receptors on the cell surface, activating EMT-related transcription factors, such as ZEB and Twist, through Smad-dependent pathways. This activation leads to the suppression of epithelial marker E-cadherin expression and the promotion of mesenchymal marker N-cadherin expression, resulting in reduced cell-cell adhesion and the loss of polarity in epithelial cells as they acquire mesenchymal characteristics. This process facilitates distant tumor spread and the formation of metastatic foci. The MiR-200 family can target and inhibit ZEB, as well as regulate key molecules in the TGF- β signaling pathway, thereby maintaining epithelial cell polarity and integrity. Consequently, the dysregulation of the MiR-200 family in cancer cells also plays a significant role in the occurrence of EMT and tumor metastasis. Key to symbols: ↓ represents downregulation; ↑ represents upregulation

Abbreviations

ACC	Acinar cell carcinoma
AKT	Protein kinase B
APC	Adenomatous polyposis coli
AR	Androgen receptor
ARE	Androgen response element
BCL9L	B-cell CLL/lymphoma 9-like protein
CK1	Casein kinase 1
CTNNB1 / β -catenin	Catenin beta 1 (gene) / β -catenin (protein)
CysLT1R	Cysteinyl leukotriene receptor 1
DBD	DNA-binding domain
DC	Destruction complex
DHT	Dihydrotestosterone
Dvl	Dishevelled
EMT	Epithelial-mesenchymal transition
ENETS	European Neuroendocrine Tumor Society
ER	Estrogen receptor
ER α	Estrogen receptor alpha
ER β	Estrogen receptor beta
ERE	Estrogen response element
FAP	Familial adenomatous polyposis
FOXA1	Forkhead box protein A1
Fzd	Frizzled
GLI	Glioma-associated oncogene homolog
GnRH	Gonadotropin-releasing hormone
GSK3 β	Glycogen synthase kinase 3 beta
Hh	Hedgehog
HSP	Heat shock protein
INSM1	Insulinoma-associated protein 1
IPMN	Intraductal papillary mucinous neoplasm
LBD	Ligand-binding domain
LEF1	Lymphoid enhancer-binding factor 1
LRP	Low-density lipoprotein receptor-related protein
MAPK/ERK	Mitogen-activated protein kinase / extracellular signal-regulated kinase

mTOR	Mammalian target of rapamycin
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
NICD	Notch intracellular domain
NTD	NH ₂ -terminal domain
PDAC	Pancreatic ductal adenocarcinoma
PI3K	Phosphatidylinositol 3-kinase
PR	Progesterone receptor
PRA	Progesterone receptor isoform A
PRB	Progesterone receptor isoform B
RFS	Recurrence-free survival
SPN	Solid-pseudopapillary neoplasm
TCF	T-cell factor
TFE3	Transcription factor binding to IGHE enhancer 3
TGF β	Transforming growth factor beta
WHO	World Health Organization
ZEB	Zinc finger E-box binding homeobox

Supplementary Information

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Supplementary Material 1.

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Author contributions

Y.Y.H was tasked with crafting the manuscript, conducting literature searches, and designing the images and tables. T.L.H initiated the research topic, supervised the writing endeavors, and provided valuable feedback and revisions to the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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The authors declare no competing interests.

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