World Journal of Clinical Cases

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World J Clin Cases 2025 December 16; 13(35): 112585

DOI: 10.12998/wjcc.v13.i35.112585

ISSN 2307-8960 (online)

SYSTEMATIC REVIEWS

Phenotypic and functional characteristics of pituitary adenoma stem cells

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Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade B

Novelty: Grade B, Grade B

Creativity or Innovation: Grade A, Grade B

Scientific Significance: Grade B, Grade C

P-Reviewer: Ikram D, MD, Researcher, Indonesia; Xu HJ, PhD, Assistant Professor, China

Received: July 31, 2025

Revised: August 20, 2025

Accepted: December 10, 2025

Published online: December 16, 2025

Processing time: 138 Days and 13.3 Hours

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Abstract

BACKGROUND

Pituitary neuroendocrine tumors (PitNETs), formerly referred to as pituitary adenomas, are prevalent intracranial neoplasms that, although often benign histologically, can demonstrate invasive growth, therapeutic resistance, and recurrence. Emerging evidence supports the presence of a subpopulation of tumor-initiating cells with stem-like properties - pituitary adenoma stem cells (PASCs) - that may drive these aggressive features. This systematic review aims to critically examine the evidence on PASCs, their phenotypic and functional characteristics, and their role in PitNET pathophysiology.

AIM

To study the molecular markers, signaling pathways, research models, and phenotypic traits of PASCs, and to assess their potential significance for future translational and clinical applications.

METHODS
A comprehensive literature search was conducted in PubMed, Scopus, and Ovid MEDLINE in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Thirty-four studies were included based on predefined eligibility criteria. Data were extracted regarding PASC isolation methods (*e.g.*, neurosphere formation, side population sorting), marker expression [*e.g.*, SRY-related HMG-box transcription factor (SOX) 2, octamer-binding transcription factor 4, CD133, Nestin], pathway involvement (*e.g.*, Wnt/beta-catenin, Notch, Sonic hedgehog), and functional behaviors such as self-renewal, differentiation, tumorigenicity, and therapy resistance.

RESULTS
Following duplicate removal, 315 unique articles were screened, with 47 full texts assessed for eligibility. Ultimately, 34 studies published between 2007 and 2025 met the inclusion criteria. The majority utilized human PitNET samples (83%), with a subset employing rat-derived cell lines (28%) or murine models (15%). PASCs were identified and characterized using various *in vitro* and *in vivo* approaches. Commonly reported stemness markers included SOX2 (59%), CD133 (38%), Nestin (35%), and octamer-binding transcription factor 4 (26%), with others such as SOX9, paired-like homeobox 1, and C-X-C chemokine receptor type 4 also frequently cited. Wnt/beta-catenin (18%) and phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (9%) signaling pathways were most implicated, followed by Notch, Sonic hedgehog, and janus kinase/signal transducer and activator of transcription cascades. Functional assays revealed consistent findings of tumor initiation (44%), self-renewal (35%), and tumor progression or invasion (35%). Notably, a minority of studies explored therapeutic interventions targeting PASCs, including gamma-secretase inhibitors and possible novel combinations of molecular agents.

CONCLUSION
The accumulating evidence on PASCs highlights their pivotal role in PitNET tumorigenesis, progression, and therapy resistance. Their molecular and functional overlap with normal pituitary stem cells underscores the need for further lineage-tracing and *in vivo* validation.

Key Words: Pituitary neuroendocrine tumors; Stem cells; Tumorigenesis; Therapy resistance; Pituitary adenoma stem cells; Pathway

Core Tip: Pituitary adenoma stem cells are a functionally distinct subpopulation within pituitary neuroendocrine tumors, exhibiting stem-like traits such as self-renewal, multipotency, and resistance to dopamine agonists and somatostatin analogs. This systematic review consolidates evidence from 34 studies, highlighting the expression of key markers like SRY-related HMG-box transcription factor 2, CD133, and Nestin, and the involvement of dysregulated pathways including Wnt/beta-catenin, Notch, Sonic hedgehog. Pituitary adenoma stem cells are implicated in tumorigenesis, invasion, and recurrence, making them compelling targets for future therapies aimed at overcoming resistance and preventing relapse in pituitary neuroendocrine tumors.

Citation: Agosti E, Gelmini L, Panciani PP, Fiorindi A, Fontanella MM, Tengattini F, Denaro L, Gagliano C, Tognetto D, Zeppieri M. Phenotypic and functional characteristics of pituitary adenoma stem cells. *World J Clin Cases* 2025; 13(35): 112585
URL: https://www.wjgnet.com/2307-8960/full/v13/i35/112585.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i35.112585

INTRODUCTION

Pituitary adenomas (PAs), now more accurately termed pituitary neuroendocrine tumors (PitNETs)[1], are among the most common intracranial neoplasms, accounting for approximately 10%-15% of all diagnosed brain tumors[2]. These epithelial-origin tumors arise from the adenohypophysis and are classified immunohistochemically based on their expression of pituitary hormones (*i.e.*, follicle-stimulating hormone, luteinizing hormone, adrenocorticotropic hormone, growth hormone, prolactin, and thyroid-stimulating hormone) and the associated pituitary lineage-specific transcription factors (*i.e.*, steroidogenic factor 1, T-box brain protein 1, and pituitary-specific transcription factor 1)[1]. Clinically, PitNETs are further characterized by their functionality. Roughly half of them are clinically non-functioning PitNETs, meaning they do not produce hormone-related symptoms despite possible immunohistochemical hormone expression[3, 4]. These non-functioning tumors are typically diagnosed due to compression-related symptoms, such as visual impairment or hypopituitarism, although the increasing use of imaging has led to more incidental findings[5]. While PitNETs are generally considered benign and are often treatable with surgery and/or pharmacotherapy, a substantial

subset (up to 35%) demonstrates aggressive clinical behavior - including invasiveness, high proliferative activity, recurrence, and resistance to standard therapies - contributing significantly to patient morbidity due to their critical anatomical location and potential for hormone hypersecretion in functioning variants[6].

The biological mechanisms underlying the development and progression of PitNETs, particularly their variable clinical behavior, remain incompletely understood. Unlike many other tumors, PitNETs are rarely associated with well-defined oncogenic mutations, although germline mutations in genes such as *AIP* or *MEN1* have been implicated in a minority of cases[7]. Most PitNETs arise sporadically, with no clear genetic driver[8], highlighting the importance of exploring alternative explanations for tumorigenesis and treatment resistance. In recent years, increasing attention has been directed toward the cancer stem cell (CSC) model as a unifying theory to explain tumor heterogeneity, recurrence, and therapeutic failure across various neoplasms[9-11]. According to this model, a distinct subpopulation of cells within the tumor (*i.e.*, CSCs) possesses stem-like properties including self-renewal, multipotency, and resistance to standard therapies[12,13]. These cells are thought to drive tumor initiation, sustain growth, and enable relapse after treatment. The identification of such stem-like cells in typically malignant tumors has radically shifted the understanding of tumor biology and treatment paradigms[14-16].

The potential existence of stem-like cells within benign tumors, such as PitNETs, challenges traditional classifications and assumptions. Although benign by histological standards, many PitNETs behave in clinically aggressive ways, raising the possibility that they may harbor a stem-like subpopulation capable of initiating and sustaining tumor growth[17-18]. Supporting this, both human and murine studies have postulated the presence of adult stem cells in the normal pituitary gland, where they are believed to maintain tissue homeostasis and contribute to the plasticity of hormone-producing cells [19-21]. This has led to the hypothesis that similar populations, termed pituitary adenoma stem cells (PASCs), might also exist within adenomas and contribute to their pathophysiology[22-25].

Evidence for PASCs has emerged from various experimental approaches, including the isolation of cells expressing stem cell-associated markers such as SRY-related HMG-box transcription factor (SOX) 2, SOX9, and paired-like homeobox 1 (PROP1), particularly in non-functioning PitNETs[26-29]. Some studies have demonstrated the nuclear co-expression of these transcription factors in subpopulations of tumor cells, suggesting a potential stem-like phenotype[30-33]. Advanced techniques such as single-cell RNA sequencing have further revealed overlapping transcriptomic signatures between normal pituitary stem cells and cells found in adenomas[34-36]. However, whether these cells directly give rise to tumor cells or exert their influence *via* paracrine mechanisms remains under debate.

Despite growing interest, our understanding of the role of PASCs in pituitary tumorigenesis remains limited. The identification and characterization of these cells have been hindered by the heterogeneity of experimental models and methodologies, and there remains no consensus on definitive markers or functional assays. Moreover, the precise contribution of PASCs to tumor initiation, progression, therapeutic resistance, and recurrence is yet to be clearly delineated. Given these gaps in knowledge, this systematic review aims to critically evaluate the current literature on PASCs, with a focus on their phenotypic features, proposed roles in tumorigenesis, and potential implications for diagnosis and therapy.

MATERIALS AND METHODS

Literature review

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Two reviewers (Agosti E and Gelmini L) independently performed a comprehensive search of the PubMed, Scopus, and Ovid MEDLINE databases. The initial search was conducted on March 21, 2025, with a final update on June 20, 2025. The search strategy employed combinations of keywords and MeSH terms related to pituitary tumors and stem cells, including: "Pituitary Neoplasms" (Mesh), "pituitary adenoma", "PitNETs", "Stem Cells", "stem cells", "cancer stem cells", "CSCs", "pituitary adenoma stem cells", "PASCs", "tumorigenesis", "self-renewal", "cell proliferation", "invasion", "aggressiveness", "pathway", "drug resistance", "drug sensitivity", "treatment response", "therapeutic resistance", and "outcome". Boolean operators were used to construct the following query: ("Pituitary Neoplasms" OR "pituitary adenoma" OR "PitNETs") AND ("Stem Cells" OR "stem cells" OR "cancer stem cells" OR "CSCs") OR "pituitary adenoma stem cells" OR "PASCs") AND ("tumorigenesis" OR "self-renewal" OR "cell proliferation" OR "invasion" OR "aggressiveness" OR "pathway" OR "drug resistance" OR "drug sensitivity" OR "treatment response" OR "therapeutic resistance" OR "outcome"). Specific search strings used for databases are available in Supplementary material. Additional relevant articles were identified through manual screening of the references of included studies.

Studies were included if they met the following criteria: (1) Published in English; (2) Contained original experimental or clinical data; (3) Focused on the identification, characterization, or functional role of PASCs or stem-like cells in PitNETs; and (4) Investigated their association with key tumorigenic features such as proliferation, invasion, recurrence, drug resistance, or treatment outcomes. Studies were excluded if they were review articles, editorials, conference abstracts, non-English publications, or if they lacked sufficient detail on methodology or findings relevant to PASCs. All citations were managed using EndNote X9, and duplicates were removed prior to screening. Titles and abstracts were screened independently by two reviewers (Agosti E and Gelmini L), and discrepancies were resolved through consensus with a third reviewer (Panciani PP). Full-text review was performed for all studies meeting the initial inclusion criteria.

Data extraction

Data were systematically extracted from each eligible study using a standardized data collection template. The following variables were recorded: (1) Cell lines (*in vitro* or patient-derived models used); (2) Identification markers (molecular or

phenotypic markers used to define stem-like cells, *e.g.*, SOX2, SOX9, PROP1); (3) Pathways (associated signaling pathways or gene networks, *e.g.*, Wnt, Notch, Hedgehog); (4) Molecular agents (biomolecular agent investigated, pharmacological compounds or biological inhibitors used in the studies); and (5) Effects on tumor behavior (*e.g.*, self-renewal, invasion, proliferation, therapeutic resistance).

Outcomes

The primary outcome was to synthesize and critically evaluate the current evidence on the existence, identification, and functional role of PASCs in the context of PitNET tumorigenesis. Secondary outcomes included the characterization of associated signaling pathways, identification of key stem cell markers, assessment of tumorigenic potential (*e.g.*, self-renewal, invasion), and responsiveness to targeted molecular agents or conventional therapies. The goal was to assess the biological and clinical relevance of PASCs as potential drivers of tumor initiation, progression, and treatment failure, thereby identifying novel diagnostic markers and therapeutic targets.

Risk of bias assessment

The Newcastle-Ottawa Scale (NOS) was employed to assess the methodological quality of the included observational and experimental studies (Figure 1). The NOS evaluates studies based on three domains: Selection, comparability, and outcome assessment, with a maximum score of nine points. Studies scoring less than seven were of low quality and excluded from quantitative synthesis, although key findings from all eligible studies were included in the qualitative analysis and narrative discussion. Specific NOS scores for each study are listed in Supplementary material.

Statistical analysis

Descriptive statistics were used to summarize findings across studies, including trends in marker expression, pathway involvement, and treatment effects. Data were presented in tabular and narrative form. All data processing and visual representation were carried out using R statistical software (version 4.2.0).

RESULTS

Literature review

Following the removal of duplicates, 315 unique articles were identified. Screening of titles and abstracts narrowed this down to 47 articles for full-text review. Of these, 34 met the inclusion criteria. Thirteen studies were excluded due to the following reasons: Lack of relevance to the research question (3 articles), not in English (1 article), and being review or meta-analysis publications (9 articles). All included studies reported at least one relevant outcome for one or more patient cohorts. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses -compliant flow diagram summarizing the selection process is presented in Figure 2.

Data analysis

A total of 34 studies, published between 2007 and 2025, were included in this systematic review. Various *in vitro* and *in vivo* models were used, with human PA samples being the most common (28 studies, 83%), followed by rat-derived cell lines such as MMQ and GH3 (8 studies, 28%) and mouse PA cell lines like AtT-20 (5 studies, 15%). Several studies used more than one model. In terms of identification markers, a wide range of stemness-related and lineage-associated markers were reported. The most frequently cited were SOX2 (19 studies, 59%), CD133 (13 studies, 38%), Nestin (11 studies, 35%), and octamer-binding transcription factor 4 (OCT4) (9 studies, 26%). Other recurrent markers included SOX9 (4 studies, 12%) and NANOG (3 studies, 8%). Additional markers investigated were S100β and glial cell line-derived neurotrophic factor family receptor alpha 2 (GFRa2), each reported in 2 studies (6%). These markers were typically identified through immunohistochemistry, quantitative polymerase chain reaction, or flow cytometry-based methods to characterize PASCs in functional and non-functional adenomas.

Regarding signaling pathways, Wnt/beta-catenin signaling was the most frequently involved (6 studies, 18%), followed by phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) (3 studies, 9%), while Notch, SHH (Sonic Hedgehog), and Janus kinase/signal transducer and activator of transcription pathways were each reported in 2 studies (6%). Additional pathways included HIPPO, epithelial-mesenchymal transition (EMT), nuclear factor kappaB, transforming growth factor-beta/bone morphogenetic protein, and histone methylation, reflecting the broad molecular heterogeneity of PASCs. In terms of molecular agents, SOX2 itself was cited not only as a marker but also as a molecular target in 4 studies (12%), while others explored agents such as delta-like non-canonical Notch ligand 1, GFRa2, sterol regulatory element binding transcription factor 1, lysine methyltransferase 5A, and developmental pluripotency associated 4. Notably, dopamine agonists and somatostatin analogs were explored in 6 studies (18%). Three studies proposed potential therapies: One tested gamma-secretase inhibitors to block Notch signaling, while two studies proposed combined therapies to increase therapeutic response.

Species variations have constituted a significant source of heterogeneity in PASC research. Although some markers, including SOX2, OCT4, and Nestin, have been reliably identified in both human and rodent PitNET samples, some molecules exhibit species-specific expression or differing functional roles. CD133 serves as a consistent stemness marker in human PitNETs; however, its expression varies in murine models, possibly indicating disparities in pituitary embryology. Similarly, GFAP expression has been more pronounced in mouse folliculo-stellate cell-derived niches compared to human malignancies. The disparities emphasize the necessity for meticulous interpretation when ex-

Modified Newcastle - Ottawa Quality Assessment Scale

Selection

1) Representativeness of the exposed cohort
   a) Consecutive eligible participants were selected, participants were randomly selected, or all participants were invited to participate from the source population
   b) Not satisfying requirements in part (a), or not stated

2) Selection of the non-exposed cohort
   a) Selected from the same source population
   b) Selected from a different source population
   c) No description

3) Ascertainment of exposure
   a) Medical record
   b) Structured interview
   c) No description

4) Demonstration that outcome of interest was not present at the start of the study
   a) Yes
   b) No or not explicitly stated

Comparability

1) Were there clearly defined inclusion and exclusion criteria?
   a) Yes
   b) No or not explicitly stated

Outcome

1) Assessment of outcome
   a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records
   b) Record linkage (*e.g.* identified through ICD codes on database records)
   c) Self-report with no reference to original structured injury data or imaging
   d) No description

2) Was follow-up long enough for outcomes to occur?
   a) Yes (≥ 12 months)
   b) No (< 3 months)

3) Adequacy of follow up
   a) Complete follow up – all participants accounted for
   b) Subjects lost to follow up unlikely to introduce bias (< 20% lost to follow up or description provided of those lost)
   c) Follow up rate < 85% and no description of those lost provided
   d) No statement

Figure 1 Modified Newcastle-Ottawa Scale.

trapolating animal research to human biology and show the significance of verifying potential markers in human cohorts prior to contemplating clinical applications.

Concerning effects on tumor behavior, tumorigenesis or tumor initiation were the most frequently reported phenotypes (15 studies, 44%), followed by self-renewal (12 studies, 35%), tumor progression or invasion (12 studies, 35%), and chemoresistance (4 studies, 12%). Recurrence, EMT, and angiogenesis were also noted as functional consequences in a smaller subset of studies. Multiple studies confirmed that PASCs may contribute to therapy resistance, support tumor regrowth post-treatment, or influence the tumor microenvironment *via* paracrine signaling (Table 1)[23-60].

DISCUSSION

The systematic review provides a comprehensive synthesis of 34 studies that collectively highlight the relevance of PASCs in the context of PitNETs. These findings confirm that PASCs are not only identifiable within both functional and non-functional PAs but also actively participate in critical processes such as self-renewal, tumorigenesis, resistance to therapy, and recurrence. The reviewed studies underscore the complexity of PitNET biology, challenging traditional perceptions of these tumors as merely benign and emphasizing the necessity to address PASCs when considering therapeutic strategies.

Table 1 Summary of the studies included in the systematic literature review

Ref.	Cell lines	Identification marker	Pathway	Molecular agent	Effects on tumor behavior
Yokoyama *et al*[37], 2007	MtT/S and MtT/E cells derived from rat prolactinoma	NA	GH-IGF1	IGF-1	Paracrine IGF-1 from GH+ cells promotes progenitor proliferation
Xu *et al*[23], 2009	Human PA samples	Nestin, CD133	NA	NA	Tumorigenesis, self-renewal, chemoresistance
Yunoue *et al*[24], 2011	Human PA samples	CD133	NA	CD133, CD34, VEGFR2, nestin	CD133+ cells are implicated as endothelial progenitors in PAs
Ma *et al*[38], 2013	Human PA samples	NA	Nucleostemin-p53; ASPP2-p53	Nucleostemin and ASPP2	Tumorigenesis, tumor progression, self-renewal
Zhao *et al*[39], 2015	Human PA samples	Nestin, CD133	NA	NA	Sphere-formation, self-renewal, chemoresistance
Mathioudakis *et al* [40], 2015	Human PA samples	GFRa2	GFRa2-RET	GFRa2	Tumorigenesis
Lampichler *et al*[30], 2015	Human PA samples; mouse pituitary adenoma cell line AtT-20	SOX2, TP53, MKI67, SOD1	Hh signaling	GLI1	Tumorigenesis
Manoranjan *et al* [31], 2016	Human PA samples	CD15, CD133, SOX2	NA	Pax7, SOX2	Tumorigenesis, self-renewal, tumor progression
Peverelli *et al*[32], 2017	Human PA samples	SOX2, POU5F1/OCT4, KLF4 and EGR1	DRD2 and SSTR2 associated inhibitory pathways	DA, SSA	Sphere-formation, tumor proliferation and invasion of CS
Mezzomo *et al*[41], 2017	Human PA samples	Underexpressed TP63 isoforms (TAp63, ΔNp63)	NA	NA	Tumorigenesis, tumor progression
Orciani *et al*[42], 2017	Human PA samples	OCT4, NANOG, KLF4, SOX2, TGFbRII, E-CADHERIN	EMT, Somatostatin signaling	SST, SSA	EMT
Gao *et al*[43], 2017	MMQ cells (rat), human PA samples	CD133, Nestin, OCT4, SOX2, D2R	D2R	DA	DA resistance
Würth *et al*[27], 2017	Human PA samples	SOX2, Oct4, CD133, Nestin, NANOG.	SSTR2, SSTR5, D2R	Somatostatin/dopamine chimera BIM-23A760	Tumorigenesis, self-renewal, angiogenesis
Horiguchi *et al*[44], 2018	Rat anterior pituitary CD9+ cells	CD9, SOX2, S100β	BMP signaling	NA	Self-renewal
Tamura *et al*[45], 2019	Human PA samples	PITX2, SNAIL1	NA	PITX2	Tumor progression, invasion of CS
Tang *et al*[26], 2019	HP75 cells	SOX2	Wnt/beta-catenin, SHH	SOX2	Tumor proliferation
Zubeldía-Brenner *et al*[46], 2019	GH3 (rat)	NA	Notch	γ-secretase inhibitor (Notch blockade)	Sphere-formation
Soukup *et al*[47], 2020	Human PA samples	SOX2	NA	SOX2	NA
Taniguchi-Ponciano *et al*[48], 2020	Human PA samples	NR5A1, TBX19, POU1F1	NA	NA	Tumorigenesis
Cai *et al*[49], 2021	MMQ cells (rat)	CD133, Nestin, HCAM, OCT4, SCA1	D2R	CD133	DA resistance
Chen *et al*[50], 2020	Human PA samples, GH3 (rat), MMQ cells (rat), mouse pituitary adenoma cell line AtT-20	DLK1/MEG3	PI3K/AKT/mTOR	DLK1	Tumorigenesis, self-renewal, tumor progression, angiogenesis

Guido *et al*[33], 2021	Rat (F344)	GFRa2, SOX2, SOX9, Nestin, CD133, CD44	NA	NA	Self-renewal
Xiao *et al*[51], 2021	Human PA samples, MMQ cells (rat)	CD133, Nestin, SOX2S	JAK2/STAT5	DA, Pimozine	Tumorigenesis, DA resistance
Nys *et al*[52], 2022	Human PA samples, Mouse PA samples (DRD2-/-)	SOX2, SOX9, TACSTD, KRT8, KRT18	NF-κB, IFN-γ, JAK/STAT	IL-6	Tumorigenesis
Saksis *et al*[53], 2023	GH3 (rat), Human PA samples	OCT4, CD133, Nestin, SOX2, CXCR4	NA	NA	Self-renewal, chemoresistance
Yuan *et al*[54], 2023	Human PA samples	SOX2, OCT4, Nestin, CD133	NA	ANXA2	Tumorigenesis, self-renewal, angiogenesis
Zhang *et al*[34], 2023	Human PA samples	SOX2, S100β, SOX9, VIM, CLDN4	NA	SREBF1	Tumorigenesis, recurrence
Li *et al*[55], 2024	Human PA samples, GH3 (rat).	NA	Wnt/beta-catenin	KMT5A	Apoptosis, tumor progression
Jotanovic *et al*[56], 2024	Human PA samples	NA	NF-κB, WnT/EMT, mTOR	NA	Bone invasion, tumor progression
Øystese *et al*[29], 2024	Human PA samples	SOX2, SOX9, PROP1	Wnt/beta-catenin, Notch, FGF, SHH, TGF- β/BMP	SOX2, SOX9, PROP1	Self-renewal
Lenders *et al*[57], 2024	Human PA samples	SF-1, PIT-1, T-PIT, SOX2, Nestin, CD133	NA	NA	Tumorigenesis of WLDL tumors
Peng *et al*[58], 2024	Human PA samples	Nestin, CD133, SOX2, OCT4	PI3K/Akt, Wnt/beta-catenin, calcium signaling, cAMP signaling, RAS	NA	Tumorigenesis, self-renewal, chemores-istance
Lang *et al*[59], 2025	Human PA samples	PIT-1, CK8/18	NA	NA	Tumor progression
Chaudhary *et al*[60], 2025	Human and mouse PA samples	DPPA4, SOX2, OCT4, NANOG	Wnt/beta-catenin, Histone methylation	DPPA4	Tumor progression, cell migration, EMT

NA: Not available; GH-IGF1: Growth hormon-insulin-like growth factor-1; PA: Pituitary adenoma; VEGFR2: Vascular endothelial growth factor receptor 2; ASPP2-p53: Tumor protein P53 binding protein 2; GFRa2: Glial-cell-line-derived neurotrophic factor family receptor alpha 2; GFRa2-RET: Glial-cell-line-derived neurotrophic factor family receptor alpha 2-rearranged during transfection; SOX2: SRY-related HMG-box transcription factor 2; GLI1: Glioma-associated oncogene homolog 1 (Zinc finger protein); MKI67: Marker of proliferation; SOD1: Superoxide dismutase 1; Pax7: Paired box 7; POU5F1: POU domain, class 5, transcription factor 1; OCT4: Octamer-binding transcription factor 4; KLF4: KLF transcription factor 4; EGR1 Early growth response 1:; DRD2: Dopamine agonist receptor subtype 2; SSTR2: Somatostatin receptor 2; RAS: Rat sarcoma; DA: Dopamine agonist; SSA: Somatostatin receptor agonist; CS: Cavernous sinus; TP63: Tumor protein P63; TGFbRII: Transforming growth factor beta receptor 2; D2R: Dopamine receptor D2; SSTR5: Somatostatin receptor 5; PITX2: Paired Like homeodomain 2; SNAIL1: Snail family transcriptional repressor 1; SHH: Sonic hedgehog; NR5A1: Nuclear receptor subfamily 5 group A member 1; TBX19: T-Box transcription factor 19; POU1F1: POU class 1 homeobox 1; HCAM: Homing cell adhesion molecule; SCA1: Stem cell antigen 1; DLK1: Delta like non-canonical Notch ligand 1; MEG3: Maternally expressed 3; PI3K/AKT/mTOR: Phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin; JAK2/STAT5: Janus kinase 2/signal transducer and activator of transcription 5A; NF-κB: Nuclear factor kappa B; IFN-γ: Interferon gamma; TACSTD: Tumor associated calcium signal transducer 2; KRT8: Keratin 8; VIM: Vimentin; CLDN4: Claudin 4; TGF- β/BMP: Transforming growth factor beta 1/bone morphogenetic protein; SF-1: Splicing factor 1; PIT-1: Pituitary-specific positive transcription factor 1; T-PIT: Pituitary T-box transcription factor TPI; WLDL: Very-low density lipoprotein; DPPA4: Developmental pluripotency associated 4; TMZ: Temozolomide.

Identification and phenotypic characterization of PASCs

One of the pivotal aspects of the review is the extensive profiling of stemness-related markers in PASCs. Xu *et al*[23] and Zhao *et al*[39] identified Nestin and CD133 as key markers associated with PASCs, supporting their self-renewing capacity and resistance to conventional treatments. Similarly, studies by Würth *et al*[27] and Chen *et al*[50] confirmed the expression of OCT4, SOX2, and NANOG in sphere-forming cells isolated from PitNETs, aligning with the phenotypic characteristics of CSCs found in other tumor types. The presence of SOX2+ cells emphasizes the potential overlap between normal pituitary stem cells and tumorigenic PASCs. This connection is reinforced by the discovery that GPS cells express GFRa2, RET, and PROP1 in both human and murine models[61]. Interestingly, CD133 and C-X-C chemokine receptor type 4 (CXCR4), as reported by Yunoue *et al*[24], were found predominantly in aggressive tumor subtypes, suggesting a correlation between marker expression and tumor invasiveness.

In our statistical synthesis, the frequency of molecular citations has been utilized as an indicator of research interest rather than a direct assessment of biological significance. We have stated that citation proportion corresponds to the quantity of existing research, but the extent of molecular function is contingent upon the particular assays and models utilized. For instance, SOX2 has undergone functional validation using clonogenic assays and tumorigenicity models, while other molecules like CD44 have predominantly been shown in descriptive immunohistochemistry studies. We have analyzed the quantitative distribution of molecules within the framework of methodological background and experimental validation, advising against excessive interpretation of frequency statistics in isolation.

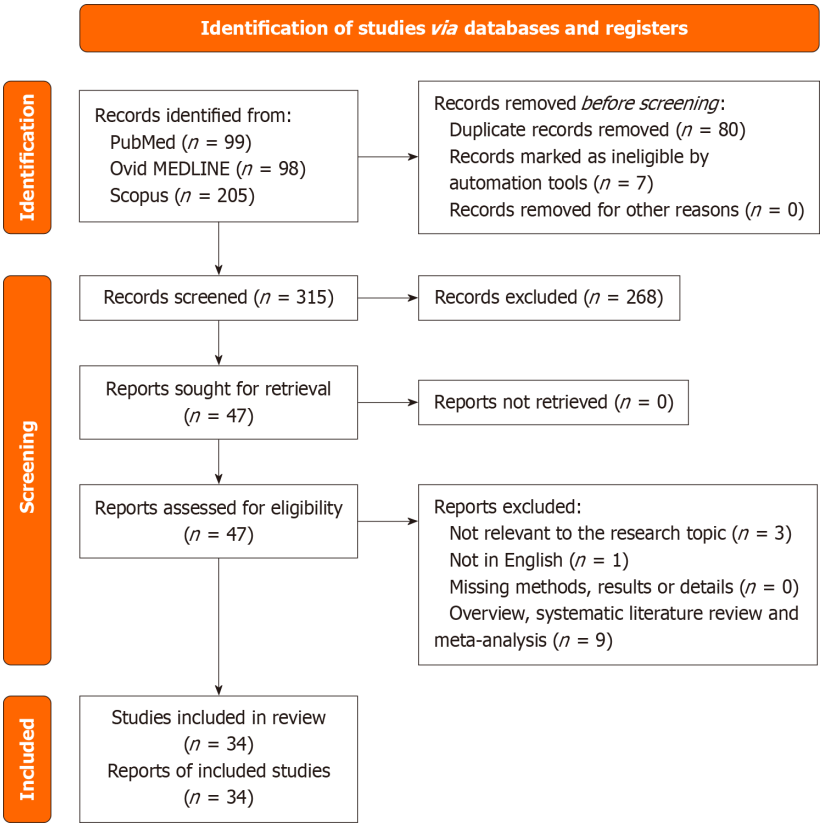

Figure 2 Flow chart according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.

Functional attributes: Self-renewal, differentiation, and tumorigenicity

PASCs demonstrate hallmark properties of stem cells, including the ability to form neurospheres, a key indicator of self-renewal. As shown by Ma *et al*[38], these spheres not only proliferate but also exhibit multilineage differentiation potential, indicating a multipotent phenotype. Würth *et al*[27] further substantiated the functional potential of PASCs through *in vivo* models, including xenografts in mice and zebrafish, where selected cells initiated tumor growth. Of note is the evidence that PASCs, like their glioma counterparts described by Bao *et al*[62] and Nadkarni *et al*[63], display chemoresistance. This parallels findings from the broader literature on CSCs and resistance mechanisms, as reported by Zhao *et al*[39], Manoranjan *et al*[31], and Carreno *et al*[64], who demonstrated that CD133+ cells were particularly recalcitrant to standard treatments.

Involvement of developmental pathways

The review also highlights the aberrant activation of key developmental pathways in PASCs, such as Wnt/beta-catenin, Notch, and SHH, all of which are crucial for stem cell maintenance and differentiation. As noted by Würth *et al*[27] and Caffarini *et al*[65], elevated expression of Notch receptors and ligands (*e.g.*, Notch1-4, Jagged1) was detected in PASC populations. This is consistent with studies by Ulasov *et al*[66] in glioblastoma models, where Notch signaling inhibition decreased tumorigenic potential. Wnt/beta-catenin signaling, extensively characterized by Chen *et al*[50], plays a pivotal role in sustaining stemness and promoting PASC-mediated tumor growth. The SHH pathway, emphasized by Orciani *et al*[42], was similarly implicated, with dysregulation promoting proliferation and survival of stem-like cells. These findings resonate with broader developmental biology studies by Øystese *et al*[29] and Cai *et al*[49], which underscore the involvement of these pathways in normal pituitary development and maintenance.

Markers of EMT and therapy resistance

The EMT has emerged as a hallmark of cancer progression and metastasis, and its activation in PASCs may signify enhanced motility and invasiveness. Chaudhary *et al*[60], Jotanovic *et al*[56], and Orciani *et al*[42] reported upregulation of EMT markers such as zinc finger E-box binding homeobox 1, twist family bHLH transcription factor 1, and snail family transcriptional repressor 2 inside populations of PASCs, suggesting that these cells possess mesenchymal features conducive to migration and invasion. These results mirror those of Hide *et al*[67] in glioma models, where stem-like cells contributed to tumor microenvironment remodeling and resistance. The expression of chemoresistance-associated markers in PASCs, including Nestin as discussed by Saksis *et al*[53] and Xiao *et al*[51], further illustrates their ability to evade standard cytotoxic therapies. Moreover, Øystese *et al*[29] and Yuan *et al*[54] reported the expression of DNA repair proteins and anti-apoptotic markers in PASCs, indicating an intrinsic resilience that contributes to tumor recurrence.

PASCs and the tumor microenvironment

The interaction between PASCs and the tumor microenvironment is another focal point of the review. As demonstrated by Nys *et al*[52] and Kuwajima *et al*[25], PASCs are capable of reprogramming surrounding stromal and immune cells to support tumorigenesis. This crosstalk, involving pathways such as PI3K/AKT/mTOR and the CXCR4/C-X-C motif chemokine ligand 12 axis, mirrors the interactions observed in glioma models and described by Liu *et al*[68] wherein GSCs recruit tumor-associated macrophages to enhance survival and therapy resistance. The studies by Yunoue *et al*[24] and Vamvoukaki *et al*[69] affirm the relevance of the C-X-C motif chemokine ligand 12/CXCR4 system in PAs, correlating with increased invasiveness and proliferation. Moreover, the role of RET/pituitary-specific positive transcription factor 1/Arf/p53 signaling in regulating cell turnover, proposed by Garcia-Lavandeira *et al*[70], introduces an additional layer of control that may influence PASCs' behavior and persistence.

Potential for clinical translation

The identification of PASCs opens avenues for the development of targeted therapies aimed at eradicating the tumorigenic core of PitNETs[43]. As suggested by Zubeldía-Brenner *et al*[46], Vamvoukaki *et al*[69], and Carreno *et al*[64], inhibiting pathways such as Notch (*via* gamma-secretase inhibitors) or targeting stemness markers like SOX2 and CD133 may provide more durable treatment responses. The concept of dual therapy, combining cytoreductive surgery with molecular agents targeting PASCs, aligns with the broader strategy used in glioblastoma treatment paradigms proposed by Yi *et al*[71] and Venugopal *et al*[72]. Another possible strategy to combat chemoresistance, proposed by Zhao *et al*[39], is the association of disulfiram with temozolomide.

Cellular heterogeneity is an inherent characteristic of PitNETs, notably pronounced in the stem-like compartment. The emergence of single-cell transcriptomic and proteomic methodologies has revealed that PASCs express a diverse range of stemness-associated markers. Nevertheless, not all of these compounds possess equivalent biological significance. Functional validation has identified molecules such as SOX2, OCT4, and NANOG as primary regulators of self-renewal and multipotency, while others, such as CD133 and Nestin, have functioned as supplementary markers of stem-like populations. Prioritizing markers with established causative roles in tumor development and resistance, rather than those with merely correlative expression, has thus become a crucial step for future translational investigations and therapeutic targeting.

Regarding dopamine agonists and somatostatin analogs therapeutic effects, there was no complete agreement among the studies investigating this issue: While Orciani *et al*[42], Peverelli *et al*[32], and Würth *et al*[27] found PASCs' sensitivity to dopamine agonists and somatostatin analogues (SST), Gao *et al*[43], Xiao *et al*[51], and Cai *et al*[49], demonstrated dopamine agonists resistance. Concerning possible new therapeutic strategies, Xiao *et al*[51] proposed the combination of pimozide and bromocriptine as a novel therapeutic strategy. In the current therapeutic landscape for PitNETs, various contemporary clinical datasets have established definitive foundations for implementing PASC-relevant pathways in practice. In acromegaly, once-daily oral paltusotine, a selective SST2 agonist, has sustained biochemical and symptomatic control following a transition from injectable somatostatin receptor ligands, as demonstrated in a peer-reviewed phase 3 study. It has also exhibited rapid and enduring responses in supplementary phase 3/extension presentations, thereby facilitating somatostatin-axis suppression in a convenient oral format that may enhance the prolonged pathway modulation necessary to influence slow-cycling PASC compartments[73,74].

Similarly, oral octreotide capsules have received approval for long-term maintenance medication and have shown sustained efficacy and positive patient-reported outcomes, thereby reinforcing the viability of chronic SST signaling regulation in suitable patients[75-77]. Long-term studies of osilodrostat in Cushing's disease have resulted in the normalization of cortisol biomarkers and concomitant enhancements in clinical outcomes. Pooled and extension reports have bolstered the evidence for sustained steroidogenesis inhibition, establishing a foundation for logical combinations that simultaneously target survival and stress-response pathways involved in PASC, such as PI3K/AKT/mTOR and janus kinase/signal transducer and activator of transcription. The selective glucocorticoid receptor modulator relacorilant has achieved its primary endpoint in the randomized-withdrawal phase 3 Gravity Recovery and Climate Experiment study, with reports from the company, congress, and trial registry indicating significant cardiometabolic advantages and regulatory advancement, thereby facilitating the mitigation of GR-driven stemness programs in combination strategies [78].

Collectively, these advancements have established a readily implementable framework for prospective testing of PASC-directed interventions (*e.g.*, gamma-secretase/Notch, Wnt/HH, or PI3K/AKT/mTOR modulators) alongside conventional endocrine therapies, with biomarker enrichment (SOX2/CD133 expression, EMT-skewed signatures) suggested to enhance translational efficacy. To consolidate the various components examined in this study, Table 2 provides a conceptual summary that categorizes the markers, models, pathways, phenotypes, and translational targets of PASC in PitNETs. This synthesis aims to provide readers with a clear framework that highlights the interaction between fundamental molecular mechanisms and novel clinical applications.

The therapeutic application of PASC indicators remains in its early stages; however, the systematic assessment of their phenotypic and functional significance has established a crucial foundation for translational research. We have highlighted that these molecular discoveries have not yet directly influenced patient management; nonetheless, they have identified potential targets for forthcoming preclinical investigations, biomarker discovery initiatives, and early-phase trials. In this regard, our research has functioned as a conduit, integrating cellular and molecular data while explicitly recognizing that extensive clinical use necessitates additional validation and longitudinal evidence. Nevertheless, challenges remain. The lack of universal PASC markers and the inherent heterogeneity of these cells complicate efforts to design universally effective therapies. Further research, particularly in lineage tracing and *in vivo* modeling, is essential to validate the stem-like properties and tumorigenic potential of PASCs across different PitNET subtypes.

Table 2 Pituitary adenoma stem cells: Markers, pathways, models, phenotypes, and translational targets

Domain	Key elements	Representative examples/notes	Translational implications
Markers of stemness	Transcription factors; surface markers	SOX2, OCT4, NANOG; CD133, Nestin	Facilitate the identification of PASC and the prospective categorization of patients based on biomarkers
Experimental models	*In vitro; in vivo; ex vivo*	Sphere-forming assays, organoids, xenografts	Simulate tumor-propagating cell dynamics and evaluate pathway inhibitors
Signaling pathways	Core developmental cascades	Wnt/beta-catenin, Notch, SHH-GLI, PI3K/AKT/mTOR, JAK/STAT	Facilitate self-renewal, plasticity, invasion, and therapeutic resistance
Associated phenotypes	Cellular functions	Self-renewal, multipotency, epithelial–mesenchymal transition (EMT), drug resistance	Phenotypic characteristics of aggressive PitNETs
Therapeutic targets	Current and emerging strategies	Somatostatin receptor ligands (SRLs), dopamine agonists, temozolomide, PRRT; experimental Notch or Wnt inhibitors	Integrate endocrine regulation with therapies aimed at stemness
Clinical context	Disease entities and therapies	Acromegaly: Oral SST2 agonist paltusotine, oral octreotide capsules; Cushing's: Osilodrostat, relacorilant; Aggressive PitNETs: TMZ, PRRT, ICIs	Exhibit the expanding translational pipeline and justification for combinatorial approaches

SOX2: SRY-related HMG-box transcription factor 2; OCT4: Octamer-binding transcription factor 4; SHH-GLI: Sonic hedgehog signaling molecule/glioma-associated oncogene homolog 1 (Zinc finger protein); PI3K/AKT/mTOR: Phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin; EMT: Epithelial–mesenchymal transition; SRLs: Somatostatin receptor ligands; SST2: Somatostatin receptor 2; JAK/STAT: Janus kinase/signal transducer and activator of transcription; PASC: Pituitary adenoma stem cells; PitNET: Pituitary neuroendocrine tumor; SRL: Somatostatin receptor ligand; TMZ: Temozolomide; PRRT: Peptide receptor radionuclide therapy; ICI: Immune checkpoint inhibitor.

Limitations of the study

First, significant heterogeneity exists among the included studies in terms of experimental models, PASC isolation techniques, and marker panels used for characterization, which limits the comparability and generalizability of findings. Second, many studies relied on *in vitro* assays without validating tumorigenic potential through robust *in vivo* models, which remains the gold standard for defining true CSC behavior. Third, a lack of standardized definitions and functional assays for PASCs introduces ambiguity in the interpretation of their stem-like properties. Additionally, the predominance of non-randomized, small-sample observational studies increases the risk of bias and overestimation of effects. Lastly, most available data are derived from non-functioning PitNETs or growth-hormone-secreting pituitary adenomas, with limited representation of other PitNET subtypes, thereby constraining the scope of conclusions across the full spectrum of PAs.

CONCLUSION

PASCs embody a critical component of PitNET biology, contributing to tumorigenesis, therapeutic resistance, and recurrence. Their characterization aligns with findings from both human and animal models and is supported by complementary evidence from developmental biology and CSC research. Future strategies must integrate our growing understanding of PASCs into clinical practice, aiming to disrupt their niche and molecular circuitry to achieve sustained tumor control and improved patient outcomes.

FOOTNOTES

Author contributions: Agosti E, Panciani PP, Fontanella MM, and Zeppieri M wrote the outline; Agosti E, Panciani PP, Tengattini F, Gelmini L, Fiorindi A, and Fontanella MM did the research; Agosti E, Panciani PP, Gelmini L, Fiorindi A, and Fontanella MM, Denaro L, Gagliano C, Tognetto D, and Zeppieri M assisted in the writing of the draft and final paper; Agosti E, Panciani PP, and Zeppieri M were responsible for the conception and design of the study; Zeppieri M assisted in the editing. All authors involved in making critical revisions of the manuscript and viewing all versions of the manuscript. All authors provided the final approval of the article.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Bai SR
L-Editor: A
P-Editor: Zhao YQ

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