Pituitary Tumors: Genetic and Molecular Factors Underlying Pathogenesis and Clinical Behavior

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Abstract
Pituitary neuroendocrine tumors (PitNETs) are the most common intracranial neoplasms. Although generally benign, they can show a clinically aggressive course, with local invasion, recurrences, and resistance to medical treatment. No universally accepted biomarkers of aggressiveness are available yet, and predicting clinical behavior of PitNETs remains a challenge. In rare cases, the presence of germline mutations in specific genes predisposes to PitNET formation, as part of syndromic diseases or familial isolated pituitary adenomas, and associates to more aggressive, invasive, and drug-resistant tumors. The vast majority of cases is represented by sporadic PitNETs. Somatic mutations in the \( \alpha \) subunit of the stimulatory G protein gene (gsp) and in the ubiquitin-specific protease 8 (USP8) gene have been recognized as pathogenetic factors in sporadic GH- and ACTH-secreting PitNETs, respectively, without an association with a worse clinical phenotype. Other molecular factors have been found to significantly affect PitNET drug responsiveness and invasive behavior. These molecules are cytoskeleton and/or scaffold proteins whose alterations prevent proper functioning of the somatostatin and dopamine receptors, targets of medical therapy, or promote the ability of tumor cells to invade surrounding tissues. The aim of the present review is to provide an overview of the genetic and molecular alterations that can contribute to determine PitNET clinical behavior. Understanding subcellular mechanisms underlying pituitary tumorigenesis and PitNET clinical phenotype will hopefully lead to identification of new potential therapeutic targets and new markers predicting the behavior and the response to therapeutic treatments of PitNETs.

Introduction

Pituitary tumors, more recently referred to as pituitary neuroendocrine tumors (PitNETs) [1, 2], are common neoplasms representing \( \sim 10\text{--}20\% \) of intracranial neo-
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PitNETs, pituitary neuroendocrine tumors; SSAs, somatostatin analogs; DAs, dopamine receptor type 2 agonists; TSG, tumor suppressor gene; FIPA, familial isolated pituitary adenomas; AD, autosomal dominant; GH, growth hormone; PRL, prolactin; XL, X-linked; X-LAG, X-linked acrogigantism; LOF, loss of function; GOF, gain of function; GPCR, G protein-coupled receptor; CNG, copy number gain; NF, nonfunctional; ACTH, adrenocorticotropic hormone.
plasms. They can be classified into clinically nonfunctioning (NF) and hormone-secreting tumors, including growth hormone (GH)-, prolactin (PRL)-, and adrenocorticotropic hormone (ACTH)-secreting tumors [1, 3]. Specific clinical features are determined by the hypersecreted hormone and/or by mass effects causing visual field deficits and neurologic manifestations.

The currently used drugs for the pharmacological treatment of PitNETs are somatostatin (SS) analogs (SSAs) and dopamine receptor type 2 (DRD2) agonists (DAs). First-generation SSAs octreotide and lanreotide represent the first-line medical treatment in acromegalic patients when surgery fails or for invasive or unresectable tumors, but about 50% of patients present resistance to treatment [4, 5]. In patients with PRL-secreting PitNETs, the DA cabergoline represents the treatment of choice, inducing PRL normalization and tumor size reduction, but resistance to DAs is displayed in a subset of patients [6]. NF-PitNET medical therapy with SSAs or DAs has demonstrated a variable and often limited efficacy. PitNETs occurring in a familial setting present a more aggressive phenotype, with increased invasiveness and resistance to standard treatments. In sporadic tumors, no molecular markers have been identified predicting clinical behavior. Somatic mutations, found in a significant percentage of patients, have been involved in tumor formation, but are not correlated with its aggressive features. Alterations in the expression or activity of cytoskeleton and scaffold proteins in PitNETs have been recently correlated with resistance to SSAs and DAs and to invasive behavior.

Pathogenesis of PitNETs: Germline and Somatic Mutations

A small proportion of PitNETs, fewer than 5%, develop secondary to germline mutations or to embryonic mutations leading to mosaicism, as part of syndromic diseases or as familial isolated pituitary adenomas. Tumors occurring in a familial setting are usually more aggressive, may present at a younger age, have a larger tumor size,
show increased invasiveness, and are often resistant to standard treatments with SSAs and DAs. In sporadic PitNETs, representing the vast majority of cases, somatic mutations found in a subgroup of patients can likely contribute to tumorigenesis.

Germline Mutations

No activating mutations of classical proto-oncogenes, as well as no loss of function mutations of tumor suppressor genes, have been found in PitNETs, with rare exceptions [7–9]. However, an increasing number of genes with germline mutations predisposing to PitNETs have been identified.

AIP

Germline loss of function mutations in the aryl hydrocarbon receptor (AhR)-interacting protein (AIP) (Table 1) gene are found in about 20% of familial isolated pituitary adenoma families [10, 11], 50% of families displaying acromegaly, and rarely in sporadically diagnosed PitNETs (<4%), particularly in young patients, where the lack of family history is explained by incomplete penetrance rather than de novo mutations [12–14].

AIP is a tumor suppressor gene with high and ubiquitous expression and conserved among species [15]. AIP is a co-chaperone able to bind multiple partners, and loss of some of these interactions may contribute to pituitary tumorigenesis. Among these, the interactions of AIP with components of the cAMP/PKA pathway are particularly interesting, due to the pathogenetic role of this pathway in GH-secreting PitNETs (Fig. 1) [16, 17]. Indeed, AIP can bind phosphodiesterases (PDE4A5 and PDE2A), PKA regulatory subunit R1A, and PKA catalytic subunit [18]. AIP might also affect the cAMP pathway acting upstream cAMP production, since it has been shown that AIP loss reduced the expression of the inhibitory G protein Gαi2, possibly leading to an increased activity of adenylyl cyclase (Fig. 1) [19, 20].

The mechanisms involved in AIP pathogenetic effects might include other putative players in addition to the components of the cAMP pathway. AIP induces tumor shrinkage by positively regulating zinc finger protein ZAC1 [21] that is also required for octreotide antiproliferative signaling [22]. Moreover, AIP stabilizes AhR, also called the dioxin receptor, an intracellular receptor and transcription factor regulating the response to halogenated aromatic hydrocarbons, by the formation of a complex with Hsp90 and p23 proteins that protect AhR from ubiquitination [23]. Nevertheless, AhR involvement in pituitary tumorigenesis remains to be demonstrated.

AIP mutation-positive patients are characterized by early-onset and usually aggressive GH-secreting PitNETs [11], often resistant to treatment with first-generation SSAs [24], but not necessarily to pasireotide [25] (Table 1). Even in the absence of mutations, AIP is frequently downregulated in sporadic GH-secreting PitNETs, in which low AIP is associated with reduced SST2 expression and with reduced responsiveness to first-generation SSAs as well [24, 26, 27]. Pretreatment with octreotide induced an increase of AIP expression, suggesting an AIP involvement in SST2 signal transduction [21, 28]. In contrast, responsiveness to pasireotide, as well as SST5 expression, is not correlated with AIP expression levels [29].

GPR101

Duplications involving the GPR101 gene (Table 1) in the Xq26.3 region cause X-linked acrogigantism (X-LAG) [30], a very rare condition of early-onset pituitary gigantism. Patients with X-LAG display GH- or GH-PRL-secreting tumors or pituitary hyperplasia.

The GPR101 gene encodes a class A, rhodopsin-like, orphan G protein-coupled receptor (GPRC) [30–32]. GPR101 protein was found to be strongly expressed in the human normal pituitary during fetal development as well as in adolescence but not in adult pituitary, suggesting that its expression is induced during development and adolescence [33]. In PitNETs, GPR101 is not expressed in sporadic cases but is strongly overexpressed in the lesions of X-LAG patients [30, 31].

The molecular mechanism of pituitary tumorigenesis involves cAMP pathway activation. Indeed, GPR101 is constitutively coupled with stimulatory G proteins, leading to intracellular cAMP accumulation [30, 34], with direct effects on somatotroph cell proliferation and GH secretion (Fig. 1). A recent study in transgenic mice has demonstrated that GPR101 constitutively activates not only Gs, but also Gα11 and Gα12/13, leading to GH secretion but not cell proliferation [35]. The pathogenetic mechanism may also involve the ability of GPR101 to increase GHRH secretion by the hypothalamus, accordingly to the elevated circulating GHRH levels described in some X-LAG patients [30, 36, 37].

The clinical features of X-LAG patients include early onset of accelerated growth, starting from the first months of life, markedly elevated GH levels resulting in significantly increased IGF-1, concomitant hyperprolactinemia in >80% of the patients, presence of acromegallic features at early age, increased appetite, female predominance, and a poor response to SSAs [36, 38, 39]. Since alterations of SST2 and AIP expression in X-LAG tumors have been
excluded [36], the molecular mechanisms underlying the pharmacological resistance to SSAs of X-LAG patients remain to be investigated.

MEN1

Germline heterozygous mutations in the MEN1 gene cause multiple endocrine neoplasia 1 (MEN1) (Table 1), an autosomal dominant disorder that presents with combination of endocrine and nonendocrine tumors. More than 1,500 MEN1 mutations distributed throughout the whole gene have been described, mainly frameshift, missense, and nonsense mutations [40, 41] without a clear genotype-phenotype correlation [42, 43]. De novo mutations occur in approximately 10% of patients, whereas most MEN1 patients have a positive family history for MEN1-associated manifestations. Somatic mutations in the MEN1 gene are not commonly found in sporadic PitNETs [44].

MEN1 is characterized by the occurrence in a patient of at least 2 of the 3 following disorders: hyperparathyroidism, gastroenteropancreatic-NETs, and PitNETs, reported in 30–40% of cases [42–44]. The most prevalent PitNET subtype is PRL-secreting (60–80%), followed by NF-PitNETs (15–40%), GH-secreting (5–10%), and, rarely, ACTH-secreting [42–44].

Menin is a 610-amino acid nuclear protein that interacts as a scaffold with various molecular partners involved in transcriptional regulation, genome stability, cell division, and proliferation [45]. Menin binds and inhibits JunD, a component of the AP1 transcription factor complex and negative regulator of RAS-dependent cell proliferation [46]. Another mechanism involved in menin-mediated antiproliferative effects is the recruitment of the mixed lineage leukemia protein to the promoters of the cyclin-dependent kinase inhibitor 1B (CDKN1B) gene, leading to multiple endocrine neoplasia type 4 (MEN4) [45] explain 1.5–3.7% of them [51] (Table 1). No germline CDKN1B mutations were found in sporadic PitNETs [52]. PitNETs are found in about 37% of MEN4 reported cases and include GH-, ACTH-, and PRL-secreting and NF-PitNETs [51]. In addition, parathyroid tumors, other NETs, including adrenal and enteropancreatic tumors, as well as tumors involving nonendocrine organs, such as lipomas and meningiomas, have been reported in patients with MEN4 [53]. Due to the small number of patients so far reported, a comprehensive phenotype has not been established yet.

CDKN1B encodes p27Kip1, a CDK inhibitor that prevents cell cycle progression from G1 to S phase, thus acting as a tumor suppressor gene [54]. Interestingly, CDKN1B transcription is regulated by menin [48].

PRKAR1A

Carney’s complex (CNC) is a familial endocrine neoplasia syndrome characterized by the presence of multiple cardiac and extra cardiac myxomas, spotty skin pigmentation, and different endocrine tumors, including GH-secreting PitNETs, adrenocortical tumors, and thyroid adenomas [55–57]. Heterozygous loss of function mutations in the PRKAR1A gene account for over 70% of all cases of CNC [58] (Table 1). The large majority of PRKAR1A mutations are nonsense, frameshift, or splice site mutations which fail to produce a mutant protein due to mRNA degradation through the nonsense-mediated mRNA decay pathway [57].

Again, the pathogenetic mechanism of somatotroph tumorigenesis involves the activation of the promotot cAMP pathway (Fig. 1). Indeed, the PRKAR1A gene encodes the type 1A regulatory subunit (R1A) of PKA. PKA is a heterotetramer composed of 2 regulatory (R) and 2 catalytic (C) subunits: R subunits inhibit the binding of cAMP and activation of the kinase activity of the C subunit. Therefore, loss of R1A increases PKA responsiveness to cAMP, promoting somatotroph cell growth [17].

Mutations in this gene have not been detected in sporadic PitNETs [59–62]; however, other mechanisms have been identified leading to loss of R1A as well. Indeed, a reduced expression of the R1A protein in GH-secreting tumors in the absence of inactivating mutations, but due to an increased degradation by proteasome, has been reported [61]. PRKACB gene locus copy number gain was found in a single patient with CNC that presented with abnormal skin pigmentation, myxomas, and acromegaly [63].
Other Genes Involved in PitNET Pathogenesis

Germline heterozygous mutations in genes encoding succinate dehydrogenase (SDH) subunits and the SDH complex assembly factor 2 protein (SDHAF2) have been described in patients with hereditary pheochromocytoma and paraganglioma (PPGL) (Table 1). The existence of a PPGL and pituitary adenoma association syndrome (3 PAs) suggests that pathogenic variants in these genes might be involved in pituitary tumorigenesis [64–66]. SDHx-mutated PitNETs are PRL- and GH-secreting or NF-PitNETs, frequently macroadenomas with an aggressive clinical course and with poor response to SSAs [64–66].

SDH is a large enzymatic complex composed of 2 subunits which form the catalytic core (SDHA and SDHB), 2 subunits which are responsible for anchoring the complex to the mitochondrial membrane (SDHC and SDHD), and an associated assembly factor (SDHAF2). SDH is mainly involved in the electron transfer chain of the mitochondria, and it is responsible for the reversible enzymatic conversion of succinate into fumarate within the citric acid cycle. Although the pathogenetic mechanism is still poorly understood, it has been hypothesized that mutations in any of the genes encoding SDH subunits might impair the electron transfer chain, mimicking hypoxia, and lead to the accumulation of succinate. Increase of hypoxia-inducible factor-1α induces resistance to apoptotic signals and enhances glycolysis, promoting tumorigenesis [67].

Recently, PitNETs have been also reported in 5 patients with pheochromocytomas harboring mutations in the MAX gene, another gene causing predisposition to familial PPGL [68–70] (Table 1). They include 3 PRL- and 2 GH-secreting PitNETs. MAX is an interacting partner for MYC and MXD1, transcription factors involved in the regulation of cell proliferation and apoptosis [71]. However, the role of MAX in PitNETs pathogenesis has not been investigated, and a causal relationship between MAX mutations and pituitary tumorigenesis has yet to be proven. Other germline mutations recently discovered as potential factors involved in PitNET pathogenesis occur in DICER1, NFI, and CABLES genes (Table 1).

Mutations in the DICER1 gene cause DICER1 syndrome, characterized by a number of unusual tumors, both benign and malignant, such as pleuropulmonary blastoma, and pituitary blastomas, very rare embryonal tumors of the pituitary gland [72]. DICER1 encodes an RNA cleavage enzyme that cleaves precursor microRNA (miRNA) into mature miRNA [73]. miRNAs are regulatory proteins that control the expression and/or degradation of specific RNA molecules. Pituitary blastomas develop in infancy, and all cases have been identified under the age of 24 months. The main clinical presentations of neonates are pressure symptoms due to the large tumor and signs and symptoms of Cushing’s disease, with high mortality [74]. A recent screening for DICER1 variants in a large cohort of Cushing’s disease patients demonstrated that DICER1 gene variants may contribute to the pathogenesis of nonsyndromic corticotropinomas [75].

GH-secreting PitNETs can rarely be part of neurofibromatosis type 1, characterized by neurofibromas, café-au-lait macules, osseous lesions, Lisch nodules, and optic pathway gliomas [76]. Germline mutations in the CABLES1 (CDK5 and ABL enzyme substrate 1) gene have been found in few cases of ACTH-secreting PitNETs [77]. In corticotrophs, CABLES1 protein negatively regulates the cell cycle in response to glucocorticoids. In mutated tumors, markedly reduced nuclear expression of p27 was observed. These ACTH-secreting PitNETs were macroadenomas with high Ki-67 index and extrasellar extension.

Somatic Mutations

In sporadic PitNETs, somatic mutations accounting for a significant percentage of cases have been found. Mutations in the GNAS gene are the only ones to be causally linked to GH-secreting PitNET pathogenesis. Other recurrent somatic genetic alterations are found in USP8 and USP48 genes in ACTH-secreting PitNETs, in the SF3B1 gene in PRL-secreting PitNETs, and in PIK3AC genes in different types of pituitary tumors. Whole-exome/exome sequencing studies revealed no other recurrent somatic mutations but abnormalities of several different genes involved in calcium and cAMP signaling [78].

GNAS

The first mutational change associated with PitNETs was identified in the GNAS1 gene, now GNAS (Table 1), encoding the α subunit of the stimulatory heterotrimeric guanine nucleotide binding proteins (G proteins) (Gsα) (Fig. 1). Amino acid substitutions in exons 8 and 9, replacing either Arg 201 with Cys, His, or Ser or Gln 227 with Arg or Leu, are found in about 40% of GH-secreting PitNETs and rarely in other types of PitNETs [79, 80].

G proteins are composed of 3 different subunits (α, β, and γ). The α subunit binds guanine nucleotides and acts as GTPase. Once activated, GPCRs facilitate the exchange of GTP for GDP on the α subunit, which in turn becomes active, dissociates from βγ, and then regulates downstream effector proteins. Among these, adenyl cyclase is
activated by Gs, with consequent accumulation of intracellular cAMP that exerts mitogenic effects in somatotrophs [17].

The mutations found in GH-secreting PitNETs involve residues critical for GTPase activity, thus preventing hydrolysis of GTP and leading to constitutive activation of Gsa. Gsa can be therefore considered the product of a proto-oncogene, converted into an oncogene (gsp) in those cells in which cAMP represents a mitogenic signal.

Gsp-positive tumors are benign, frequently very small, well differentiated, and densely granulated, in agreement with their hypersecretory activity. They are characterized by an increased responsivity to treatment with SSAs [81–83], although no increase of SSTs has been described in these tumors [84–86]. Overall, gsp mutations show a limited oncogenic potential and associate with a benign phenotype, with the only exception in a patient with a lethal prolactinoma, in which gsp mutation represented the second hit for the transition from prolactinoma to acromegaly [87].

This reduced oncogenic potential could be explained by the existence of intracellular regulatory mechanisms in gsp-mutated tumors able to counteract the activation of the cAMP pathway, including an increased phosphodiesterase 4 (PDE4) activity [88, 89], an increased expression of CREB and inducible cAMP early repressor [90], and a reduced stability of the mutated Gsa protein [91].

Germline-activating mutations of the GNAS gene are considered lethal to the embryo [92], but activating mutations occurring as an early postzygotic event result in the mosaic disease McCune-Albright syndrome (MAS) (Table 1) [93]. This rare syndromic condition predisposes to acrogigantism and affects bones (polysototic fibrous dysplasia), skin (cafe-au-lait macules), and several endocrine tissues (endocrine hyperactivity), such as gonads, pituitary, thyroid, and adrenal cortex [93, 94]. Most commonly, the onset of MAS is in early childhood. These tissue-specific effects are due to mosaic-activating mutations at the Arg201 residue. 10–25% of MAS patients develop GH excess, due to GH-secreting PitNETs or hyperplasia, often accompanied by hyperprolactinemia [95].

It has been found that gsp mutations are localized on the maternal allele in sporadic as well as in MAS GH-secreting PitNETs [96], since in somatotrophs, the Gsa transcript mainly derives from the maternal allele due to tissue-specific paternal imprinting [97, 98].

USP8

Somatic mutations in the USP8 (ubiquitin-specific protease 8) gene are found in 21–62% of ACTH-secreting PitNETs [99–104] (Table 1), but not in other types of pituitary tumors [78, 100]. USP8 is a deubiquitinating enzyme, and among its targets, the EGF receptor (EGFR) is crucial in the tumorigenic mechanism. Indeed, by deubiquitination, USP8 impairs EGFR proteosomal degradation, promoting EGFR recycling and signaling, in particular towards ERK phosphorylation that in corticotrophs results in an increased POMC transcription [99].

USP8 mutations cluster in the 14-3-3 protein binding motif (exon 14; residues 715–720). In particular, 4 mutations account for over 80% of the total number of mutations (S718del, P720R, S718P, and P720Q), and only 2 individual pathogenic variants (D721N and T735I) were outside the 14-3-3 binding motif. Since Ser718 and Pro720 are required for 14-3-3 binding, their substitution prevents USP8 interaction with 14-3-3, increasing the proteolytic cleavage of USP8, required for its catalytic activity [99, 100].

Recent studies showed that other possible substrates of USP8 are deregulated in USP8-mutated tumors, suggesting that they can contribute to ACTH-secreting PitNET pathogenesis [105]. USP8-mutated tumors are characterized by small size, high POMC expression, and ACTH secretion [99, 106]. They are mostly found in women and associated with a greater probability of surgical remission than wild-type tumors [99, 106], although a higher risk of recurrence has been reported as well [102, 103]. An increased expression of SST5 in USP8-mutated tumors has suggested a possible better responsiveness to pasireotide of this subgroup of corticotropinomas [101], but no studies have validated this hypothesis up to now. Interestingly, a de novo germline mutation of USP8 (S719P) was found in a young female patient with Cushing disease [107], supporting the key role of USP8 in ACTH-secreting PitNET pathogenesis.

Somatic Mutations in Other Genes

Mutations affecting another member of the ubiquitin-specific protease family, USP48, have been described in 23% of USP8 wild-type ACTH-secreting PitNETs [108]. Differently from USP8, the pathogenetic mechanism does not involve ERK activation but the NF-κB pathway, which is implicated in the CRH-induced transcriptional activation of the POMC gene [108].

The same work described the somatic mutation V600E in BRAF in 16.4% of ACTH-secreting PitNETs [108]. BRAF mutant enhances the promoter activity and transcription of POMC. The authors found that primary corticotroph tumor cells harboring BRAF V600E are sensitive to the BRAF inhibitor vemurafenib [108]. As for
USP8, also BRAF and USP48 somatic mutations were not detected in other types of PitNETs, suggesting a specificity for ACTH-secreting PitNETs.

Recently, the somatic mutation R625H in the gene encoding splicing factor 3 subunit B1 (SF3B1) was identified by whole-genome sequencing in 21 patients with PRL-secreting PitNETs [109]. In 227 PRL-secreting PitNETs, SF3B1 mutation R625H was found in 19.8% of tumor tissue samples, whereas no SF3B1 mutations have been found in other types of PitNETs [109]. SF3B1-mutated PRL-secreting tumors displayed higher PRL levels and shorter progression-free survival compared to wild-type patients [109]. In vitro experiments showed that SF3B1 R625H enhanced proliferation and suppressed apoptosis of GH3 and MMQ cells. Interestingly, the authors found that SF3B1 R625H caused aberrant splicing of estrogen-related receptor gamma, which resulted in stronger binding of pituitary-specific positive transcription factor 1, leading to excessive estrogen-independent PRL transcription [109].

Activating somatic mutations of PIK3CA have been detected in different types of PitNETs, including ACTH- and PRL-secreting and NF PitNETs [110, 111]. This gene encodes the p110-α catalytic subunit of PI3K, and its activating mutations lead to constitutive activation of the AKT pathway. These mutations were associated with increased PitNET invasiveness [110].

**Clinical Behavior of Pituitary Tumors: The Role of Scaffold Proteins**

Although genetic findings provide insights into the clinical characteristics of mutant pituitary tumors, the genetic causes of sporadic and hereditary tumors are unknown in most cases, and the molecular basis of the tumor biological behavior, clinical presentations, and therapeutic responses remain to be investigated. In the last years, the expression and the activity of specific scaffold proteins have been correlated with pharmacological resistance and invasiveness of pituitary tumors.

In particular, 2 major cytoskeleton actin-binding proteins, filamin A (FLNA) and coflin, as well as the scaffold proteins β-arrestins, emerged as key regulators of proper functioning of the molecular mechanisms that in pitu-
itary tumor cells are required to determine drug responsiveness. Cell cytoskeleton, once believed to be only a structural component of the cell, is now recognized as a complex, dynamic, and multifunctional network of protein filaments that plays several cellular function, ranging from cell movement and shape maintenance to cell differentiation, division, and intracellular transport. FLNA and cofilin are able to bind actin, the protein subunit that originates microfilaments by polymerization. Specifically, FLNA is involved in actin filament cross-linking, while cofilin in actin filament remodeling (Fig. 2a, b). β-Arrestin-1 and -2 are versatile scaffold proteins that participate in GPCR desensitization, endocytosis, intracellular trafficking, and signal transduction, and alterations in their expression in PitNETs might have important consequences on the efficacy of medical therapy.

**Filamin A**

FLNA is a member of the family of filamins that also includes filamins B and C. FLNA is ubiquitously expressed and is the most abundant isoform [112]. FLNA gene is located on chromosome Xq28 [113]. In mice, the absence of the FLNA protein induces in males embryonic lethality and in females cardiac malformations and skeletal defects [114]. In humans, most hemizygous males harboring FLNA loss of function mutations die early during embryogenesis. In females, these mutations cause periventricular nodular heterotopia, a localized neuronal migration disorder, or other clinical disorders, called filaminopathies [115, 116] that also include congenital malformations induced by FLNA gain of function mutations [117, 118].

FLNA (2647 amino acids, 280 kDa) contains an actin-binding domain at the N-terminus, followed by 24 immu-
In HEK293 cells, FLNA regulates DRD2 internalization and recycling [124], supporting FLNA involvement in the regulation of the DRD2 route after endocytosis. A protective effect of FLNA from receptor degradation was also demonstrated for other receptors, including calcium-sensing receptor [125], calcitonin receptor [126], cystic fibrosis transmembrane conductance regulator [127], and the high-affinity IgG receptor FcgammaRI [128]. FLNA was required for efficient recycling of SST2 in GH-secreting PitNETs [129] and chemokine receptor CCR2 and β2-adrenergic receptor [130].

The molecular events leading to FLNA-reduced expression in resistant tumors remain to be investigated. To date, no alterations in the FLNA gene CpG island with the highest probability to have regulatory functions have been found, excluding an epigenetic silencing [121].

Due to these essential functions of FLNA for DRD2 expression and signaling in lactotrophs, loss of FLNA expression and/or function may be one of the mechanisms involved in resistance of PRL-secreting PitNETs to dopaminergic drugs. FLNA expression was correlated with DRD2 expression also in GH-secreting PitNETs [131], suggesting that FLNA function in regulating DRD2 is conserved in different pituitary tumor types.

FLNA Role in Regulating SST2

Although FLNA can directly bind the SST2 first intracellular loop by its repeats 19–20 [132], FLNA protein expression did not correlate with SST2 expression in GH-secreting PitNET tissues [133], in striking contrast with data on DRD2 in prolactinomas [121]. In addition, FLNA was not required for localization of SST2 on the plasma membrane of human tumoral somatotroph cells [133], in agreement with data in melanoma cells [132]. However, single-molecule microscopy analysis in CHO cells recently showed that SST2 spatial arrangement and mobility at the plasma membrane are controlled by dynamic SST2-FLNA interactions [134]. Moreover, FLNA was required for the formation of SST2 clusters and their alignment along actin fibers in CHO cells. In GH-secreting PitNET cells, FLNA was essential for SST2 internalization upon agonist incubation (Fig. 3) [129]. Despite FLNA being a binding partner of β-arrestin-2, FLNA knockdown did not prevent the formation of β-arrestin-2–SST2 complexes in GH3 cells but significantly impaired SST2 loading into cytosolic vesicles positive for the early endocytic and recycling markers, Rab5 and 4, respectively, and prevented SST2 recycling to the cell membrane [129]. In addition, SST2-FLNA interaction resulted necessary to prevent activated SST2 lysosomal degradation and maintain SST2 stability after prolonged agonist stimu-
Overall, these data demonstrated that FLNA is a molecular platform able to connect SST2 with components of the machinery of intracellular trafficking, and that FLNA alterations might profoundly impact on the physiological processes of receptor internalization and recycling.

Moreover, FLNA scaffold functions are required for an efficient SST2 signal transduction cascade (Fig. 3). Indeed, in human GH-secreting PitNET primary cultured cells, silencing of FLNA abolished SST2-induced reduction of cyclin D1 and activation of caspase 3/7, required for the antiproliferative and proapoptotic effects of SST2, respectively [133]. Overexpression of the dominant negative mutant FLNA21–24 (containing only FLNA repeats from 21 to 24, representing the scaffold domain of FLNA) in GH3 cells prevented SST2 effects on apoptosis and ERK1/2 inhibition, suggesting that FLNA scaffold properties are required for the recruitment of signal transduction molecules to activated SST2 [133].

These mechanisms could explain resistance to SSAs even if in presence of SST2. Indeed, the absence or reduced expression of FLNA determines the loss of coupling of SST2 with downstream signal transduction molecules.

In GH-secreting PitNETs, a positive correlation between FLNA and SST2 expression only existed in not SSA-pretreated patients who were controlled with SSAs, corroborating an FLNA involvement in SST2 regulation and signaling [131]. The same study revealed that in GH-secreting PitNETs, FLNA expression was correlated with SST5 expression [131]. This observation suggests a possible contribution for FLNA in determining pasireotide responsiveness in PitNETs. In this regard, it would be of great interest to investigate FLNA role in the regulation of SST5 in ACTH-secreting PitNETs.

FLNA Activity Modulation

It is worth noting that the evaluation of FLNA protein or transcript expression levels usually detected by immunohistochemistry and qRT-PCR, respectively, does not take into account posttranslational modifications that are crucial in determining FLNA activity. One of the main mechanisms that controls FLNA functions is phosphorylation on Ser2152, in the repeat 20, that modifies FLNA-binding properties [135, 136], conformation [137], intracellular localization [130, 138], and its proteolytic cleavage by calpain [139–142].

In vitro experiments in GH-secreting PitNET cells showed that the activation of the CAMP/PKA pathway significantly increased FLNA phosphorylation at Ser2152 [143], with dramatic effects on its function. Indeed, the overexpression of a phosphomimicking FLNA S2152D mutant completely abolished SST2 signal transduction in GH3 cells [143]. This mutant interacts constitutively with SST2, but loses the ability to bind inhibitory G proteins, leading to signal transduction termination (Fig. 3). Thus, although the expression of FLNA is a prerequisite for SST2 signaling, the evaluation of FLNA phosphorylation status is needed to establish whether FLNA is functioning as a scaffold protein allowing SST2 signal transduction or as a signal termination protein that prevents SSA efficacy. No data are available on the effects of FLNA phosphorylation on DRD2 functions.

Another mechanism that regulates FLNA binding to its interaction partners is alternative splicing that gives origin to different FLNA variants. In particular, FLNA splice variant-1 contains an internal deletion of 41 amino acids (residues 2127–2167) [144], located in the domain of interaction with SST2 and DRD2, and including Ser2152 target of phosphorylation, thus suggesting a potentially altered ability in binding SST2 and DRD2 and in functioning as a scaffold for their signaling. No data are available testing the expression of FLNA splice variant-1 in the pituitary. Further studies in a large series of patients evaluating FLNA expression as well as its phosphorylation level and its splicing variants are thus needed to validate FLNA as a marker able to predict PitNET responsiveness to medical treatment with SSAs and DAs.

Cofilin

Cofilin-1 (also called cofilin) belongs to the ADF/cofilin family, together with cofilin 2 (a muscle type of cofilin) and actin-depolymerizing factor or destrin (ADF), and represents the most abundant and ubiquitous member of this family. In mice, deletion of the cofilin gene is embryonic lethal, due to defects in proliferation, polarization, and migration of neural crest cells [145, 146].

Cofilin is a small protein of 19 kDa able to bind both globular (G)-actin and filamentous (F)-actin. It contains an actin-depolymerizing factor homology (ADF-H) domain and a nuclear localization signal. Cofilin activity promotes cell migration, due to the dual action to depolymerize adenosine diphosphate-bound actin filaments near the pointed ends and to sever pre-existing actin filaments. The consequent increase of the number of both free G-actin monomers and actin-free barbed ends, from which F-actin polymerizes, promotes actin polymerization [147] (Fig. 2b). Cofilin activity is tightly regulated, and phosphorylation at Ser3 is the main regulatory mechanism [148]. This posttranslational modification prevents cofilin’s ability to bind actin, thus inactivating cofilin. Ser3 phosphorylation is mediated by the Rho small GTPases, through a cascade of kinases, including PAK,
ROCK, and LIMK. Alterations of cofilin and its phosphorylation pathway have been described in human cancer, with potential effects on tumor development, progression, invasion, and metastasis (reviewed in [149]).

Cofilin Role in NF-PitNET Invasiveness
Recent data demonstrated a key role for cofilin in regulating the invasiveness of NF-PitNETs. In vitro experiments performed in the human NF-PitNET HP75 cell line showed that the overexpression of cofilin induced an increase of cell migration [150]. This effect was reproduced by the constitutively active cofilin phosphodeficient mutant S3A, but not phosphomimicking S3D [150], suggesting a promigratory action of dephosphorylated cofilin only (Fig. 3). Accordingly, S3A cofilin, but not S3D, colocalized with F-actin in membrane protrusions in HP75 cells [150].

Analysis of cofilin phosphorylation in human NF-PitNET tissues confirmed a correlation of cofilin phosphorylation status with tumor invasiveness [150]. Western blot analysis demonstrated higher phosphorylated cofilin (P-cofilin)/total cofilin ratio in noninvasive NF-PitNETs than in invasive tumors. Moreover, immunohistochemistry analysis showed high immunoreactivity for P-cofilin in noninvasive tumors and a low or absent P-cofilin staining in invasive tumors [150].

Notably, the phosphorylation status of cofilin in NF-PitNET cells can be regulated by DAs. In vitro experiments in primary NF-PitNET cultured cells demonstrated that the DRD2 agonist promotes a ROCK-dependent LIMK phosphorylation, which in turn increases cofilin phosphorylation [150]. The activation of this pathway induces a downstream inhibition of cell migration and invasion [150] (Fig. 3).

Overall, cofilin, and more precisely its phosphorylation status, might represent a potential new biomarker predictive of NF-PitNET invasiveness and recurrence. The effects of DAs in reducing cofilin activity and cell invasion need to be further investigated to provide useful information for the management of patients and the use of adjuvant therapies.

Cofilin Role in GH-Secreting PitNET Invasiveness
A crucial role of cofilin in regulating cell motility has been shown also in GH-secreting PitNET cells. In GH3 cells, transfection of S3D cofilin was able to reduce GH3 cell invasion, whereas no effect was observed after transfection of S3A or wild-type cofilin [151]. These results are in contrast with the promigratory effects of S3A cofilin observed in NF-PitNETs [150], suggesting that in different types of pituitary tumors, the mechanisms by which cofilin activity is regulated and the consequent effects on actin cytoskeleton remodeling are different.

Similar to DRD2, SST2 was able to exert inhibitory effects on cell migration and cell invasion by activating RhoA and inducing a ROCK-mediated increase of cofilin phosphorylation in GH3 and primary cultured GH-secreting pituitary tumoral cells [151] (Fig. 3). The molecular mechanism employed by SST2 to activate the RhoA/ROCK/cofilin pathway involves FLNA, as demonstrated by both FLNA genetic silencing and transfection of FLNA dominant negative mutants preventing FLNA binding to SST2 (FLNA 19–20) or to signaling molecules (FLNA 21–24) [151].

Confocal microscopy and co-immunoprecipitation assays demonstrated that upon agonist incubation, SST2 co-localized with FLNA and cofilin at the plasma membrane. Moreover, FLNA is essential for cofilin recruitment to SST2, as demonstrated by FLNA knockdown [151]. These data revealed that FLNA act as a scaffold promoting connections between SST2, molecular components of the cofilin pathway, and microfilaments, enabling a direct effect of SST2 on actin cytoskeleton dynamics.

β-Arrestins
In mammals, nonvisual β-arrestin-1 and β-arrestin-2 are ubiquitously expressed adaptor proteins that function to regulate desensitization, internalization, trafficking, and signaling of a number of GPCRs [152, 153]. In brief, upon GPCR activation by agonist binding, the receptor is phosphorylated by G protein-coupled receptor kinases, allowing recruitment of β-arrestins. This leads to G protein-mediated signal termination (desensitization), by sterically disrupting GPCR/G protein coupling. In order to mediate GPCR endocytosis, β-arrestins coordinate with components of the endocytotic machinery, such as clathrin, adaptor protein 2 (AP2), and phosphoinositides, targeting receptor to clathrin-coated pits. In addition, β-arrestins are also able of generating their own signal transduction pathways, independently from G protein activation, by binding and regulating various signaling molecules, including ERK, JNK, p38, Akt, PI3 kinase, and RhoA [153]. Regarding pituitary tumors, β-arrestins have been implicated in the regulation of both SSTs and DRD2 internalization and/or signaling, with crucial implication on PitNET clinical behavior.

β-Arrestins and SSA Responsiveness
The different subtypes of SSTs differ in their patterns of β-arrestin mobilization and endosomal sorting [154]. Based on the agonist-induced arrestin-receptor binding
properties, GPCRs can be classified in class A receptors, characterized by higher affinity for β-arrestin-2 than β-arrestin-1 and a transient and weak β-arrestin-receptor interaction, and class B receptors, with similar affinities for β-arrestin-1 and -2 and strong β-arrestin-receptor interaction [155]. These properties affect the fate of the internalized receptors and the recycling rate. Indeed, class A receptors are directed to clathrin-coated pits where the complex with β-arrestin dissociates at or near the plasma membrane, whereas class B receptors remain tightly associated with β-arrestin and they internalize as a stable unit into early endosomes [155].

SST2 has been classified as a class B receptor, since its activation results in a robust recruitment of both β-arrestin-1 and -2 and in a stable colocalization with β-arrestin in the same endocytic vesicles, while activated SST5 and SST3 only bind β-arrestin-2 and rapidly dissociate [154, 156, 157]. On the contrary, SST1 and SST4 show a β-arrestin-independent trafficking [154].

In GH-secreting pituitary cells, β-arrestin-2 is essential for SST5 internalization. Indeed, the naturally occurring SST5 mutant R240W, found in an acromegalic patient resistant to treatment with octreotide [158], failed in recruiting β-arrestin-2 in the rat pituitary cell line GH3 and showed impaired ligand-induced internalization [156], as well as an altered signal transduction [159, 160]. Regarding SST2, the recruitment of β-arrestin-2 was not sufficient to ensure proper internalization and recycling, as demonstrated by the impairment of both these processes in GH3 cells silenced for FLNA, despite β-arrestin-2 recruitment [129].

β-Arrestin expression in PitNETs might have an impact on their clinical behavior, affecting the efficacy of SSA (Fig. 3). Indeed, a low expression of β-arrestin-1, but not β-arrestin-2, transcripts in GH- and PRL-secreting PitNETs was correlated with better tumor responsiveness to octreotide in terms of GH suppression both in vitro and in vivo [161]. In acromegalic patients, low β-arrestin-1 and -2 mRNA expression and high SST2/β-arrestins ratio were associated with responsiveness to long-term treatment with SSAs [162]. However, no correlation between β-arrestin-1 mRNA level and SSA response was found in a recent study [163].

β-Arrestins and DA Responsiveness

Although several studies demonstrated a role for β-arrestins in regulating DRD2 internalization and signaling [164], few data are available in pituitary tumor cells. Recently, our group showed that DRD2 antiproliferative signaling in PRL-secreting and NF-PitNETs required the expression of β-arrestin-2 [165] (Fig. 3). DRD2 agonist BIM53097 induced a reduction of AKT phosphorylation in rat tumoral lactotroph cells MMQ and in a subset of human primary cultured NF-PitNET cells, characterized by in vitro responsiveness to DRD2 antimitotic effects and expression of β-arrestin-2 protein [165]. A causal role for β-arrestin-2 was demonstrated by its genetic silencing that prevented DRD2 inhibitory effects on AKT and cell proliferation in MMQ cells. Accordingly, β-arrestin-2 transfection in unresponsive NF-PitNETs restored the ability of the DRD2 agonist to inhibit both AKT phosphorylation and cell growth [165]. The molecular mechanism involved has been demonstrated in the mouse striatum. Upon DRD2 stimulation, β-arrestin-2 is recruited to the receptor and functions as a scaffold for the formation of a multiprotein complex containing AKT and its negative regulator, protein phosphatase 2A, allowing AKT dephosphorylation [166]. From these data, β-arrestin-2 emerged as a potential biomarker predicting NF-PitNETs’ responsiveness to treatment with DAs.

Conclusions

Genetic and molecular alterations so far identified in PitNETs contribute to determine tumor clinical behavior. The presence of germline mutations in specific genes predisposing to PitNET formation is generally associated with more aggressive, invasive, and drug-resistant tumors, but the vast majority of PitNETs are sporadic. Somatic mutations associated with PitNET pathogenesis have been identified in significant percentages of patients, even though mutated tumors showed a similar or even better clinical phenotype compared to wild-type ones.

Alterations of some specific cytoskeleton and/or scaffold proteins have been found to significantly affect PitNET pharmacological resistance and invasive behavior. However, standardized studies conducted in a large series of patients proving the clinical usefulness of these potential biomarkers are still lacking. Although several progresses have been made in understanding molecular mechanisms underlying pituitary tumorigenesis and PitNET clinical phenotype, further studies are needed to identify biomarkers predicting the behavior and the response to therapeutic treatments of PitNETs.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.
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Author Contributions

Anna Spada: drafting the work, review and editing, supervision, and final approval of the version to be published. Giovanna Mantovani: drafting the work, review and editing, supervision, and final approval of the version to be published. Donatella Treppiedi: drafting the work, review, and final approval. Federica Mangili: drafting the work, review, and final approval. Rosa Catalano: drafting the work, review, and final approval. Giulia Carosi: drafting the work, review, and final approval. Elisa Sala: drafting the work, review, and final approval. Erika Peverelli: drafting the work, review and editing, supervision, and final approval of the version to be published.

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