AIP and the somatostatin system in pituitary tumours

Alejandro Ibáñez-Costa and Márta Korbonits

Centre for Endocrinology, William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University of London, London, UK

Correspondence should be addressed to M Korbonits
Email
m.korbonits@qmul.ac.uk

Abstract

Classic somatostatin analogues aimed at somatostatin receptor type 2, such as octreotide and lanreotide, represent the mainstay of medical treatment for acromegaly. These agents have the potential to decrease hormone secretion and reduce tumour size. Patients with a germline mutation in the aryl hydrocarbon receptor-interacting protein gene, *AIP*, develop young-onset acromegaly, poorly responsive to pharmacological therapy. In this review, we summarise the most recent studies on AIP-related pituitary adenomas, paying special attention to the causes of somatostatin resistance; the somatostatin receptor profile including type 2, type 5 and truncated variants; the role of G proteins in this pathology; the use of first and second generation somatostatin analogues; and the role of ZAC1, a zinc-finger protein with expression linked to AIP in somatotrophinoma models and acting as a key mediator of octreotide response.

Key Words

- ▶ pituitary adenomas
- ▶ AIP
- ▶ acromegaly
- ▶ somatostatin
- ▶ ZAC1

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Introduction

Pituitary adenomas are usually benign tumours of the anterior pituitary, which represent 15.5% of intracranial neoplasms (Ostrom *et al.* 2015). They are frequently associated with severe comorbidities due to mass effect and/or the hormone hypersecretion, such as hypogonadism, hypopituitarism, visual disturbances, hypertension, diabetes, emotional disturbances, changes in appearance, growth abnormalities and many others (Asa & Ezzat 2002, Aflorei & Korbonits 2014). These endocrine tumours are unicellular in origin, arising from a monoclonal expansion of a genetically mutated cell (Alexander *et al.* 1990, Herman *et al.* 1990, Melmed 1994). The primary initiating cause for pituitary tumorigenesis has been found to be a gain-of-function mutation in the *GNAS* (Landis *et al.* 1989) and *USP8* (Ma *et al.* 2015, Reincke *et al.* 2015) genes in a significant proportion of somatotroph and corticotroph adenomas, while amplification in *PIK3CA* could be a permissive phenomenon (Finelli *et al.* 2000,

Lin *et al.* 2009, Murat *et al.* 2012). A few cases of corticotroph adenomas have also been identified with germline variants in the *CABLES1* gene (Hernández-Ramírez *et al.* 2017a).

Several studies using transgenic mouse models have demonstrated that either the inactivation (Jacks *et al.* 1992, Kiyokawa *et al.* 1996) or the overexpression (Abbud *et al.* 2005) of cell cycle regulators may initiate pituitary tumorigenesis. This was supported by the finding that about 80% of the human pituitary adenomas show at least one alteration in cell cycle regulators (Sapochnik *et al.* 2016). In the pituitary, classic oncogenes are rarely mutated (Ewing *et al.* 2007), but a growing set of genes have been identified where loss or gain of function leads to pituitary tumorigenesis (Caimari & Korbonits 2016). A familial background can be identified in about 5% of cases either as part of syndromic disease affecting other endocrine organs, including multiple endocrine neoplasia

type 1 and 4, Carney's complex, neurofibromatosis (NF1), DICER1 syndrome and syndromes related to succinate dehydrogenase (SDH) genes or affecting only the pituitary as in familial isolated pituitary adenomas (FIPA) (Beckers & Daly 2007, Leontiou *et al.* 2008, Kopczak *et al.* 2014, Lecoq *et al.* 2015).

Particularly, FIPA is characterised by the manifestation of pituitary tumours in two or more members of the same family in the absence of other syndromic clinical features. FIPA can also present as simplex disease. It is a heterogeneous condition, which includes patients with low penetrance inactivating germline mutations in the aryl hydrocarbon receptor-interacting protein (AIP) gene (Vierimaa *et al.* 2006) in 17% of FIPA families (Hernández-Ramírez *et al.* 2015) and patients with the recently described X-linked acrogigantism (XLAG) (Trivellin *et al.* 2014), which comprise germline or somatic duplications involving *GPR101* gene in the Xq26.3 region. Nevertheless, most of FIPA families harbour a currently unknown genetic mutation.

AIP mutation-positive patients are characterised by early onset and usually aggressive growth hormone (GH), prolactin (PRL) or GH-PRL adenomas, rarely other types of pituitary tumours and very rarely concomitant hyperplasia. Patients usually present in the second or third decade (Hernández-Ramírez *et al.* 2015) and are less responsive to somatostatin analogues (SSA) (Daly *et al.* 2010). Germline mutations in AIP gene has also been described in sporadic pituitary tumour patients, explained by low penetrance rather than *de novo* mutations in these families (Leontiou *et al.* 2008, Jaffrain-Rea *et al.* 2013, Hernández-Ramírez *et al.* 2015, Matsumoto *et al.* 2016). AIP mutation-negative FIPA cases present at a similar age of onset than sporadic pituitary adenoma patients (Hernández-Ramírez *et al.* 2015).

Patient with XLAG display GH, GH-PRL-secreting adenomas, sometimes with neighbouring hyperplasia or have somatotroph or somatotroph & lactotroph hyperplasia without an adenoma. Most of the cases result from *de novo* germline or embryonic mosaic somatic mutations (Beckers *et al.* 2015, Daly *et al.* 2016a,b, Iacovazzo *et al.* 2016b, Trivellin *et al.* 2016).

In this review, we summarise the most recent studies on AIP-related pituitary adenomas, paying special attention to the causes of the resistance to treatment in acromegaly. For readability, and because often referring to both human, mouse or rat species together, genes/mRNA (italicised) and proteins (not italicised) will always be capitalised.

AIP: function and malfunction

AIP encodes a 330 amino-acid 37 kDa protein, which is highly conserved among species and widely distributed in the organism (Trivellin & Korbonits 2011). AIP is a co-chaperone with an N-terminal immunophilin-like domain (Linnert *et al.* 2012), which is unable to mediate immunophilin responses (Carver *et al.* 1998, Laenger *et al.* 2009) and a highly conserved C-terminal domain with three tetratricopeptide repeat (TPR) motifs and a C-terminal α -7 helix (Morgan *et al.* 2012), which mediate its interactions with a number of partners (Trivellin & Korbonits 2011). According to experimental data, AIP has a long half-life of 32.7 h in humans and 30.4 h in mice, which may indicate that it is an abundant and highly structured protein (Hernández-Ramírez *et al.* 2016).

AIP is considered to be a tumour suppressor gene in the pituitary, as loss-of-function mutations predispose to pituitary adenomas often with invasive characteristics. Interestingly, sporadic GH-secreting pituitary adenomas with low AIP expression also show markers of increased invasion (Jaffrain-Rea *et al.* 2009, Kasuki Jomori de Pinho *et al.* 2011, Kasuki *et al.* 2012). AIP, a protein with characteristic seven antiparallel alpha helices, has numerous binding partners and loss of some of these interactions may contribute to tumorigenesis.

AIP is a co-chaperone to Hsp90, probably its most important binding partner. As Hsp90 can bind to 60% of the human kinome and 30% of E3 ubiquitin ligases (Schopf *et al.* 2017, Taipale *et al.* 2010), there are plenty of proteins whose function AIP, a protein with high and ubiquitous expression (Fagerberg *et al.* 2014), could theoretically influence.

Aryl hydrocarbon receptor (AhR)

AIP is essential for the stabilization of AhR in the cytoplasm, by the formation of a complex with Hsp90 and p23 proteins, preventing the ubiquitin-mediated degradation of AhR (Kazlauskas *et al.* 2000); upon ligand binding, AhR experiences a conformational change and is translocated to the nucleus, where it acts as a transcription factor of certain genes, such as P450, a drug-metabolizing enzyme (Fujii-Kuriyama & Mimura 2005). In pituitary adenomas, reduced AhR was associated with low AIP expression (Jaffrain-Rea *et al.* 2009), particularly AIP mutation-positive samples showed a frequent loss of cytoplasmic and nuclear AhR, while AIP overexpression was associated to AhR nuclear immunopositivity.

Guanine nucleotide-binding proteins (G proteins)

AIP was found to be associated with $G\alpha_{13}$, $G\alpha_q$ and possibly regulate the abundance of $G\alpha_i$ -2 (Nakata *et al.* 2009, Tuominen *et al.* 2015, Ritvonen *et al.* 2017). These interactions could influence multiple signalling pathways, with the $G\alpha_i$ -cAMP pathway being especially relevant regarding somatotroph cells and somatostatin action (see section below).

Cyclic nucleotide phosphodiesterases (PDE)

A superfamily of enzymes that breakdown cAMP and/or cGMP and therefore regulate their abundance in cells (Beavo 1995) may interact with AIP (Hernández-Ramírez *et al.* 2017b). Particularly, AIP was able to reversibly inhibit the enzymatic activity of PDE4A5 (rat counterpart of human PDE4A4) (Bolger *et al.* 2003). In humans, PDE4A4 and PDE4A8 enzymes were overexpressed in functioning and non-functioning pituitary adenomas in comparison to normal pituitary tissue (Bolger *et al.* 2016), and in line with this, both PDE4A5 and PDE4A4 were able to interact with wild-type AIP (Leontiou *et al.* 2008, Bolger *et al.* 2016), but they did not interact with mutant variants. Moreover, another PDE, PDE2A3 was suggested to interact with AIP inhibiting the nuclear translocation of AhR, and subsequently the transcription of certain genes (de Oliveira *et al.* 2007), although further data are needed to strengthen this relationship.

Somatostatin and its receptors

Somatostatin (SST) was isolated in ovine hypothalamus by its ability to inhibit GH secretion (Brazeau *et al.* 1973). SST is widely distributed throughout the human central nervous system and also in peripheral tissues, where it has a broad range of biological actions including regulation of neurotransmission, inhibition of pituitary and gastrointestinal hormones, pancreatic enzymes and neuropeptides, etc. (Lamberts 1988, Schettini 1991, Martel *et al.* 2012). SST gene is transcribed to yield the pre-pro somatostatin-encoding mRNA (Shen *et al.* 1982, Naylor *et al.* 1983, Shen & Rutter 1984), which is subsequently translated and the protein is processed to give rise to SST, an active peptide of 28 amino acids (Schally *et al.* 1980, Brown *et al.* 1981), which is commonly further processed into a shorter active variant of 14 amino acids, generally named SST-14 or simply SST (Epelbaum 1986, Martel *et al.* 2012).

SST binds with similar affinity to all its 5 receptor subtypes, named SSTR1–SSTR5, which belong to the seven transmembrane domains (TMD), G protein-coupled receptor superfamily class A (Gahete *et al.* 2010, Theodoropoulou & Stalla 2013). SSTRs were characterised, for the first time in pituitary cells, in the rat GH-PRL-secreting GH4C1 cell line (Schonbrunn & Tashjian 1978), and later, their structure was identified in human, mouse, rat and other species (Patel 1999). SSTRs are encoded by 5 separate genes, which are intronless, share a common YANSCANPVLY motif in the seventh TMD (Olias *et al.* 2004, Durán-Prado *et al.* 2009) and give rise to 5 different SSTR variants in humans, including a splice variant of the subtype 2 in mice (Patel 1999, Olias *et al.* 2004). In addition to the canonical, full-length SSTRs, two novel truncated variants of SSTR5 have been recently identified and characterised in humans, which were termed sst5TMD5 and sst5TMD4, based on the number of TMDs (Durán-Prado *et al.* 2009). Subsequent studies have demonstrated that these receptors are functional, and they show distinct distribution in normal tissues and present unique ligand-selective signalling properties and subcellular distribution. Specifically, these receptors are infrequently present in normal tissues, and, while sst5TMD5 is present only in a subset of pituitary adenomas, sst5TMD4 is normally present in pituitary tumours (Durán-Prado *et al.* 2009, 2010, Luque *et al.* 2015).

It has been observed that each SSTR subtype specially evokes one or more particular SST actions, and considering that they are usually co-expressed, it has been proposed that the specific effect is determined by the combined effect of quantity and type of SSTR subtype expressed in each cell, and the particular signalling routes activated in response to SST. The binding of a ligand, either endogenous or synthetic, to the different SSTRs exert a conformational change in the receptor leading to activation of G proteins and the subsequent signalling pathways (Eglen 2005, Ben-Shlomo & Melmed 2010, Shpakov 2012, Theodoropoulou & Stalla 2013). These pathways can be common among SSTRs, such as cAMP, adenylate cyclase or Ca^{2+} , or different, considering that most of them are receptor, ligand or dose specific. One example is the apoptotic pathway p53/BAX, which is activated mainly through SSTR3 (Sharma *et al.* 1996, War *et al.* 2015). As well as the paradoxically stimulatory effect on GH release observed using very low concentration of SST and cortistatin, an endogenous neuropeptide similar to SST (Ibáñez-Costa *et al.* 2017), in primate pituitary primary cultures, which is mediated exclusively by SSTR5 through adenylyl cyclase/cAMP/protein kinase A

and intracellular Ca^{2+} pathways (Córdoba-Chacón *et al.* 2012). Thus, the specific cascades triggered are complex as (i) SSTRs frequently co-localise; therefore, the final response will depend on the SSTRs' interaction pattern (Cakir *et al.* 2010); (ii) they can form homo- and heterodimers (Durán-Prado *et al.* 2008), not only with each other, but with dopamine receptors, especially the type 2 (DRD2) and δ - and μ -opioid receptors (OPRD1 and OPRM1) (Rocheville *et al.* 2000, Pfeiffer *et al.* 2002, Baragli *et al.* 2007, Somvanshi & Kumar 2014); (iii) SSTRs may display a constitutive activity independently from ligand (Acunzo *et al.* 2008, Ben-Shlomo *et al.* 2013, Eigler *et al.* 2014) and (iv) SSTRs, like many other GPCRs, may be regulated by endocytosis, internal trafficking and arrestin-mediated desensitization mechanisms (Hofland & Lamberts 2003, Tulipano *et al.* 2004, Gatto *et al.* 2013a).

Somatostatin analogues and pituitary adenomas

In addition to, or instead of, surgery, several medical therapeutic approaches are available for functioning pituitary adenomas. Lactotroph tumours are generally very sensitive to dopamine agonists aimed at DRD2, such as cabergoline, decreasing PRL secretion and tumour size, achieving the total remission in a high percentage of patients (Colao & Savastano 2011).

SST was first discovered due to its role in decreasing the GH release of ovine somatotrophes. Since somatotroph adenomas causing acromegaly and gigantism are characterized by the expression of SSTRs, especially SSTR2 and SSTR5 at the mRNA level (Taboada *et al.* 2008, Durán-Prado *et al.* 2009, 2010, Neto *et al.* 2009, Gatto *et al.* 2013b) and protein level (Gatto *et al.* 2013b, Chinezu *et al.* 2014, Iacovazzo *et al.* 2016a), SST was thought to be an important therapeutic agent. However, the clinical usefulness of SST is limited by its short half-life in circulation (less than 3 min) (Patel & Wheatley 1983). Therefore, to overcome this obstacle, synthetic SSAs were developed, such as octreotide and lanreotide, which selectively bind to SSTR2 and can be used to treat neuroendocrine tumours (Bauer *et al.* 1982, Taylor *et al.* 1988, Barbieri *et al.* 2014). In the case of somatotrophinomas, SSAs aimed at SSTR2 are commonly used in the pre- and post-surgical treatment to decrease GH and insulin-like growth factor 1 (IGF1) secretion and tumour size (Melmed 2009, Melmed *et al.* 2015, Puig Domingo 2015). Additionally, thyrotroph tumours

display SSTR2, SSTR3 and SSTR5 (Yoshihara *et al.* 2007, Gatto *et al.* 2012) and octreotide is successfully used to treat these tumours, normalizing TSH levels and decreasing tumour size (Caron *et al.* 2001, Gatto *et al.* 2012, van Varsseveld *et al.* 2014).

In a well-conducted study of unselected acromegaly patients treated with octreotide, 25% of the subjects showed a full clinical benefit: decreased tumour size and normalised both GH and IGF1 levels (Mercado *et al.* 2007). Therefore, resistance or partial resistance is not so rare, even in patients with high SSTR expression on the tumour after surgery (Colao *et al.* 2011, Theodoropoulou & Stalla 2013, Cuevas-Ramos & Fleseriu 2014). The cause of this lack of response is still unknown. A multi-receptor SSA was developed, pasireotide (Bruns *et al.* 2002), which can bind SSTR5 (IC_{50} : 0.16 ± 0.01 nmol/L), SSTR2 (1.0 ± 0.1 nmol/L), SSTR3 (1.5 ± 0.3 nmol/L) and SSTR1 (9.3 ± 0.1 nmol/L) with high affinity, with the hypothesis that simultaneous targeting of more than one SSTR may be more effective in the treatment of patients who are not responsive or who escape from SSTR2 agonist treatment. Another strategy was to develop individual SSTR1, SSTR2 and SSTR5 agonists for potential therapeutic use (Shimon *et al.* 1997b, Zatelli *et al.* 2003, 2005, 2006). Somatotroph and lactotroph adenomas frequently have SSTR1, SSTR5 and SSTR2 expression (Hofland *et al.* 2004, Thodou *et al.* 2006, Taboada *et al.* 2007, Fusco *et al.* 2008, Cuny *et al.* 2012, Ibáñez-Costa *et al.* 2016); and corticotroph adenomas typically express SSTR5 (Arnaldi & Boscaro 2010, Feelders *et al.* 2010, Colao *et al.* 2012, 2014, Golor *et al.* 2012, Lu *et al.* 2013, Ibáñez-Costa *et al.* 2016). Classic SSAs aimed to SSTR2 are not effective although corticotroph tumours express high levels of SSTR5 followed by SSTR2 (Hofland *et al.* 2005, 2010, Batista *et al.* 2006, de Bruin *et al.* 2009b, Tateno *et al.* 2009, Lupp *et al.* 2012, van der Pas *et al.* 2013, Ibáñez-Costa *et al.* 2016), probably, at least partly, because high levels of glucocorticoids decrease SSTR2 levels (de Bruin *et al.* 2009a). Several studies focused on the role of SSA on gonadotroph-derived tumours, particularly on non-functioning pituitary adenomas, tumours with gonadotroph origin but without hormone hypersecretion. These studies have shown that SSTR2-aimed SSAs are usually ineffective (Kopczak *et al.* 2014, Peverelli *et al.* 2015), although there is high expression of SSTR3 and SSTR2 and lower expression of SSTR5 (Taboada *et al.* 2007, Zatelli *et al.* 2007, Florio *et al.* 2008, Tateno *et al.* 2009, Hofland *et al.* 2010, Lee *et al.* 2015, Ibáñez-Costa *et al.* 2016). An *in vitro* study which used individual and combined SSTR

agonists suggested that SSTR1 agonists might be useful (Zatelli *et al.* 2004), and moreover, that pasireotide may reduce cell viability *in vitro* via the inhibition of VEGF (Zatelli *et al.* 2007). Indeed, the use of pasireotide was proposed for non-functioning pituitary adenoma patients (Colao *et al.* 2008), as it has been reflected in two clinical trials (NCT01620138 and NCT01283542; <https://clinicaltrials.gov>).

The use of somatostatin analogues for acromegaly treatment

The clinical use and efficacy of SSA in acromegaly patients has been established (Oberg & Lamberts 2016); however, the intracellular signalling pathways activated and the precise mechanism of effect is still debated.

Some of the approaches used cell lines, either pituitary-derived from murine models, such as GH3, GC, GH4C1 or other cell types, such as CHO-K1 or HEK-293. The responses are variable depending on cell lines as they may miss some key components of SST pathway. For example, GH3 cells do not always express all SSTRs, sometimes not even SSTR2 (Garcia & Myers 1994, Kim *et al.* 2005) or p27kip in the case of GH3 or GC cells (Qian *et al.* 2000, Martín-Rodríguez *et al.* 2015), p27kip being an effector of certain antiproliferative SST-mediated responses (Pages *et al.* 1999, Hubina *et al.* 2006, Grant *et al.* 2008, Zhou *et al.* 2012, Aoki *et al.* 2014, Kiseljick-Vassiliades *et al.* 2015).

Primary cultures of adenomas derived from acromegaly patients are valuable tools to assess SSA response. Samples from clinically responsive patients show better *in vitro* response than clinically partially responsive patients (Shimon *et al.* 1997b, Hofland *et al.* 2004, Murray *et al.* 2004, Jaquet *et al.* 2005b, Ibáñez-Costa *et al.* 2016). The use of specific individual agonists for each SSTR, either peptidic (Shimon *et al.* 1997a) or non-peptidic (Rohrer *et al.* 1998) molecules, has provided key information on the control of the regulation of pituitary hormones secretion in the pituitary. Particularly, in somatotrophinomas, the use of SSTR2 and/or SSTR5 agonists was able to decrease GH release (Shimon *et al.* 1997b, Danila *et al.* 2001, Saveanu *et al.* 2001, 2002, 2006, Jaquet *et al.* 2005a,b, Zatelli *et al.* 2005, Peverelli *et al.* 2013), nevertheless, the simultaneous activation of SSTR2 and SSTR5 did not always show a greater effect on GH release than the single activation of the receptors (Shimon *et al.* 1997b, Zatelli *et al.* 2005). In octreotide- and lanreotide-

resistant somatotrophinomas, an SSTR1-aimed analogue was able to inhibit GH secretion *in vitro* (Matrone *et al.* 2004). In mixed GH-PRL-secreting adenomas, the use of SSTR5-aimed analogues alone (Zatelli *et al.* 2005, Gruszka *et al.* 2012) or in combination with SSTR2 agonists (Fusco *et al.* 2008), were able to decrease prolactin secretion.

Pasireotide is able to decrease GH secretion and alter other functional endpoints in somatotrophinoma cell cultures (Murray *et al.* 2004, Ibáñez-Costa *et al.* 2016, Gatto *et al.* 2017).

In vitro and *in vivo* studies provided a list of parameters which allows to predict SSA responsiveness of somatotrophinomas, such as receptor expression, GNAS mutation, granulation pattern or MRI characteristics.

Somatostatin receptors

SSTR2 SSTR2 mRNA expression, and/or SSTR2/SSTR5 ratio, has been directly correlated with a reduction in GH/IGF1 levels and tumour size after surgery using SSTR2-aimed drugs (Taboada *et al.* 2008, Neto *et al.* 2009). SSTR2, but not SSTR5 expression, is associated with acute response to octreotide (Gatto *et al.* 2013b). High SSTR2 immunoreactivity was associated with good response to SSA (Ferone *et al.* 2008, Fougner *et al.* 2008, Casar-Borota *et al.* 2013, Wildemberg *et al.* 2013, Iacovazzo *et al.* 2016a). A recent study showed that SSTR2 mRNA levels positively correlated to GH reduction *in vitro* in response to octreotide, and a trend in response to pasireotide (Gatto *et al.* 2017). Somatotrophinomas presenting lower SSTR2 mRNA levels and a lower SSTR2/SSTR5 mRNA ratio showed a better response to pasireotide compared to octreotide.

SSTR5 Although SSTR5 is broadly expressed in somatotrophinomas, few data are available from human studies on responsiveness to compounds activating SSTR5, probably due to the recent introduction of pasireotide. The first such study on acromegaly patients resistant to octreotide showed that the expression of SSTR5 may predict responsiveness to pasireotide treatment; the study observed that patients lacking SSTR5 immunoreactivity in their adenoma sample were resistant to pasireotide, but cases with a high SSTR5 staining score had a better IGF1 response (Iacovazzo *et al.* 2016a). Interestingly, some differences were observed between the actions of octreotide and pasireotide on gene expression regulation when

tested on primary culture of human somatotrophinomas: both octreotide and pasireotide decreased *GH* mRNA, but only pasireotide was able to alter *SSTR2* and *SSTR5* gene expression, it decreased *SSTR2* and moderately augmented *SSTR5* expression. This could potentially contribute to enhance *in vivo* response to pasireotide (Ibáñez-Costa *et al.* 2016). Further studies are needed to clarify the effect on first and second generation SSAs on *SSTR* expression.

SSTR5 truncated variants The presence of *sst5TMD4* is inversely correlated to the anti-secretory effect of octreotide *in vitro* (Durán-Prado *et al.* 2010) and *in vivo* (Durán-Prado *et al.* 2010, Luque *et al.* 2015).

GNAS mutation

The recurrent somatic mutations in *GNAS* gene coding for the α -subunit of the stimulatory G protein Gs, commonly named gsp mutation, have been associated with particular clinical characteristics: smaller and less invading densely granulated tumours, normally appearing in older patients (Landis *et al.* 1990, Spada *et al.* 1990, Faglia *et al.* 1996, Yang *et al.* 1996, Barlier *et al.* 1998, Kim *et al.* 2001, Freda *et al.* 2007). The implication of gsp mutation in SSA response has been widely discussed (Larkin *et al.* 2013); nevertheless, a recent meta-analysis revealed that *GNAS*-positive patients have an approximately 10% greater reduction in GH levels in response to an acute octreotide suppression test (Efstathiadou *et al.* 2015). Additionally, *GNAS* positive patients show high levels of *SSTR2* mRNA (Taboada *et al.* 2011) and low levels of *sst5TMD4* (Luque *et al.* 2015).

Granulation pattern

Pituitary adenomas have been classified according to their granulation pattern in electron microscopy analysis as densely or sparsely granulated tumours. Cytokeratin staining is used in clinical practice to characterise densely granulated adenomas having cytotertain staining with perinuclear pattern and sprasely granulated adenomas having dot-like pattern (Obari *et al.* 2008). Sparsely granulated somatotrophinomas occur in younger patients, are larger and more invasive than densely granulated tumours and typically express *SSTR5* but not *SSTR2* (Mayr *et al.* 2013), while densely granulated adenomas present higher levels of *SSTR2* and are more responsive

to SSA treatment (Obari *et al.* 2008, Fougner *et al.* 2012, Kato *et al.* 2012, Brzana *et al.* 2013, Larkin *et al.* 2013).

MRI T2 signal intensity

Hypointense GH-secreting adenomas on T2-weighted MRI are frequently densely granulated adenomas and are associated with a better response to SSAs (Hagiwara *et al.* 2003, Puig-Domingo *et al.* 2010, Heck *et al.* 2012, 2016). The level of *SSTR5*, but not *SSTR2*, is negatively correlated with T2 intensity (Shen *et al.* 2016). Hypointense adenomas are smaller than hyper- and iso-intense adenomas, presenting less invasion of cavernous sinuses and optic chiasm compression, but show higher IGF1 levels (Potorac *et al.* 2015).

Epigenetic regulation of AIP in SSA response

MicroRNAs (miRNAs) are small endogenous non-coding RNA molecules (18–25 nucleotides), which may impair protein expression (Bartel 2004, Gadelha *et al.* 2013a). miR-107 is overexpressed in somatotrophinomas and non-functioning pituitary adenomas (Trivellin *et al.* 2012). miR-107 inhibited AIP expression *in vitro* but there was no correlation between miR-107 expression and AIP expression in human samples. Another miR, miR-34a was highly expressed in pituitary adenomas with lower AIP protein levels than in high AIP expression adenomas (Denes *et al.* 2015). *In vitro*, the overexpression of miR-34a induced an inhibition of endogenous AIP in HEK293 and GH3 cell lines; miR-34a levels were inversely correlated with the response to SSA treatment, miR-34a levels were lower in those patients controlled with octreotide LAR than in uncontrolled patients. The role of miRNAs in SSA response needs further investigations.

The role of AIP and ZAC1 in SSA response in somatotrophinomas

Korbonits and coworkers suggested that AIP has a key role in SSA response (Chahal *et al.* 2012, Gadelha *et al.* 2013b). Indeed, most of the patients with AIP mutation-positive somatotroph adenomas are, at least partially, resistant to pharmacological treatment with SSAs; nevertheless, the causes of this resistance are complex and may be related to several intracellular characteristics of the mutant tumoural somatotrophes. AIP mutation-positive patients are less responsive to *SSTR2*-specific SSAs (Leontiou *et al.*

2008, Jaffrain-Rea *et al.* 2009, Daly *et al.* 2010, Oriola *et al.* 2013, Iacovazzo *et al.* 2016a). The abundance of the receptors may be involved; sporadic GH tumours with low AIP protein expression are less likely to be controlled using octreotide (Kasuki *et al.* 2012) and present lower SSTR2 and SSTR3 and similar SSTR5 levels than tumours with high AIP protein expression (Iacovazzo *et al.* 2016a), while AIP mutation-positive tumours presented higher levels of SSTR5 than sporadic patients (Chahal *et al.* 2012).

AIP mutation-positive somatotroph tumours are frequently sparsely granulated adenomas (Leontiou *et al.* 2008, Hernández-Ramírez *et al.* 2015) and sparsely granulated pituitary adenomas are known to have poorer response to SSAs (Fougner *et al.* 2012, Brzana *et al.* 2013). Patients with GNAS mutations respond better to SSAs (Efsthadiadou *et al.* 2015), while the presence of AIP and GNAS mutations seems to be mutually exclusive in somatotrophinomas (Hernández-Ramírez *et al.* 2015). Recent studies performed on human and mouse somatotrophinomas demonstrated that AIP is essential to maintain relatively low levels of cAMP in normal somatotrophs, and the lack of AIP causes an accumulation of cAMP through defective Gαi-2 signalling, which leads to a downregulation of phosphorylated extracellular signal-regulated kinases 1/2 (p-ERK1/2) and p-CREB (Tuominen *et al.* 2015). This point was supported

by the fact that low Gαi-2 levels were observed in sporadic somatotrophinomas with decreased AIP immunoreactivity, and a positive association between AIP and Gαi-2 was found at protein level, which suggests a combined regulation (Ritvonen *et al.* 2017). AIP expression was associated to higher Gαi-2 and lower Ki67. *In vitro* Gαi-3 silencing revealed that AIP deficiency might lead to cAMP accumulation via Gαi-3, although its expression at protein level was not affected by the presence or absence of AIP (Tuominen *et al.* 2015).

AIP seems to be directly involved in SST signalling pathways: it has been observed that octreotide treatment induced an increase in AIP both at mRNA and protein levels in GH3 cell line; furthermore, patients treated preoperatively with lanreotide showed increased AIP immunostaining in the somatotroph adenomas compared to samples from age-, sex- and tumour size-matched acromegaly patients (Chahal *et al.* 2012, Jaffrain-Rea *et al.* 2013). A novel mechanism of action of octreotide was described involving PI3K signalling pathway, which results in an increase in the expression of ZAC1, a zinc finger protein that regulates cell cycle progression (Theodoropoulou *et al.* 2006). In line with this, octreotide treatment increases ZAC1 mRNA expression (Theodoropoulou *et al.* 2006, Chahal *et al.* 2012), which may link AIP to the ZAC1-mediated antiproliferative

Figure 1

Summary of the proposed model of SSA-AIP-ZAC1 pathway on somatotrophinoma cells. (A) High levels of AIP. AIP (alone or via AHR/ARNT), ZAC1 and p53 directly activate gene transcription; p53 arrests cell cycle, through p21 activation, and increases apoptosis. Octreotide triggers ZAC1/p53 activation through somatostatin receptor 2 (SSTR2) binding and GSK3β pathway. Octreotide increased AIP and ZAC1 expression. G proteins activate the signalling pathway when SSTR2 binds its ligand, such the inhibition of adenylate cyclase (AC), which reduces cAMP levels. In summary, octreotide decreases cell proliferation (green arrow) and activates the apoptotic pathway (pink arrow) through SSTR2 in somatotrophinomas. (B) Low levels or mutated AIP. ZAC1 expression is decreased when AIP is downregulated, and in AIP mutated patients, presumably disrupting the ZAC1/p53 route. Lower SSTR2 has been reported in some studies in AIP-mutated patients, which may also contribute to the lower effect of SSTR2 aimed SSAs. Lack of AIP reduces the expression of Gαi-2 subunit, involved in blocking the AC, which could hinder SST signalling. In summary, the lack of AIP impairs the effect of octreotide, leading to a less activation of apoptotic pathways and increasing the activation of cell proliferation. Arrow-headed lines and bar-headed lines indicate activation and inhibition, respectively.

response (Fig. 1A). As octreotide treatment caused elevated AIP and heterologous overexpression of wild-type AIP increased *ZAC1* expression, while *AIP* silencing reduced *ZAC1* expression (Fig. 1B; Chahal *et al.* 2012), these all point to an SST-AIP-ZAC1 pathway. In line with this, a recent study revealed that *ZAC1* may be a mediator of octreotide antiproliferative effect on gastric cancer cells (Wang *et al.* 2017).

ZAC1 is encoded by *PLAGL1* gene – it is a seven-zinc finger protein functionally related to p53, including tumour suppressor effects through induction of cell cycle arrest at G1 and apoptosis (Spengler *et al.* 1997, Varrault *et al.* 1998, Theodoropoulou *et al.* 2010). *PLAGL1* is an imprinted gene highly expressed during embryonic development (Piras *et al.* 2000, Valente & Auladell 2001, Valente *et al.* 2005, Varrault *et al.* 2006). Postnatally, *ZAC1* is highly expressed in the pituitary, mostly in GH and PRL cells in mice, the expression being lower in FSH cells (Pagotto *et al.* 1999). In humans, GH-, PRL- and ACTH-secreting adenomas express *PLAGL1*, but its expression in gonadotroph-derived tumours is very low (Pagotto *et al.* 2000, Theodoropoulou *et al.* 2009). It is remarkable that *PLAGL1* gene is located on the chromosome 6q24–25, a region that has been frequently related to loss of heterozygosity events in breast, ovarian and adrenal tumours (Bilanges *et al.* 1999, Cvetkovic *et al.* 2004, Lemeta *et al.* 2004, 2006), and also in non-functioning pituitary adenomas (Pagotto *et al.* 2000). It has been reported that high *ZAC1* immunostaining is associated to a good prognosis in non-functioning pituitary adenomas (Noh *et al.* 2009), a type of pituitary tumour that display very low *ZAC1* expression compared to normal pituitary or somatotrophinomas (Vieria Neto *et al.* 2013).

Concluding remarks

In summary, there are several factors that lead to reduced SSA responsiveness: low *SSTR2*, low *SSTR2/SSTR5* ratio, younger age, male gender, high *sst5TMD4* expression, hyperintense T2 on MRI, sparsely granulation pattern, low AIP expression, no *GNAS* mutation, higher basal cAMP levels due to a defective Gαi-2 signalling, low *ZAC1* levels and presumably a disrupted *ZAC1*-p53 antiproliferative effect in response to SSAs. The molecular mechanisms connecting all these factors are still unclear and further data and better models are required to fully understand the mechanism of effect of SSAs.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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