Emerging role of signal transducer and activator of transcription 3 (STAT3) in pituitary adenomas

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Abstract. Pituitary adenomas are benign tumours that can cause an individual various clinical manifestations including tumour mass effects and/or the diverse effects of abnormal pituitary hormone secretion. Given the morbidity and limited treatment options for pituitary adenomas, there is a need for better biomarkers and treatment options. One molecule that is of specific interest is the signal transducer and activator of transcription 3 (STAT3), a transcription factor that plays a critical role in mediating cytokine-induced changes in gene expression. In addition, STAT3 controls cell proliferation by regulating mitochondrial activity. Not only does activation of STAT3 play a crucial role in tumorigenesis, including pituitary tumorigenesis, but a number of studies also demonstrate pharmacological STAT3 inhibition as a promising treatment approach for many types of tumours, including pituitary tumours. This review will focus on the role of STAT3 in different pituitary adenomas, in particular, growth hormone-producing adenomas and null cell adenomas. Furthermore, how STAT3 is involved in the cell proliferation and hormone regulation in pituitary adenomas and its potential role as a molecular therapeutic target in pituitary adenomas will be summarized.

Key words: Signal transducer and activator of transcription 3 (STAT3), Pituitary adenomas, Biomarker

Introduction

Pituitary adenomas are common, occurring in almost 17% of the population over the lifetime [1, 2]. They represent approximately 10% of all intracranial tumours [3]. They have the ability to cause a plethora of problems, including headaches (neurological problems), hormone hypersecretion (endocrinological problems) and loss of vision (ophthalmological problems). Currently, there are few treatment options for pituitary adenomas including surgery, radiotherapy and medical therapy. Transsphenoidal surgery is the first treatment option for most of the patients with adrenocorticotropic hormone (ACTH)-, growth hormone (GH)-, thyroid-stimulating hormone (TSH)-producing pituitary adenoma and non-functioning pituitary macroadenomas. Dopamine agonists and somatostatin analogues are two main classes of medications used for medical therapy for pituitary adenomas. In general, dopamine agonists are first-line medical therapy primarily for hormonal and tumour size control for prolactin (PRL)-producing pituitary adenomas and somatostatin analogues are used post transsphenoidal surgery and occasionally primary medical therapy for GH-producing adenomas. Both classes of medications have been used as second- or third-line therapy for other types of pituitary adenomas. However, these methods are not suited for every patient and thus research is currently being conducted in order to identify potential biomarkers that can act as a therapeutic target and/or predict pituitary tumour behaviours. In this review, we examined the potential role of signal transducer and activator of transcription 3 (STAT3), a transcription factor that plays a critical role in mediating cytokine-induced changes in gene expression in pituitary adenomas, as this molecule has been found to be overexpressed and/or overactivated in a wide variety of tumours, including pituitary adenomas.

STAT3

STAT proteins are part of cytoplasmic inducible transcription factors that are responsible for transducing extracellular signals to the nucleus from the surface of the cell [4-9]. There are seven members of the STAT family: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6 [4-7, 10]. Within the STAT family, STAT3 is responsible for the expression of genes relating
to cancer progression. Additionally, STAT3 can upregulate genes that promote anti-apoptosis, angiogenesis, metastasis, and cell cycle progression as well as down regulating growth suppressor genes [4-6, 10, 11]. The tyrosine phosphorylated STAT3 (pY-STAT3) regulates the transcription of target genes, and the phosphorylation of the serine residue in 727 (pS-STAT3) increases mitochondrial function, resulting in enhanced cell growth.

**STAT3 Expression in Human Pituitary Tumours**

Previous studies suggest the importance of STAT3 in a variety of cancers as well as in *in vitro* and *in vivo* models of pituitary adenomas, which will be reviewed in detail in later sections. The highest STAT3 expression level is detected in GH-producing pituitary adenomas by immunohistochemistry, suggesting the specific role of STAT3 in this type of pituitary adenoma [12]. With regard to pS-STAT3 in human pituitary adenoma tissues, we examined pS-STAT3 expression levels in 23 pituitary adenoma tissues by immunohistochemistry [13]. Most of the somatotroph adenomas have strong immunoreactivity for pS-STAT3. Expression profiles of STAT3 and its upstream molecules in sporadic pituitary null cell adenomas have also been investigated. Feng J *et al.* reported the association between activation of the IL6-R/JAK2/STAT3/MMP9 pathway and invasiveness of pituitary null cell adenomas based on clinicopathological features in 52 patients [14]. As previously mentioned, a study conducted on 23 pituitary adenoma tissues reveals strong STAT3 serine phosphorylation in human somatotroph adenomas but negative or weak immunoreactivity in other types of pituitary adenomas [13]. Another study investigates the role of STAT3 gene promoter methylation and mRNA expression in 102 patients with pituitary adenomas [15]. Low STAT3 methylation status is associated with invasive pituitary adenomas as only 12.1% of invasive pituitary adenomas have methylated STAT3 gene promoters. Additionally, PRL, IGF-1, ACTH and more than one hormone hypersecretion is more commonly found in adenomas with unmethylated STAT3. As the specific rs744166 STAT3 polymorphism is associated with an increased risk of cancer development [16-19], polymorphisms of STAT3 has been examined in order to uncover any associations between STAT3 rs744166 and pituitary adenoma characteristics such as invasiveness, hormonal activity, and recurrence [20]. The STAT3 rs744166 G/G genotype is associated with recurrence of pituitary adenomas. Taken together, these studies support the potential role of STAT3 as a biomarker for treatment of different pituitary adenomas.

**Potential Link between STAT3 and Pituitary Carcinomas**

Currently, there are no articles discussing the direct link between STAT3 and pituitary carcinomas. Additionally, there are few molecular studies of pituitary carcinomas, presumably due to the rarity of this type of pituitary tumour. One study analyzed the patterns of gene expression in pituitary carcinomas and pituitary adenomas through high-density oligonucleotide arrays, reverse transcriptase-quantitative PCR and protein expression [21]. The results showed higher expression of galectin-3 gene in pituitary carcinomas compared to pituitary adenomas which indicate its potential important role in the development of pituitary carcinomas. Galectin-3 was seen to increase phosphorylation of tyrosine STAT3 [22]. Higher expression levels of galectin-3 is associated with enhanced cancer cell proliferation and resistance to chemotherapy [23]. Silencing of galectin-3 in cultured human osteosarcomas resulted in decreased cell migration and invasion abilities as well as inhibition of phosphorylated STAT3 expression [24]. These studies exhibit the potential link from STAT3 expression to development of pituitary carcinomas with a focus on the expression of galectin-3. However, more studies are required in order to confirm the direct link between STAT3 expression and pituitary carcinoma development.

**STAT3 in the Normal Pituitary Gland**

Normal pituitary cells were reported to have the lower STAT3 expression compared to somatotroph adenoma cells and non-functioning pituitary adenoma cells [12]. Currently, there are no publications indicating a direct impact on pituitary development by the STAT family. However, certain signaling pathways involved in regulating pituitary development also control the activity of STATs. Such a pathway is the FGF signaling pathway, thus linking the plausible implication of the STAT family in pituitary development [25]. Further examples suggesting the involvement of STAT family in pituitary development include research concerning leukemia inhibitory factor (LIF) [26]. The LIF-related cytokines presumably act through promoting activity of the JAK family and this allows the phosphorylation of STAT family members to occur. Evidence indicates that LIF stimulates proopiomelanocortin (POMC) in fetal pituitary corticotrophs, offering support that it has a role in pituitary development [25]. In relation to the STAT family, the study offered support for the hypothesis that multiple STAT family members are involved in mediating LIF effects in AtT20 cells. This was seen as STAT1 and STAT3 tyrosyl phosphorylation was influenced by LIF in AtT20 cells.
which further supports the involvement of STAT families through multiple signaling pathways in pituitary development.

Insight into the importance of STAT3 was further provided in studies using knockout mice. Activity of STAT3 was found early within the development of the mouse therefore suggesting its importance in early embryogenesis. This is further supported by results showing STAT3-deficient mice dying earlier in embryogenesis. Additionally, in STAT3-deficient T cells, it was discovered that they exhibit a reduced proliferative response to IL-6 which can be attributed to the defect in IL-6-mediated suppression of apoptosis [27]. Further studies using pituitary-specific STAT3 knockout mice and/or transgenic mice expressing a constitutively active form of STAT3 (STAT3-CA) in pituitary cells are required to uncover the role of STAT3 in pituitary development.

**STAT3 in Experimental Models of Pituitary Adenomas**

Several lines of evidence support the emerging roles of STAT3 in the pituitary tumorigenesis and pituitary hormone regulation. STAT3 acts as a transcriptional factor in pituitary adenomas, which regulates several genes responsible for hormone regulation and cell proliferation of pituitary adenomas. STAT3 also regulates mitochondrial functions, which are associated with cell proliferation and resistance to somatostatin analogues. The following sections review the roles of STAT3 using in vitro and in vivo models of pituitary adenomas. Representative transformed immortalized pituitary adenoma cell lines [28-35] (Table 1) have been used to investigate the regulation of hormone production and secretion, cell proliferation, migration, invasion, and apoptosis. Cell responses to hormones might vary among different cell lines [36, 37].

### Roles of STAT3 in the Regulation of Pituitary Hormones

Analysis of the GH gene reveals several prospective STAT3 binding sites in the promoter region of the GH gene [12], indicating that GH could potentially be a direct STAT3 target. The involvement of tyrosine phosphorylated STAT3 in GH production has been demonstrated using in vitro models. Not only did insulin and IGF-1 play a role in the negative-feedback system at the pituitary gland to inhibit GH expression [38], they also activate pY-STAT3 and inhibit GH expression in rat mammosomatotroph pituitary adenoma cells, GH4 cells [13]. In addition, genetic STAT3 down-regulation or overexpression of dominant negative form of STAT3 (STAT3-Y705F) results in increased GH production in GH4 cells. In contrast, introduction of STAT3-CA increased GH expression and reduced PRL expression in rat mammosomatotroph GH3 cells. Also, pharmacological inhibition of STAT3 suppressed GH production but augmented PRL production [12]. Zhou C et al. reported that a specific STAT3 inhibitor, S3I-201, suppresses GH mRNA expression and GH secretion in primary cells from human somatotroph adenomas in a concentration-dependent manner [12]. A recent study demonstrated that atiprimod, a novel compound belonging to the azaspirane class of cationic amphiphilic drugs, can reduce GH expression in GH3 cells [39]. Furthermore, GH was shown to activate pY-STAT3 [40]. These findings suggest that enhanced GH production itself may accelerate its expression, and therefore pharmacological inhibition of STAT3 would be a novel therapeutic approach to suppress enhanced GH production.

pY-STAT3 is activated by a novel germline mutation

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**Table 1** Pituitary adenoma cell lines

| Cell line | Hormone | Origin | Species | Reference |
|-----------|---------|--------|---------|-----------|
| GH1       | GH, PRL | Mammosomatotroph adenoma | Rat | [28] |
| GH3       | GH, PRL | Mammosomatotroph adenoma | Rat | [29] |
| GH4C1     | GH, PRL | Mammosomatotroph adenoma | Rat | [29] |
| M/t/S/M   | GH, PRL | Mammosomatotroph adenoma | Rat | [30] |
| MMQ       | PRL     | Lactotroph adenoma | Rat | [31] |
| PRL235    | PRL     | Lactotroph adenoma | Rat | [32] |
| RC-4B/C   | GH, PRL, ACTH, FSH, LH, TSH | Mixed | Rat | [33] |
| AtT20     | ACTH    | Corticotroph adenoma | Mouse | [34] |
| HP75      | FSH, LH, gonadotropin α-subunit | Gonadotroph adenoma | Human | [35] |

GH, Growth hormone; PRL, Prolactin; ACTH, Adrenocorticotropic hormone; FSH, Follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone
of Aryl Hydrocarbon Receptor Interacting Protein (AIP) gene, which is associated with familial pituitary adenomas [41]. The deletion of the AIP gene by clustered regularly interspaced short palindromic repeats (CRISPR) can enhance pY-STAT3, resulting in an increase in GH secretion in GH3 cells [41]. Another mutation of the AIP gene associated with familial isolated pituitary adenoma was reported to suppress STAT3 tyrosine phosphorylation in GH3 cells [42].

There are a limited number of studies investigating the role of STAT3 in the regulation of other pituitary hormones. Tomida M et al. demonstrated that cytokines, including LIF and IL-6, phosphorylate STAT3 tyrosine and inhibit PRL secretion in rat pituitary MtT/SM cells [43]. Overexpression of STAT3-CA leads to disruption of the negative-feedback system in AtT-20 cells [44]. However, STAT3 serine phosphorylation has no impact on hormone regulation [12, 13, 44].

**Involvement of STAT3 in the Pituitary Cell Proliferation**

With regard to the effect of pY-STAT3 on pituitary cell proliferation, overexpression of STAT3 as well as STAT3-CA were reported to enhance pituitary adenoma cell proliferation [12, 13]. GH3 cells with pY-STAT3 activated by deletion of AIP gene lead to increased cell proliferation [41]. The roles of microRNAs (miRs) in the regulation of STAT3 in pituitary adenomas were reported by Grzywa et al. [45]. miR-410-3p can upregulate cell proliferation and invasiveness via STAT3 in AtT-20 cells and RC-4B/C cells but inhibit them in GH3 cells. Additionally, enhanced STAT3 serine phosphorylation via Src by FGF4R388 leads to STAT3 translocation to the mitochondria [13]. The mitochondrial serine STAT3 can enhance mitochondrial function, resulting in increased pituitary adenoma cell proliferation [13, 46]. Further studies using mouse models of pituitary adenomas are required to determine if STAT3 is involved in the initiation and/or progression of pituitary adenoma.

With regard to pharmacological STAT3 inhibition, a STAT3 inhibitor, S3I-201, can reduce GH-producing pituitary adenoma cell growth in vitro and in vivo in a concentration-dependent manner [12]. Also, another STAT3 inhibitor, atiprimod was reported to induce caspase-dependent apoptosis by targeting STAT3 in GH3 cells [39]. BP-1-102, which can inhibit STAT3 phosphorylation, dimerization, and DNA-binding activity, suppresses cell proliferation and induces apoptosis in AtT20 cells [47]. Taken together, pharmacological inhibition of STAT3 would be a promising approach to suppress pituitary tumour growth.

The Effects of Pituitary-targeting Drugs on STAT3

A limited number of studies reported the effects of pituitary-targeting drugs on pY-STAT3, which may explain mechanisms underlying the suppressive effects of these drugs on hormone production and pituitary tumour cell growth. An et al. reported the inhibitory effect of metformin, an antidiabetic drug, on GH secretion in vitro and in vivo [48], which is mediated by inhibition of STAT3 signaling. Bromocriptine can reduce pY-STAT3 in the skeletal muscle tissues in a concentration-dependent manner [49]. Octreotide reduced STAT3 tyrosine phosphorylation in GH3 cells [50]. Also, pasireotide, a somatostatin analog with higher affinity to somatostatin receptor 5 compared to octreotide, inhibits STAT3 serine phosphorylation and its translocation to mitochondria via phosphatase 2A. These findings suggest that pasireotide can be a better treatment option for pituitary adenomas with serine-phosphorylated STAT3 [46]. Further studies are required to determine the effects of these therapeutic agents on the STAT3 pathway in pituitary adenomas and establish a better treatment approach based on the phosphorylation status of STAT3.

Roles of STAT3 in Normal Cells and Cancer Cells

The following sections review the roles of STAT3 in normal cells and cancer cells as well as STAT3 inhibitors, which have been under development in recent years.

**STAT3 Pathway**

In terms of the STAT3 pathway, cytokines, such as interleukin-6 (IL-6), bind to their receptors and lead to the homodimerization of glycoprotein 130 (gp130) [51, 52]. The dimerization of gp130 results in activation of janus kinases (JAKs) that phosphorylate tyrosine residues [4-6, 53]. Within the JAK family, JAK1 and JAK2 are the ones mainly associated with STAT3 [4-6, 54]. STAT3 activity occurs for the most part due to pY-STAT3 which allows functional dimers to be formed and binding to DNA, hence regulating transcription of target genes [4-6, 55].

STAT3 can also go through various post-translational modifications and one of these modifications is pS-STAT3. Serine phosphorylation is mediated by several kinases such as mitogen-activated protein kinases (MAPKs), protein kinase C epsilon (PKCe), and the mammalian target of rapamycin (mTOR) and these occur downstream of activation of STAT3 by cytokines [56]. In addition, STAT3 serine phosphorylation can modify
STAT3 activation through inhibition of the tyrosine phosphorylation and is responsible for important factors within the mitochondria organelle [57-59]. pS-STAT3 enhances mitochondrial function, leading to promotion of cell growth [57-62].

**Negative Regulators of STAT3**

The major endogenous negative regulators of STAT3 include protein inhibitor of activated STAT3 (PIAS3), suppressor of cytokine signaling (SOCS), and protein tyrosine phosphatase (PTPs) [63-71]. Most notably, in tumours with increased levels of phosphorylated STAT3, there is a lower level of Src homology region 2 (SH2)-containing protein tyrosine phosphatase (SHP) 2 thus supporting how SHP2 can act as a tumour suppressor [72].

**STAT3 in Cancer**

STAT3 has been identified as an oncogenic transcription factor that is involved in malignant transformation. In a variety of cancer cells [73-80], there is upregulation and constitutive activation of STAT3, which can be linked to cell proliferation, angiogenesis, invasion, anti-apoptosis, immune invasion and metastasis. Additionally, most transformed cells are reliant on STAT3 for proliferation and survival, suggesting that STAT3 remains an ideal therapeutic target [81].

Activators of STAT3 include growth factors, cytokines and hormones, which are regulated and terminated by negative feedback loops. There are four mechanisms involved in the activation of STAT3 which include: disrupting the negative regulation system, positive feedback mechanism, excessive stimulation by upstream kinases and somatic mutations within STAT3 [82].

PIAS3 are directly involved with STAT3 by interacting and limiting downstream transcriptional events [64, 83]. Reduced SOCS3 expression is related to constitutively active STAT3, which promotes tumour development in a variety of cancers [64]. As well, PTPs can negatively control STAT3 signaling through dephosphorylation of their binding partners as described through the loss of SHP1 in cancers [64].

Dysregulated positive feedback systems lead to activation of STAT3 by receptor tyrosine kinases resulting in cancer cell growth. Small molecules, such as NF-kB [84], IL-6 [85, 86], plasminogen activator inhibitor 1 (PAI1) [87], are involved in the activated STAT3 pathway in cancer. Changes in upstream kinases, such as JAK, Src, EGFR, can lead to constitutive activation of STAT3 and thus promotes malignancies [85, 88, 89]. Mutations that drive constitutive activation of STAT3 are found in human neoplasms [90-95]. miRs are non-coding RNAs that can have oncogenic or tumour suppressor properties depending on the malignancy. The use of miRs to inhibit STAT3 through interactions with upstream kinases or negative modulators can promote apoptosis [96, 97].

Serine phosphorylation of STAT3 also plays an important role in cell survival as phosphorylated serine STAT3 can promote aerobic glycolysis. When translocated to the mitochondria, the serine phosphorylated form of STAT3 can regulate respiration and control signaling within the organelle and lead to increased cancer growth, indicating the importance of STAT3 in tumour development [57-62].

**STAT3 Inhibitors for Cancer**

Overexpression and/or hyperactivation of STAT3 are found in a variety of cancers. Aggressive cancer behaviours may be associated with the status of phosphorylated tyrosine and/or serine STAT3. This led to studies of inhibition of STAT3 as a therapeutic target for cancer treatment. Studies using different STAT3 inhibitors ranging from proteins to drugs, small molecules and allosteric inhibitors are summarized in Table 2.

S3I-201 is a chemical inhibitor of STAT3 activity by blocking dimerization and STAT3 DNA-binding and transcriptional activities. S3I-201 has been shown to suppress tumour growth and induce apoptosis in breast cancer cells and pituitary adenoma cells [12, 98, 99]. CYD0618 [100], MM-206 [101], C188 [102] and K116 [103] are allosteric STAT3 inhibitors, which reduce cancer growth in vitro and/or in vivo (Table 2). Although the allosteric STAT3 inhibitors have high selectivity, they have some drawbacks [104]. Most of these inhibitors have relatively low aqueous solubility and bioavailability. Mutations of allosteric sites in STAT3 may be associated with the status of phosphorylated serine STAT3.

**Future Directions**

In summary, lines of evidence discussed in this review support the importance of STAT3 in the pituitary
tumorigenesis and hormone regulation in pituitary adenomas as depicted in Fig. 1 and Table 3. STAT3 regulates cellular functions in pituitary adenomas, including cell proliferation and hormone regulation, suggesting STAT3 as a potential biomarker and molecular therapeutic target for pituitary adenomas. As pituitary tumours are located outside the blood-brain-barrier, novel drugs targeting STAT3 can be delivered to pituitary tumours. Studies in the form of basic, preclinical, and clinical studies are still required to confirm the relevance and importance of STAT3 in pituitary adenomas.

**Conflict of Interest**

The author(s) declared no potential conflicts of interest with respect to the authorship and/or publication of this article.
**Table 3** The roles of STAT3 in pituitary tumorigenesis and hormone production/secretion

| STAT3        | Pituitary tumour growth, invasion, recurrence | Hormone production/secretion | Pituitary adenoma models | References |
|--------------|---------------------------------------------|-----------------------------|--------------------------|------------|
| pY-STAT3     | correlation with invasiveness                | ↑GH                         | Human null cell adenomas | [14]       |
|              | ↑cell-growth                                |                             | Human somatotroph adenoma cells | [12]       |
|              | ↑cell-growth                                | ↑GH                         | GH3 cells                | [12, 41]   |
|              | ↑cell-growth                                | ↑GH                         | GH4 cells                | [13]       |
|              | unknown                                     | ↑PRL                        | M1T/SM cells             | [43]       |
|              | no effect                                    | ↑ACTH                       | AtT20 cells              | [44]       |
|              | ↑cell-growth                                | unknown                     | AtT20 cells              | [47]       |
| pS-STAT3     | unknown                                     | strong immunoreactivity in human somatotroph adenomas |                              | [13]       |
|              | ↑cell-growth                                | no effect                   | GH4 cells                | [13, 46]   |
|              | ↑cell-growth                                | no effect                   | AtT20 cells              | [44]       |
| Low STAT3 methylation status | correlation with invasiveness | correlation with PRL, IGF-1, and/or ACTH immunoreactivity | Human pituitary adenomas | [15]       |
| STAT3 rs744166 G/G genotype | correlation with recurrence | unknown                     | Human pituitary adenomas | [16]       |

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**Note**

During the peer review of this article, a new paper was published showing the involvement of STAT3/5 in the transcriptional regulation of the POMC gene in corticotroph adenomas (Araki T, Tone Y, Yamamoto M, Kameda H, Ben-Shlomo A, et al. Two distinctive POMC promoters modify gene expression in Cushing’s disease. *J Clin Endocrinol Metab.* (2021) Jun 1; dgab387 Epub ahead of print).

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