Regulation of Pituitary Function by Cytokines

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The pituitary plays a key role in the endocrine system of the body. Years of research have proven that cytokines, molecules typical of the immune system, play important roles in pituitary function and regulation. Cytokines act in an autocrine or paracrine fashion in the pituitary, affecting hormone secretion and pituitary growth. This review focuses on the role of cytokines in the normal and adenomatous pituitary, with special emphasis on interleukin-6 (IL-6) because of its opposite effects on normal and tumoral pituitary cells. This review does not address the putative involvement of cytokines in the rare entity of lymphocytic hypophysitis, which is a type of chronic inflammation that primarily affects the pituitary gland and involves autoimmune infiltrates, nor does it refer to pituitary function in children with inflammatory disorders.

**Key Words**
Pituitary · Cytokines · Senescence

**Abstract**
Research performed on the pituitary has proven that cytokines play an important role in maintaining pituitary physiology, affecting not only cell proliferation but also hormone secretion. The effects of cytokines can be autocrine or paracrine. This review gives an overview on the effects of the most studied cytokines in the pituitary. Special interest is focused on interleukin-6 (IL-6) because it has the distinctive characteristic of stimulating pituitary tumor cell growth, but has the opposite effect on normal pituitary cells. On the other hand, IL-6 is a cytokine of interest in the pituitary because recent work has shown that it promotes and maintains senescence in certain types of tumors. Given that the majority of pituitary adenomas are microadenomas and the fact that clinically inapparent pituitary tumors are quite common, senescence, perhaps mediated by IL-6, is an attractive mechanism for explaining the benign nature of pituitary tumors.

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**Relevant Cytokines in the Anterior Pituitary**

**Inflammatory Cytokines: IL-1 and Tumor Necrosis Factor-α**

Interleukin-1

IL-1 production has been shown in rat anterior pituitary [1] and in human pituitary adenomas in vitro [2], and recent evidence points to a role of this cytokine in the development of the rat fetal pituitary [3]. IL-1 receptors
have been characterized in normal mouse anterior pituitary cells [4], in normal rat pituitary [5] and in the rat corticotrophic tumor cell line AtT-20 [4, 6].

IL-1 also regulates pituitary cell growth, inhibiting the growth of normal rat pituitary cells in a dose- and time-dependent manner, although it has no effect on the growth of GH3 cells [7]. This effect was completely reversed by IL-1 receptor antagonist, which is also expressed in the anterior pituitary [8]. IL-1β stimulates normal rat pituitary proliferation [8].

Although the literature is not entirely consistent, the available evidence proves that IL-1 directly stimulates the secretion of most hormones of the rat anterior pituitary, with the exception of prolactin (PRL), the secretion of which is apparently inhibited [9–11]. In human corticotroph cell cultures, it stimulates the release of adrenocorticotrophic hormone (ACTH) and of growth hormone (GH) in GH3 cells [12], and ACTH secretion in stimulated AtT-20 cells [13].

Tumor Necrosis Factor-α
Tumor necrosis factor-α (TNF-α) gene expression has been demonstrated by RT-PCR in pituitary adenoma tissue and culture [2], but its synthesis in normal pituitary has not yet been determined [9].

TNF binding sites have been detected on the rat and mouse anterior pituitary lobes [14]. Two classes of TNF receptors have been identified in several types of species according to their molecular weights, known as p55 (or p60) and p75 (or p80). The mRNAs of both of these are expressed on AtT-20 corticotrophs, while the pituitary folliculostellate (FS) cell line, TtT/GF, expresses only p55 [15].

TNF-α has been shown to have direct effects on anterior pituitary cells in culture, blunting the release of ACTH and other pituitary hormones in response to hypothalamic factors [16]. However, in the treatment of hemipituitaries, it results in a dose-related increase in ACTH, GH, and thyroid-stimulating hormone (TSH) secretion, while PRL secretion is not affected [17], although it causes its release in dispersed anterior pituitary cell culture [18]. In cultured rat anterior pituitary cells, chronic treatment suppressed basal and growth hormone-releasing hormone-stimulated GH release, basal and thyroid-releasing hormone-induced PRL, and basal TSH, while it enhanced the maximal TSH response to thyroid-releasing hormone [19]. In the normal human pituitary, it activates the PRL promoter [20].

Other Cytokines: Leukemia Inhibitory Factor, Macrophage Migration Inhibitory Factor, Interferon-γ and IL-2
Leukemia Inhibitory Factor
Leukemia inhibitory factor (LIF) protein and mRNA have been detected in fetal ACTH-secreting cells at 14 and 16 weeks of gestation as well as in normal and adenomatous adult corticotroph and somatotroph cells [21]. In pituitary explant cultures, LIF mRNA was detected and increased by protein synthesis inhibitors [22]. In the mouse, LIF mRNA was induced by lipopolysaccharide (LPS) intraperitoneal injection [23].

LIF binding sites have been demonstrated in developing human fetal pituitary, in hormone- and non-hormone-secreting cells, particularly in ACTH-secreting ones [21]. LIF receptor mRNA was also demonstrated in mouse pituitary by RT-PCR and is induced in vivo by LPS [23]. Specific LIF binding sites are present in murine AtT-20 cells [23].

LIF stimulates ACTH secretion in vitro as well as in vivo [24].

Macrophage Migration Inhibitory Factor
Migration inhibitory factor (MIF) is expressed in the pituitary, and this expression increases after LPS treatment [25]. Also, there are results which suggest that FS cells are both a source of and a target for MIF and that it possibly serves as a paracrine/autocrine factor in the pituitary gland that contributes to the protective neuroendocrine response to endotoxin [26]. Another study shows that MIF is expressed to a greater extent in cell nuclei in pituitary adenomas than in normal pituitary tissue, and the authors speculate that it may play a role in the control of the cell cycle, but whether its higher level in adenomas is a cause or a consequence of the tumorigenic process remains to be clarified [27].

Interferon-γ
Recently, it was discovered that interferon-γ (IFN-γ) inhibits ACTH production in AtT-20 cells, as well as their proliferation, through a novel Janus kinase-signal transducer and activator of transcription 1/nuclear factor-κB inhibitory signaling pathway [28]. Older data show that rat anterior pituitary cultures respond to IFN-γ with reduced secretion of ACTH, GH, and PRL, an action that is mediated by FS cells [29]. IFN-γ as well as IFN-α and IFN-β stimulate PRL release in primary rat pituitary cultures, and this effect would be mediated through IL-6 [9].
Interleukin-2

IL-2 production and receptor presence in pituitary cells of different species have been described [30–32]. IL-2 receptors are expressed on the membranes of AtT-20 and human corticotrophs and normal human anterior pituitary, and TGF-β interacts with the type II receptor (TGF-βRII) of its receptor, which uses the gp130 protein as an initial cellular signal transducer without activating tyrosine kinases.

There is evidence that IL-6 is expressed in rat fetal pituitary between 18 and 36 weeks of gestation and that it plays a role in pituitary organogenesis [3]. Both IL-6 mRNA and protein production by anterior pituitary cells has been reported by several groups [45–47]. This production can be increased by many compounds, such as IL-1 [46], TNF-α, pituitary adenylate cyclase-activating polypeptide, phorbol esters (phorbol myristate acetate), LPS, vasoactive intestinal polypeptide, forskolin and IFN-γ [reviewed in 9]. Estrogens also affect IL-6 production in the pituitary, reducing its release upon pituitary adenylate cyclase-activating polypeptide stimulation in TtT/GF cells [48]. Glucocorticoids also play a role in IL-6 regulation in the pituitary. Their suppression in peripheral tissues augments LPS-induced IL-6 transcripts in the pituitary, and IL-6 transcript levels increase after adrenalectomy in the rat [49]. IL-6 production has been localized in the adrenocortical FS cells of the pituitary [50], while in adenomas it is produced by the tumor cells themselves [reviewed in 9]. IL-6 mRNA has also been detected in corticotroph adenoma cell cultures and other adenoma cell types, such as prolactinomas, nonfunctioning adenomas, and somatotrophinomas [reviewed in 9].

The IL-6 receptor (IL-6R) is composed of a specific cytokine-binding receptor chain, called IL-6Rα (IL-6Rα), and the glycoprotein gp130, which is crucial for the cell signal transduction once IL-6 binds to its receptor site. The IL-6Rα chain was found to be expressed in rat anterior pituitary cells [51, 52] and normal and adenomatous human pituitary [51], and IL-6R mRNA was identified in the human pituitary cell line HP75 derived from a clinically nonfunctioning pituitary tumor [53]. gp130 mRNA has also been proven to be expressed in human pituitaries as well as in tumoral pituitary [51].

There is much evidence supporting the action of IL-6 on hormone secretion [54]. IL-6 stimulates the release of ACTH from AtT-20 cells and enhances its release from rat hemipituitary glands. IL-6 also stimulates both...
<table>
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<tr>
<th>Cytokine</th>
<th>Normal human pituitary</th>
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<td>IL-1β</td>
<td>ND</td>
<td>yes</td>
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<td>ND</td>
</tr>
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<td></td>
<td>Receptors</td>
<td>IL-1β receptor binding sites</td>
<td>characterized, homogeneously distributed; upregulated by CRF</td>
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<td>ND</td>
<td>characterized; upregulated by LPS</td>
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<td></td>
<td>Proliferation</td>
<td>controversial; inhibition, reversed by IL-1ra; IL-1β stimulates</td>
<td>up to 72 h no effect</td>
<td>ND</td>
<td>no effect</td>
<td>stimulates</td>
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<td>Hormone secretion</td>
<td>IL-1α has no effect on ACTH, while IL-1β does, as well as on GH, LH and TSH, while it inhibits PRL</td>
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<td>stimulation of ACTH in corticotroph cell cultures</td>
<td>GH</td>
<td>IL-1β increases CRH-stimulated ACTH secretion</td>
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<td>Production</td>
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<td>inhibits, estrogen-dependently</td>
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<td>inhibits</td>
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<td>activates the PRL promoter</td>
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<td>inhibits</td>
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<td>inhibits ACTH production</td>
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<tr>
<td>IFN-γ</td>
<td>Production</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<td>reduces ACTH and GH and stimulates PRL through IL-6</td>
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<td>ND</td>
<td>inhibits ACTH production</td>
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<td>Production</td>
<td>yes</td>
<td>in adenocorticotrophinomas</td>
<td>expression in all endocrine cell types; colocalizes with ACTH, GH and PRL; also colocalizes with TSH, LH and FSH</td>
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<td>yes</td>
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<tr>
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<td>in adenocorticotrophinomas</td>
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<td>inhibition</td>
<td>ND</td>
<td>inhibition of LH, FSH and GH release</td>
<td>ND</td>
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<tr>
<td></td>
<td>Hormone secretion</td>
<td>ND</td>
<td>ND</td>
<td>PRL release</td>
<td>enhances ACTH secretion</td>
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<table>
<thead>
<tr>
<th></th>
<th>Normal human pituitary</th>
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<th>Normal mouse pituitary</th>
<th>Human adenoma</th>
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<th>ArT-20 cells</th>
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<td>TGF-β₁, TGF-β₂ and TGF-β₃ in lactotrophs</td>
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<td>ND</td>
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<td>have been described</td>
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<td>decreases in cyclin D1 and p27 mRNA</td>
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<td>TGF-β₁ inhibits PRL secretion</td>
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<td>Production</td>
<td>yes</td>
<td>increased in estrogen-treated animals</td>
<td>in dopamine receptor knockout mice</td>
<td>enhanced in prolactinomas and reduced in corticotrophinomas</td>
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<tr>
<td>Receptors</td>
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<td>ND</td>
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<tr>
<td>Proliferation</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>stimulates</td>
<td>inhibits</td>
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<tr>
<td>Hormone secretion</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>inhibits ACTH</td>
<td>ND</td>
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<tr>
<td>Production</td>
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<td>mRNA; expression stimulated by LPS, TNF-α, IFN, PACAP and VIP; produced by FS cells</td>
<td>ND</td>
<td>protein in all adenoma types, FS cells negative; expressed in different tumor types; mainly in ACTH and GH-secreting tumors</td>
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<td>rat anterior pituitary</td>
<td>ND</td>
<td>mainly in ACTH and GH-secreting tumors; mRNA hardly found</td>
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<td>stimulates/inhibits</td>
<td>stimulates</td>
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<td>stimulates GH and PRL secretion and suppresses TSH secretion</td>
<td>ACTH, PRL, GH, LH and FSH</td>
<td>ND</td>
<td>stimulates GH secretion in somatotrophinomas; IL-6 stimulates both ACTH secretion and POMC gene expression in corticotroph adenoma cell cultures</td>
<td>stimulates GH and PRL</td>
<td>ACTH secretion</td>
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ND = Not determined, at least with the references that the authors possess; β₂ = tumor growth factor-β isoform 2; TGF-β₃ = tumor growth factor-β isoform 3; PACAP = pituitary adenylate cyclase-activating polypeptide.
ACTH secretion and proopiomelanocortin gene expression in corticotrophic adenoma cell cultures [55], and stimulates GH secretion in somatotrophinomas [56]. Furthermore, IL-6 stimulates the release of PRL, GH and LH from dispersed cell cultures of normal rat pituitary cells [reviewed in 57] and GH release from rat pituitary glands [54]. IL-6 also stimulates PRL and GH release from lactosomatotrophic GH3 cells [32].

Role of IL-6 in Pituitary Growth: Normal and Adenomatous Pituitary

IL-6 has the distinct capacity to inhibit normal pituitary cells on the one hand, but to promote tumor growth on the other [32]. It promotes the DNA synthesis and cell proliferation of GH3 cells, but at the same concentrations it inhibits the growth of normal anterior pituitary cells [32]. It stimulates the growth of TtT/GF cells [58] and the proliferation of the MtT/E rat tumor pituitary cells [59]. Furthermore, IL-6 has opposite effects, inhibitory or stimulatory, in different tumors such as ACTH-, PRL-, GH-secreting and nonfunctioning adenomas, with no apparent association between the kind of response and tumor type or size [60].

These different effects in normal and tumoral pituitaries have not yet been elucidated, but may be given by differences in the induction of activating signal pathways or stimulation of cytokine-signaling inhibitor production by the IL-6/gp130 complex [61].

IL-6 also plays an important role in pituitary tumor progression for various reasons. It acts as a stimulatory growth factor and enhances the release of vascular endothelial growth factor from FS cells [62], therefore promoting vessel formation. It has been demonstrated that a transition zone rich in FS is present between normal pituitary tissue and adenomatous tissue. After mutation and transformation of a normal pituitary cell to a tumor-al one, the IL-6 secreted by these surrounding FS cells may act in a paracrine manner to promote the development of an adenoma, by favoring tumor cell number expansion, vessel formation and perhaps extracellular matrix remodeling through the matrix metalloproteinases that the FS cells produce [50]. Additional evidence of this was given when the rat somatotrophin pituitary MtT/S cell line stably expressing gp130 sense (the gp130 protein is overexpressed in these cells) or antisense (the gp130 protein is inhibited) was coinoculated with the TtT/GF cell line in nude mice [63]. gp130 sense clones overexpress gp130 protein because they were transfected with gp130 cDNA put in the correct orientation for transcription. On the other hand, the gp130 antisense clones were transfected with the gp130 cDNA strand which is transcribed as an mRNA that has a complementary sequence to the mRNA of gp130, and can pair with it in the cell, inhibiting its translation to protein. Other MtT/S cells (control clones) were stably transfected with the empty vectors that hold the sense or antisense gp130 cDNA. At low concentrations, MtT/S sense and control clones generated tumors of a smaller size than those derived from these same clones plus TtT/GF cells, showing a dependence on FS cells. In both cases, MtT/S gp130 antisense clones had an impaired tumor development. Furthermore, vessel density was significantly lower in tumors derived from gp130 antisense plus TtT/GF cells [63]. The fact that IL-6 is growth-stimulatory in many pituitary adenomas makes it an attractive candidate as an autocrine/paracrine stimulator of adenoma progression [9, 61]. Bearing all this in mind, suppressing the paracrine activity of IL-6 produced by FS cells may slow down or even stop pituitary tumor development.

Paracrine and Autocrine Role of IL-6 in Pituitary Tumors and Senescence

The anterior pituitary gland commonly develops benign tumors that are usually linked to high levels of trophic hormone production. This is reflected in the finding of clinically inapparent pituitary tumors in up to 20% of the population through autopsy and imaging studies. Pituitary adenomas are usually benign, they rarely develop invasive features, and metastases are usually not associated with hyperplasia. These characteristics raise the question whether there is a mechanism by which the development of pituitary tumors is restricted.

Small benign neoplasms develop in many tissues, and several factors may account for this. In vitro studies have proven that, under certain circumstances, oncogenic signaling can paradoxically give way to a growth arrest response [64]. This arrested growth presents a senescent phenotype, leading to the speculation that in vivo mechanisms may exist which stop tumor development, explaining the proliferative arrest of benign tumors [65], such as pituitary adenomas. Recent work [66, 67] has demonstrated that oncogene-induced senescence (OIS) constitutes an in vivo mechanism that contributes to protection against cancer.

A recent paper [68] reported a role of cytokines in OIS. It proves that the avoidance of malignant transformation
in keratinocytes through OIS involves the activation of a cytokine and chemokine response. Since IL-6 can act as a potent inducer of growth arrest and/or differentiation and correlates with RAS\textsuperscript{V12}-induced senescence in embryonic fibroblasts, the authors focused their attention on this cytokine as a candidate gene for mediating OIS. Their findings show that IL-6 is required for both induction and maintenance of OIS, and acts in a cell-autonomous fashion to enable OIS. They suggest that IL-6 would act in an autocrine manner to regulate OIS because it is blocked by siIL-6 mRNA and requires an intact IL-6R. The results presented in this paper prove that IL-8 also plays a role in OIS; apparently, C/EBP\textsubscript{β} is also involved in an IL-6-dependent manner, and the knockdown of its gene leads to an OIS bypass. Thus, the critical role of IL-6 in OIS is shared by IL-8, as the knockdown of IL-8 leads to an efficient cell bypass of OIS [68].

To obtain a better understanding of tumor senescence, suitable in vivo models, which have not yet been developed, are required. Several mechanisms underlying pituitary senescence have recently been studied. One involves activation of DNA damage and p53/p21 senescence induced by the securin properties of the pituitary tumor transforming gene (PTTG), a protein discovered in pituitary tumor cells [69]. PTTG also behaves as a protooncogene, and high PTTG as well as other oncogene levels can trigger OIS. Pituitary-specific senescent features that are not associated with telomere shortening can be observed in PTTG-null mice, supporting the presence of premature pituitary cell senescence. Additionally, an intracellular disequilibrium of PTTG apparently activates, among other effects, senescence pathways that contribute to the explanation of the very low incidence of pituitary carcinomas observed [70, 71].

Pituitary adenomas could constitute faithful in vivo models of senescence. When an oncogenic threat is present, a response that blocks proliferation but allows the cell to continue living and perform its physiological functions could be beneficial for the organism. This scenario can be related to pituitary cells under oncogenic stress: tumorous cells may develop; however, they do not develop into malignant tumors through the activation of senescence, and therefore, hormones continue to be secreted.

It is likely that in the pituitary, OIS may be mediated by IL-6 [72] (fig. 1). The fact that IL-6 is a cytokine that participates in pituitary tumor development, in addition to the new findings of its role in OIS, suggests the involvement of endogenous IL-6 in the development of pituitary adenoma OIS.

**Conclusions**

With the research done so far, it becomes evident that the local production of cytokines plays a role in pituitary physiology. The changes in the levels of cytokines participate in the endocrine homeostasis of the pituitary and also play a role in the tumoral pituitary.

The finding that IL-6 induces tumor senescence and the fact that IL-6 is an important cytokine in pituitary adenomas shape our thinking in the direction of targeting this cytokine for effective therapy for tumor silencing and prevention of adenoma progression towards malignancy through induction of OIS. Pituitary tumors provide an interesting model to further understand the protective role of OIS and cytokines against malignant transformation.

**References**


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