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Pituitary Action of Cytokines: Focus on BMP-4 and gp130 Family

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Abstract
The anterior pituitary can develop benign tumors of different sizes, classified as micro- and macroadenomas, frequently associated with high levels of hormone production, leading to different associated syndromes like Cushing's disease, acromegaly or prolactinomas. Much work has been done in order to understand the signaling pathways and the factors and hormones involved in the pituitary tumorigenic process. In recent years, much evidence has been collected and it is now well documented that cytokines of the gp130 family, such as interleukin-6, that use gp130 as a common signaling protein stimulate not only the proliferation but also the hormone secretion of pituitary cells. Experiments in vivo have shown that the overexpression of the gp130 receptor resulted in pituitary abnormal growth. Moreover, it has been recently described that bone morphogenetic protein-4 (BMP-4), a member of the TGF-β family, has a stimulatory role on lactosomatotropic cells promoting the development of prolactinomas but it has an inhibitory action on the corticotropic lineage. This inhibitory action prevents Cushing's disease progression. Furthermore, BMP-4 mediates the antiproliferative action of retinoic acid in these cells. The present review highlights the most recent work about gp130 and TGF-β cytokine families and their role in pituitary tumorigenesis.

Pituitary adenomas are neuroendocrine tumors that produce different endocrine and metabolic alterations, including hyperprolactinemia and Cushing's disease among others. The different clinical features produced by pituitary tumors are the result of the overproduction of hormones by the different pituitary cell lineages. The tumoral development process in the pituitary gland involves the clonal expansion of transformed cells stimulated by steroids, hypothalamic hormones and growth factors/cytokines in cooperation. Members of the interleukin (IL)-6 and bone morphogenetic protein (BMP) families have been shown to play important roles in the pathophysiology of the anterior pituitary gland.

Although most adenohypophyseal-origin adenomas are benign tumors, some of them have an invasive char-

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acteristic, representing biologically intermediate forms between the sharply demarcated benign adenomas and the rarely observed metastatic pituitary carcinomas [1–3]. Recent studies about the pituitary tumorigenic process provided new data not only of the factors but also the signaling pathways involved during the process [1–3]. In this review we will focus on two families of cytokines that have important roles during pituitary adenoma development, the IL-6 and the TGF-β families. We will discuss their action from three different points of view: their expression and paracrine-autocrine action, their activity pointing to their stimulatory-inhibitory roles, and finally the in vivo significance of their action.

gp130 and TGF-β Families

Cytokines were originally described as signaling molecules regulating inflammatory and immune responses in multicellular organisms. It is now widely known that they also play important roles in most organs and are key players in the interaction between the immune and neuroendocrine systems [4, 5].

Cytokines that belong to the IL-6 cytokine family or the gp130 cytokine family, such as IL-6, leukemia inhibitory factor, IL-11, oncostatin M, ciliary neurotrophic factor, cardiotropin-1, cardiotropin-like related cytokine and stimulating neurotrophin-1/B cell-stimulating factor-3, begin their signal transduction pathway by the binding of the ligand to a specific receptor. This initial extracellular binding then triggers the association of their α-subunits with another membrane glycoprotein with a molecular mass of 130 kDa, denominated gp130 [6, 7], which functions as an initial intracellular signal transducer [8], leading to the activation of the JAK/STAT pathway. Studies using recombinant cytokines and different cell lines or primary cell cultures have linked gp130 signaling to a wide array of organ systems and biological functions. gp130 cytokines have been shown to be synthesized in tissues including hematopoietic tissues, reproductive tissues, thymus, heart, liver, pituitary, and nervous system and found to play roles in the regulation of cell differentiation, proliferation, cell survival, hormone secretion and inflammatory response [reviewed in 9]. Many studies have also linked gp130 cytokines with physiological and pathological roles in different organs; gene knockouts gp130 [10], STAT3 [11] and JAK1 [12] lead to mice with lethal phenotypes. A conditional gp130 knockout in mice where gp130 was inactivated by conditional gene targeting after birth, exhibited neurological, cardiac, hematopoietic, immunological, hepatic, and pulmonary defects, confirms the widespread importance of gp130 signaling [13].

The TGF-β family is a still growing superfamily of cytokines with widespread distribution and diverse biological functions. They fall into several subfamilies including the TGF-β_1, -β_2, and -β_3, the BMPs, the nodals, the activins and inhibins, the anti-müllerian hormone and the members of the glial cell line-derived neurotrophic factor family [14, 15]. These factors regulate many different cellular events, including cell differentiation during embryonic development, cell adhesion, migration, proliferation, death and transformation throughout the lifespan of the organism [14, 15]. The signal transduction pathway of the superfamily begins with the ligand binding to its specific receptor type II. Upon ligand binding the receptor type II heterodimerizes with and phosphorylates receptor type I kinase, resulting in its activation. Receptor type I activation allows the signal propagation through recognition and phosphorylation of the Smad subgroup known as receptor-activated Smads (R-Smads). After phosphorylation the R-Smads undergo heteromeric complexes with the Co-Smad, Smad-4 that is the only Smad protein common to all R-Smads [16]. The activated Smad complexes are then translocated into the nucleus and in association with other nuclear cofactors bind to target sequences to regulate gene transcription. In this review we will focus on one of the members of the TGF-β family, namely BMPs.

gp130 and BMPs Action in the Pituitary Gland

Much work has been done in order to find out not only the genes but also the molecular pathogenetic mechanism of the development of pituitary tumors. In recent years much evidence has been collected and now it is well known that cytokines of the IL-6 and TGF-β families are involved during the pituitary tumoral process.

Expression and Paracrine-Autocrine Action

Many members of the gp130 cytokine family have been studied in different pituitary tumoral models. One of them is IL-6, which has an intriguing role in regulating pituitary cell growth. IL-6 production by anterior pituitary cells as well as the presence of IL-6 mRNA has been demonstrated by several groups [4, 17–20]. In the normal pituitary, IL-6 production has been localized to folliculostellate (FS) cells suggesting that under normal physiological situations IL-6 acts in a paracrine manner [18]. On

the contrary, in pituitary adenomas, IL-6 is produced by the tumor cells themselves [reviewed in 4, 21, 22], thus under pathological situations IL-6 has a paracrine or autocrine action. Production of IL-6 by anterior pituitary cells can be increased by many stimuli including IL-1, phorbol esters (PMA), lipopolysaccharide, vasoactive intestinal polypeptide, forskolin, interferons, TNF-α, and pituitary adenylate cyclase-activating polypeptide [reviewed in 4, 19, 23], whereas glucocorticoids play an inhibitory effect on IL-6 production not only by anterior pituitary cells but also in aggregate cultures [24].

BMP-4 is one of the members of the TGF-β superfamily whose role has been studied in the pituitary tumorigenesis process. During pituitary organogenesis, BMP-2 and BMP-4 have been shown to play an important paracrine/autocrine role during the initial steps of the anterior pituitary development [25]. For instance in a first stage, BMP-4 is required for the proliferation of the Rathke's pouch placode, which gives rise to PRL-secreting cells, among others. The overexpression of noggin or a dominant negative BMP receptor (BMPR1A) in the anterior pituitary leads to an arrest in the development of PRL-secreting cells [25]. During the second pituitary organogenesis stage an inhibition of BMP-2 ventrodorsal gradient by an FGF8 dorsoventral gradient leads to corticotropic differentiation [26–28]. Overexpression of FGF8 in the developmental pituitary results in Pit-1 lineage cell absence and corticotrope enhanced differentiation, suggesting that it is necessary to inhibit BMP signaling for normal corticotropic development [29]. These controlled and sequential series of gradients of specific signaling molecules in turn appear to coordinate the expression of specific combinations of transcription factor-encoding genes, many of which as tissue-specific or tissue-restricted factors that serially dictate cell-type determination and terminal differentiation events that underlie the differentiated cell phenotype [30]. Thus, during pituitary organogenesis, BMP members have an autocrine/paracrine role within the organ.

BMP-4 has an intriguing pattern expression and role in regulating pituitary cell growth. When we compared the gene expression pattern of normal anterior pituitaries versus prolactinomas, we observed that the BMP extracellular inhibitor noggin is down-regulated in spontaneously developed prolactinomas taken from dopamine D2 receptor-deficient (D2R–/–) female mice, as compared to the normal pituitary of wild-type mice [31]. On the contrary, BMP-4 is overexpressed in different prolactinoma models, including the D2R–/– mice, estradiol-induced rat prolactinomas and human prolactinomas, as compared to normal tissue and other pituitary adenoma types [31]. Furthermore, recently we demonstrated that BMP-4 is expressed in the normal adenohypophysis and that most of the BMP-4-immunopositive cells are somatotropes and corticotropes but not lactotropes [32]. On the other hand, in pituitary adenomas, BMP-4 is expressed at low variable levels in corticotropinoma cells derived from tumoral tissue of patients with Cushing's disease [32] but at high levels in prolactinoma cells [31]. Recently the retinoic acid effect on BMP-4 transcription and expression has been studied in AtT-20 corticotropic cells and an induction in both was observed [32]. Moreover, the activin/BMP system has also been described in the development of human pituitary gonadotropinomas and non-functioning adenomas [33].

Stimulatory-Inhibitory Roles

Several in vitro assays support the action of IL-6 on both hormone secretion and cell proliferation. IL-6 stimulates the release of adrenocorticotropic hormone (ACTH) from AtT-20 cells and enhances ACTH release from rat hemipituitary glands [34]. IL-6 also stimulates both ACTH secretion and proopiomelanocortin (POMC) gene expression in corticotropic adenoma cell cultures [24]. This stimulatory action of IL-6 on human corticotropic adenoma cells function provides evidence for a direct action of IL-6 on corticotropic pituitary cells. Furthermore, IL-6 stimulates the release of prolactin (PRL), growth hormone (GH) and luteinizing hormone from dispersed cell cultures of normal rat pituitary cells [reviewed in 23] and GH release from rat hemipituitary glands [34]. IL-6 also stimulates PRL and GH release from lactosomatotropic GH3 cells [35]. Also, this cytokine has a stimulatory effect on DNA synthesis and cell number of GH3, but yet at the same concentrations it inhibits the growth of normal anterior pituitary cells [35]. It also stimulates the growth of TtT/GF FS cells [36], as well as the proliferation of the MtT/E rat tumor pituitary cell line [37]. Furthermore, IL-6 has opposite effects, inhibitory or stimulatory, in different tumors (ACTH-, PRL-, GH-secreting and non-functioning adenomas), with no apparent association between the kind of response and tumor type or size [38]. Also, IL-6 has different effects in normal or transformed cells, it stimulates the growth of pituitary tumor cells [35] whereas the same concentration of IL-6 inhibits the growth of normal endocrine cells [35]. Other members such as IL-11 and ciliary neurotrophic factor have also been studied. Both of them stimulate the proliferation of pituitary FS and GH3 cells [39]. Besides, IL-11 also stimulates the secretion of

the angiogenic factor vascular endothelial growth factor by FS cells [39].

In recent years much work has been done in order to understand the role of BMP-4 during pituitary pathogenesis. In vitro experiments showed that BMP-4 stimulates GH3 cell proliferation and also promotes the expression of c-Myc in human prolactinomas, while it has no action in other human pituitary tumors [31]. BMP-4 action on GH3 cell proliferation involves an overlapping intracellular signaling mechanism between BMP-4 and estrogens [31]. Their action was partially inhibited by blocking either pathway with the reciprocal antagonist, showing that the BMP-4 effects are partially mediated by the estrogen receptor and that conversely, estradiol effects are partially mediated by BMP-4. Moreover, by co-immunoprecipitation studies, we demonstrated that Smad-4 physically interacts with the estrogen receptor, providing direct evidence of this intracellular crosstalk [31]. On the contrary, using AtT-20 corticotropinoma cells as a model, we described that BMP-4 inhibits both the basal ACTH production and forskolin-induced ACTH stimulation in a dose-dependent manner [32]. This is in agreement with recently published data showing that BMP-4 has an inhibitory effect on the transcriptional activity of POMC promoter [40]. Also, BMP-4 inhibits not only AtT-20 cell proliferation but also c-myc promoter transcriptional activity, showing its inhibitory action on corticotropic cells [32]. Retinoic acid administration has been shown to completely block corticotropic tumor growth and reverses the endocrine alterations and symptoms of Cushing's disease [41, 42], but this inhibitory mechanism over cell proliferation is still not clear. Moreover, both BMP-4 and retinoic acid inhibit AtT-20 cell proliferation, but there was no further inhibition in the presence of both factors even at low doses suggesting that they may share an overlapping mechanism [32]. In cells in which the BMP-4 pathway was blocked, the inhibitory action of retinoic acid was abolished supporting the notion of a crosstalk with the BMP-4-signaling pathway [32]. This is the first evidence showing that BMP-4 has an opposite effect in lactotropic and corticotropic cells – it stimulates lactotropic but inhibits corticotropic pathophysiology. This role is similar to the one observed during pituitary organogenesis.

In vivo Experiments

Several studies have postulated the possibility that gp130 cytokines, through the gp130 glycoprotein-mediated signal transduction cascades, could play an important role in the tumorigenic process in different tissues [43–46]. Thus, the importance of the gp130 cytokines in function and growth of pituitary cells could indicate that some genetic events that occur during pituitary pathogenesis would be mediated by signaling response originating from gp130 cytokines. In vivo experiments also provide further evidence for IL-6 involvement during pituitary tumorigenesis. Therefore, the gp130 cytokines should be considered as feasible candidates to generate a favorable environment for cell transformation events in the pituitary gland. GH3 cells have innate capacity to develop tumors in nude mice [47–49]. They respond to angiogenic and growth factors and do not need the presence of other pituitary cells (i.e. FS cells). Hence, GH3 cells represent a good model to study the influence of gp130 protein expression levels during tumor formation. In order to study the role of the cytokine transducer gp130 glycoprotein during the tumorigenic process, we generated stable lactosomatotropic GH3 clones expressing different gp130 levels and these cells were injected in athymic nude mice. In contrast to mice injected with cells overexpressing gp130, those injected with cells expressing low gp130 levels showed a severely impaired in vivo tumor development, providing initial in vivo evidence supporting a link between gp130 and pituitary abnormal growth [50]. The overexpression of gp130 did not significantly modify the cellular behavior, this might indicate that pituitary gp130 endogenous levels fulfill for a normal functional cellular response. Similarly, in transgenic mice that overexpress gp130, the activation-signaling pathway downstream of gp130 in the heart is not enhanced [51], suggesting that gp130 overexpression does not always induce changes in the cell biology, which is in accordance with the results in GH3 gp130 clones.

One paracrine mechanism by which IL-6 induces cell proliferation is in the dependence of the MtT/S somatotropic cell line on the gp130 cytokine producing a TtT/GF FS cell line to generate tumors in nude mice [52]. The mechanism by which TtT/GF cells contribute to MtT/S cell tumorigenicity may be through the paracrine secretion of cytokines and growth factors that stimulate MtT/S growth. In concordance with this, IL-6 or other gp130 cytokine secreted by TtT/GF cells may have a main role in stimulating MtT/S in vivo tumorigenesis. Recently, we have demonstrated that MtT/S clones overexpressing gp130 protein (gp130-S) and MtT/S clones with reduced levels of gp130 protein (gp130-AS) respond differently when injected in nude mice, the ones with low levels of gp130 had impaired tumor development [53]. It is also important to mention that MtT/S tumorigenic behavior depends on the initial cell concentration; at high concentrations their in vivo

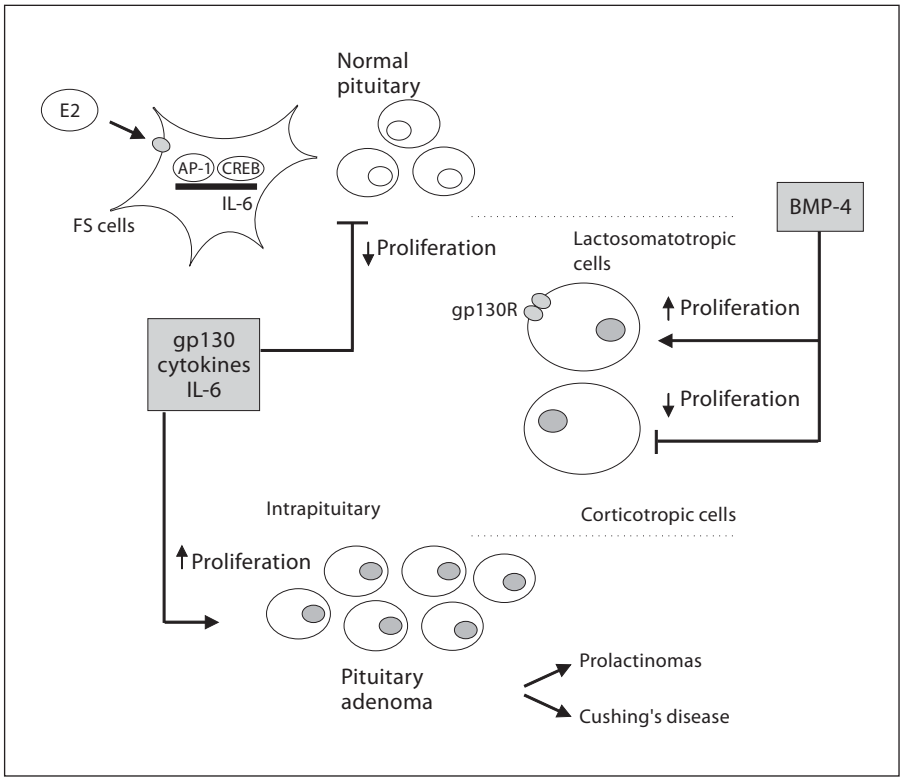

Fig. 1. gp130 and BMP-4 cytokine families' action on the anterior pituitary tumorigenic process. During the anterior pituitary tumorigenic process that leads among others to the development of prolactinomas and Cushing's disease, folliculostellate (FS) or other pituitary cell sources produce and secrete gp130 cytokines in response to hormones or growth factors (i.e. estrogen). In turn, these cytokines stimulate the expression of other hormonal/functional parameters in the pituitary. As shown, IL-6 has an opposite effect in normal or transformed cells, i.e. it inhibits the proliferation of normal cells but promotes the growth of the transformed ones. Furthermore, BMP-4 presents a stimulatory action on lactosomatotropic cells promoting the development of prolactinomas, but it has an inhibitory role on the corticotropic lineage resulting in the prevention of Cushing's disease.

growth would be mediated by either autocrine stimuli, circulating cytokines, or at this cell concentration they may become independent of gp130 cytokines. In these conditions, an additional induction of the gp130-signaling pathway by TtT/GF cells does not affect MtT/S tumor development. MtT/S behavior at high concentrations is similar to that of GH3 cells [22]. On the contrary, at low concentrations, TtT/GF cells are essential for MtT/S cells to develop their tumorigenic potential, suggesting that they depend on the TtT7GF paracrine action.

Thus, gp130 plays a critical role both in cellular models in which cells do not depend on FS cells (GH3 and MtT/S high concentrations) and in cells that depend on FS paracrine stimulus (MtT/S low concentrations), underlying the influence of gp130 in pituitary tumor lacto/somatotropic development. Taken together, these data contribute to support gp130 cytokines as candidates that would favor the development and/or growth of pituitary tumors.

Given that Smad proteins mediate BMP-4 signaling and to further study the role of BMP-4 in tumor formation in nude mice in vivo, we generated GH3 or AtT-20 clones stably transfected with a Smad-4 dominant negative (GH3-Smad-4dn). GH3-Smad-4dn cells formed small low-growing tumors that did not express c-Myc as compared to control cells [31]. Tumor growth and c-Myc expression were recovered when the Smad-4dn expression was lost, proving direct evidence that BMP-4/Smad-4 are involved in prolactinoma development in vivo [31]. On the other hand, at low cell concentration, AtT-20 cells present no tumorigenic capacity when injected in nude mice but AtT-20 Smad-4dn clones developed visible tumors starting at 1 week after injection as well as symptoms of Cushing's disease [32]. Therefore, inhibition of the BMP-4 signaling results in an increase of the AtT-20 cells' tumorigenic potential demonstrating an inhibitory role of BMP-4 in the development of corticotropic tumors in vivo [32].

gp130 cytokines play an autocrine/paracrine role in the regulation of pituitary function in physiologic and pathophysiologic conditions. Several studies provide the basis for this role, showing the expression and secretion of these cytokines and expression of their receptors in normal pituitary gland and pituitary adenomas. The above-reviewed evidence demonstrates the participation of the gp130 receptor in an autocrine/paracrine stimulation of GH3 and MtT/S cell growth in vivo, supporting the notion that gp130 cytokines are determinants of cel-

lular behavior and communication that lead to pituitary tumor development (fig. 1).

BMP-4, a corticotropic growth inhibitor, is expressed in the normal pituitary but has a reduced expression in corticotropic tumors. In analogy to the situation during pituitary organogenesis, this distinctive expression may allow corticotropic tumoral growth promotion. On the contrary, BMP-4 overexpression in prolactinomas and its stimulatory effect on these cells promotes pituitary prolactinoma pathogenesis. At this stage it is not clear which is the trigger for BMP-4 differential expression (high levels in prolactinomas but low levels in Cushing's corticotrope) in adult pituitary tumor cells; it may be caused by different overlapping factors: its own overexpression/reduced expression, the lower expression of its inhibitor noggin (which in normal cells may control BMP-4 action), an altered expression of its signal transducer Smad-4 or a crosstalk with other hormones or factors. Thus, BMP-4 acts as an autocrine/paracrine regulator (fig. 1) not only of normal but also of transformed adult pituitary cells and it has a pituitary lineage cell specificity during the tumorigenic process.

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