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Molecular transduction mechanisms of cytokine–hormone interactions: role of gp130 cytokines

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Highly sophisticated mechanisms confer on the immune system the capacity to respond with a certain degree of autonomy. However, the final outcome of an immune response depends on the interaction of the immune system with other systems. The immune and neuroendocrine systems have an intimate cross-communication that makes possible a satisfactory response to environmental changes. Part of this interaction occurs through cytokines and steroid hormones. The last step of this cross-talk is the molecular level. As a model of interaction, this review focuses on the gp130 cytokine family. These cytokines, as well as their receptors, are expressed in pituitary cells. They regulate hormone production as well as growth of pituitary cells. During acute or chronic inflammation or infection, systemic, hypothalamic and hypophyseal gp130 cytokines act on anterior pituitary cells, integrating the neuroendocrine–immune response. Disruptions of these pathways may lead not only to abnormal growth of pituitary cells but also to immune disorders, for which, based on recent findings, targeting these cytokines might be a novel therapeutic approach.

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The neuroendocrine and immune systems have to be considered as anatomically and functionally interconnected units; both express and respond to a large number of common regulatory molecules, such as cytokines, hormones, neuropeptides and neurotransmitters.

The importance of the role that cytokines play in modulating the neuroendocrine–immune interconnection is extensively reflected in the anterior pituitary, where different cytokines are expressed to exert an important physiological role (Arzt *et al.* 1999). Among them, the gp130 cytokines of the interleukin-6 (IL-6) family constitute a well-known example, since they play important roles in function, growth and neuroendocrine responses of the gland. Several groups have demonstrated in great detail the expression of specific receptors and synthesis of gp130 cytokines in different types of pituitary cells. We will focus on this family as an example model of the integrative neuroendocrine–immune network.

The gp130 cytokines and their receptors

The IL-6 family of cytokines contains, among other cytokines, IL-6, leukaemia inhibitory factor (LIF), IL-11, oncostatin M (OSM) and ciliary neurotrophic factor (CNTF). This group is named the gp130 cytokine family because all of them use the glycoprotein gp130 as a common signal transducer after binding their specific receptor. Upon ligand binding, all IL-6 family cytokines recruit gp130 to their receptor complexes. The nature of these complexes depends on the specific ligand. After association of the IL-6–IL-6R complex with gp130, homodimerization of gp130 occurs and starts IL-6 signal transduction. Like the IL-6R complex, gp130 is an indispensable component of the IL-11R (Hirano, 1994). The IL-11 receptor complex forms a hexamer, consisting of two molecules of IL-11, IL-11R and gp130. Leukaemia inhibitory factor binds to the LIF receptor α-subunit (LIFRα), which has structural similarity to gp130, and induces the heterodimer LIFR–gp130. Oncostatin M triggers formation of the LIFR–gp130

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heterodimer and was also found to use another heterodimer composed of gp130 and OSM-specific receptor component (OSMRα). Ciliary neurotrophic factor binds to the CNTF receptor α-subunit (CNTFRα), whose extracellular regions are structurally similar to those of IL-6Rα. The resultant CNTF–CNTFRα complex induces the formation of the LIFRα–gp130 heterodimer. Cardiotropin-1 (CT-1) has been suggested to induce this type of heterodimer either by direct binding to LIFR or by binding to CT1 specific receptor (CT1Rα) (Hirano, 1994).

Considering that gp130 is ubiquitously expressed, the specific responsiveness of a given cell type to a member of the gp130 cytokine family is therefore mainly determined by the selective expression of their respective specific α-receptor subunits and/or the cytokines themselves. This takes place in different cell types within the pituitary gland, where not only the expression of gp130 (Shimon *et al.* 1997; Kurotani *et al.* 2001) but also the expression of specific gp130 cytokine receptors have been described, providing the basis for an auto/paracrine role of these cytokines in the regulation of pituitary hormone secretion and cell growth (Arzt, 2001).

Expression and function of the IL-6 family of cytokines in the anterior pituitary

The expression and direct action of the IL-6 family of cytokines in the anterior pituitary have been extensively demonstrated. The role and relevance of this cytokine family in neuroendocrine–immune circuits (discussed in detail in this review) are based on this expression, which is summarized below for IL-6, LIF, IL-11 and CNTF.

Interleukin-6 mRNA has been detected in normal and tumoural human pituitaries (Arzt *et al.* 1999). Interleukin-6 is produced mainly by folliculostellate (FS) cells in normal pituitaries (Vankelecom *et al.* 1989) and by tumour cells in pituitary adenomas, where IL-6 expression correlates with biological aggression (Arzt *et al.* 1999). Lipopolisacharide (LPS) and interleukin-1 stimulate IL-6 in normal human pituitaries and pituitary adenomas, respectively. Accordingly, the FS cell line TtT/GF releases IL-6 by LPS and pituitary adenylate cyclase-activating polypeptide (PACAP), which stimulates IL-6 transcription at the TRH response element (TRE) and cAMP response element (CRE) sites of the IL-6 promoter (Carbia Nagashima *et al.* 2003). Interleukin-6 has inhibitory or stimulatory effects in different pituitary tumours. Inhibition of IL-6 by oestrogens, which are important factors in the pathogenesis of lactotroph tumours, has been reported in TtT/GF cells (Carbia Nagashima *et al.* 2003). Moreover, expression of IL-6 and its effects on human pituitary tumour cell growth have been demonstrated (Borg *et al.* 2003). All these data suggest a direct role of IL-6 in the control of cell proliferation in the pituitary gland.

Leukaemia inhibitory factor protein and mRNA, as well as LIF binding sites, have been demonstrated in developing human fetal pituitary and in normal and adenomatous human adult tissue (Akita *et al.* 1996*a*). Leukaemia inhibitory factor and LIF receptor mRNAs were found in pituitary cells, where they are induced *in vivo* by LPS (Wang *et al.* 1996). Specific LIF binding sites are also present in murine AtT-20 cells. Leukaemia inhibitory factor also regulates the proliferation of hormone producing cells, as demonstrated in AtT-20 cells (Stefana *et al.* 1996).

Interleukin-11 mRNA was detected in pituitary FS, lactosomatotrophic (Perez Castro *et al.* 2000) and corticotrophic cells (Auernhammer & Melmed, 1999), and the mRNA for the α-chain specific for the IL-11R is expressed in both cell types. Interleukin-11 stimulates the proliferation of FS and lactosomatotrophic GH3 cells (Perez Castro *et al.* 2000).

It has been shown that FS and lactosomatotrophic cells express CNTF mRNA and protein (Perez Castro *et al.* 2000), as well as the mRNA for the α-chain specific for the CNTFR. This expression is also detected in normal cells (Auernhammer & Melmed, 1999; Perez Castro *et al.* 2000), and the mRNA for the CNTFR was detected in tumours secreting prolactin (PRL), growth hormone (GH) and in non-functioning tumours (Perez Castro *et al.* 2001). Ciliary neurotrophic factor stimulates the proliferation of FS and GH3 cells (Perez Castro *et al.* 2001).

Reduced levels of gp130 protein in GH3 and MtT/S (pituitary somatotrophic cell line) cells stably transfected with gp130 antisense cDNA blocked cell growth and hormone secretion stimulated by CNTF and led to severely impaired *in vivo* tumour development in athymic nude mice (Perez Castro *et al.* 2003; Graciarena *et al.* 2004). These data provide evidence supporting a link between gp130 and abnormal pituitary growth and, as will be discussed below, between gp130 and hormone secretion.

Signalling by gp130 in neuroendocrine pituitary cells

Signalling by gp130 occurs via the JAK/STAT (Janus kinase/signal transducer and activator of transcription) pathway. After specific binding of the IL-6 family cytokine receptors, the kinases associated with the gp130 intracellular regions, namely JAK1, JAK2 and Tyk2, become activated and phosphorylate the cytoplasmic tail of gp130, generating docking sites for molecules with Src-homology-2 (SH2) domain, such as STAT1 and STAT3. The STAT proteins are thus recruited and phosphorylated. They dimerize and translocate to the nucleus, where they regulate transcription of target genes.

It has been demonstrated that the action of LIF on corticotroph cells depends on STAT3. Using progressive 5′-deletions of proopiomelanocortin (POMC) promoter, it has been shown that the LIF-responsive POMC promoter region contains two juxtaposed sequences

related to the STAT3 DNA binding motif (Bousquet *et al.* 2000). Accordingly, it has been demonstrated that lactosomatotrophs GH3 and MtT/S cells stably transfected with gp130 antisense (AS) cDNA have lower STAT3 transcriptional activity than wild-type cells or clones carrying the gp130 sense cDNA (Perez Castro *et al.* 2003). Pituitary MtT/S gp130-AS clones show reduced STAT3 phosphorylation and diminished total STAT3 levels (Graciarena *et al.* 2004).

SOCS proteins are a family of inhibitors that down-regulate the JAK/STAT pathway. Negative regulation of cytokine function is critical to prevent excessive hypothalamic–pituitary–adrenal (HPA) axis activation. Activation of corticotroph JAK/STAT cascade by gp130 cytokines not only induces POMC expression but also SOCS-3 expression (Auernhammer *et al.* 1999). Several studies have demonstrated that the intracellular gp130 negative regulation exerted by SOCS proteins is functional in pituitary cells. In AtT-20 cells, IL-11 stimulates the expression of SOCS-3, and overexpression of SOCS-3 caused a significant inhibition of IL-11-induced ACTH secretion (Auernhammer & Melmed, 1999). Corticotroph cells stably overexpressing SOCS-3 also show a significant inhibition of LIF-induced POMC promoter activation, POMC transcription and ACTH secretion (Bousquet *et al.* 1999). In addition, SOCS-3 mRNA was also stimulated in GH3 wild-type and GH3 clones stably transfected with gp130 sense in response to CNTF, while it was blunted in the gp130 antisense clones (Perez Castro *et al.* 2003).

The gp130 cytokines and their role as neuroendocrine–immune regulators

An increase in cytokine levels constitutes a fundamental event in the host defense. Among other actions, cytokines stimulate the HPA axis and induce a rise of glucocorticoids (GC) and other hormones, such as PRL and GH (Druker *et al.* 2006). Considering the importance of both HPA axis- GC-induced immunosuppression and PRL/GH stimulation of immune function, the regulatory action of gp130 cytokines on the pituitary physiology, i.e. secretion of ACTH and PRL, represents two important models of neuroendocrine and immune interaction that will be discussed bellow. Since alterations in these regulatory circuits may lead to disturbances of the immune response, understanding the involvement of gp130 in these mechanisms might suggest new therapeutic options.

Regulation of ACTH by gp130 cytokines

The gp130 cytokines are powerful stimuli for ACTH secretion by pituitary corticotrophs *in vitro* and *in vivo* in different species (Arzt *et al.* 1999; Arzt, 2001). Interleukin-6 stimulates the release of ACTH in rats, in which IL-1β and IL-6 synergize to induce an early ACTH response and anti-IL-6 antibody can block the IL-1-induced increase in plasma ACTH. Further evidence for this stimulatory action has been provided *in vitro* by employing cell cultures, in which IL-6 stimulates the release of ACTH from AtT-20 cells and enhances ACTH release from rat hemipituitary glands. Interleukin-6 also stimulates both ACTH secretion and POMC gene expression in corticotroph adenoma cell cultures (Páez Pereda *et al.* 2000). Glucocorticoids have an inhibitory effect on IL-6 production by anterior pituitary cells (Spangelo *et al.* 1990). Adrenalectomy in the rat causes an increase of IL-6 mRNA levels, suggesting the presence of a negative feedback of GCs on IL-6 production by the pituitary (Arzt *et al.* 1999). Glucocorticoids are potent suppressors of intratumoural IL-6 production (Páez Pereda *et al.* 2000).

Leukaemia inhibitory factor stimulates ACTH secretion in mouse pituitary primary cell culture (Stefana *et al.* 1996). Also, LIF stimulates ACTH secretion and POMC mRNA expression in AtT-20 cells (Akita *et al.* 1996*a*). In addition, LIF potentiates the stimulatory action of corticotrophin releasing hormone (CRH) on ACTH secretion (Akita *et al.* 1996*b*). *In vivo* studies further underline the functional importance of the action of LIF on ACTH secretion. Intraperitoneal LIF administration resulted in a fourfold increase of ACTH plasma levels in mice (Chesnokova *et al.* 1998), and in non-human primates, systemic intracarotid administration of recombinant human LIF was followed by an increase in plasma ACTH levels (Akita *et al.* 1996*a*). Leukaemia inhibitory factor maintains HPA axis activation by decreasing glucocorticoid receptor (GR) expression (Kariagina *et al.* 2005). A defect in the activation of the HPA axis was observed in LIF gene knockout (KO) mice (Akita *et al.* 1996*b*). Levels of ACTH are diminished after fasting in the KO animals, and replacement of LIF restores the HPA axis response (Akita *et al.* 1996*b*). An increase in IL-1β, IL-6 and SOCS-3 levels was reported in LIF KO mice. The observed high pituitary levels of pro-inflammatory cytokines, together with the attenuation of the HPA axis stress response resulted in a stronger inflammatory process (Chesnokova *et al.* 2002). SOCS-3 acts to counter regulate the HPA axis response to inflammation (Chesnokova *et al.* 2002).

Among other cell types, cells from the anterior pituitary have been identified as direct targets for bacterial LPS, where it enhances the intrapituitary secretion of IL-6 *in vivo*. Lipopolysaccharide-induced IL-6 production *in vitro* by FS cells occurs via the specific membrane-bound CD14-Toll proteins, which represent the classical LPS receptor, and the p38α mitogen activated protein kinase (MAPK) NF-κB pathway (Lohrer *et al.* 2000). Lipopolysaccharide stimulates IL-6 both in monolayer and in re-aggregate pituitary cell cultures, but a significant enhancement of ACTH secretion by LPS was observed only in aggregates (Gloddek *et al.* 2001). Moreover,

a neutralizing antibody against mouse IL-6 inhibited LPS-induced ACTH secretion in aggregates (Gloddek *et al.* 2001). This intrapituitary IL-6-mediated system represents a pituitary-specific mechanism that supports the activation of the HPA axis and improves the rise of anti-inflammatory GCs during infection/inflammation.

Studies have also shown that LPS induces mouse LIF mRNA to a greater extent than LIF receptor mRNA (Wang *et al.* 1996). These results are concordant with the induction of murine pituitary LIF expression and elevated plasma levels of ACTH and corticosterone in mice after injection of LPS (Chesnokova *et al.* 2002).

The above-described direct action of LPS on pituitary cells constitutes an additional pathway to control the activated immune system. In this pathway, bacterial LPS induces the release of cytokines, such as IL-6 and LIF. Then, these cytokines induce, in a paracrine manner, the secretion of ACTH which, through the increase in levels of GCs, rapidly suppresses the activated immune response. Thus, during acute or chronic inflammation or infection, systemic or hypophyseal gp130 cytokines, such as LIF and IL-6, contribute to the integration of the neuroendocrine and immune responses by acting on anterior pituitary cells in order to prevent overshooting and harmful effects of the activated immune system.

Regulation of prolactin by gp130 cytokines

It was demonstrated that IL-6 stimulates the release of PRL and GH from dispersed cell cultures of normal rat pituitary cells. Interleukin-6 also enhances GH release from rat hemipituitary glands. Interleukin-6 stimulates PRL and GH release from lactosomatotrophic GH3 cells (Arzt *et al.* 1993). Ciliary neurotrophic factor stimulates PRL and GH production by these cells (Perez Castro *et al.* 2000). Interleukin-11 and CNTF exert a similar stimulation on GH mRNA expression in cell cultures from acromegalic tumours, and CNTF stimulates PRL secretion in cell cultures of prolactinomas (Perez Castro *et al.* 2001). In monolayer cell cultures from normal rat anterior pituitary, IL-11 and CNTF had no significant effect on the release of either GH or PRL and on GH mRNA. However, when the cells were in aggregate cultures, in which the three-dimensional structure of the cells is reconstituted, both cytokines significantly stimulated both PRL and GH secretion. These studies show that the three-dimensional structure of the gland, in which FS cells are involved, is of critical importance for the regulatory action of gp130 cytokines in anterior pituitary cells (Perez Castro *et al.* 2001). In contrast, LIF suppressed PRL levels in pituitary cultures without changing GH levels (Ben-Shlomo *et al.* 2003).

Another piece of evidence for the induction of PRL by gp130 cytokines was obtained by employing cells stably transfected with a gp130 AS cDNA. The gp130-AS clones which, as stated above, have low gp130 levels and have impaired STAT3 activity and SOCS-3 expression, showed reduced proliferation and PRL and GH secretion in response to gp130 cytokines (Perez Castro *et al.* 2003). These results indicate that normal gp130 levels are essential to maintain PRL secretion and underline the relevance of the gp130 cytokines in the pituitary for maintaining neuroendocrine–immune homeostasis.

Conclusions and perspectives

In this review we have summarized data supporting the concept that gp130 cytokines are expressed and act in the pituitary gland and have an important role in the control of neuroendocrine–immune circuits. These cytokines are involved in the pathogenesis of autoimmune diseases in which the neuroendocrine–immune circuits are altered. Pathogenic processes, such as abnormal growth of pituitary cells (i.e. pituitary adenomas), may also involve the action of gp130 cytokines. Recently, research has focused on the role that gp130 receptor ligands, in particular CNTF, may play as potential therapeutic targets in obesity (Febbraio, 2007). Ciliary neurotrophic factor enhances fatty-acid oxidation in muscle and reduces insulin resistance in obese diabetic mice and, as such, CNTF treatment may have therapeutic potential for individuals with diabetes (Ahima, 2006, Watt *et al.* 2006). A Phase I trial, not designed to provide information as to clinical efficacy, showed that CNTF is safe for the human retina and might have application for eye diseases (Sieving *et al.* 2006). Future studies will establish the possibility to expand the use of gp130 cytokines as tools for pituitary-related diseases.

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