ACTH Action on the Adrenal

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The adrenocorticotropin hormone (ACTH)

The adrenocorticotropin (ACTH) hormone, a 39-amino acid peptide, is synthesized by the corticotroph cells of anterior pituitary from a large precursor molecule, the pro-opio-melano-cortin (POMC). ACTH is highly conserved in mammals since only amino acids 31 and 33 vary between higher mammals and primates. ACTH is the principal regulator of cortisol production by the adrenal cortex. The biological activity of the ACTH molecule depends on the first 24 amino-terminal amino acids while fragments of less than 20 amino acids are ineffective. The residue 25-39 is important for stability increasing the half-life of the molecule.

The synthesis of POMC, its post-translational modifications, and the secretion of ACTH are under the absolute control of corticotropin-releasing hormone (CRH, also termed Corticotropin-releasing factor – CRF) and to a lesser degree to arginine vasopressin (AVP). Both hormones are synthesized in the parvocellular cells of the paraventricular (PVN) hypothalamic nucleus and are under the negative control of circulating glucocorticoids. It should be noted here that magnocellular AVP follows a distinct regulatory and secretory path: it is transferred to posterior pituitary by axonal transport and its synthesis and secretion are under the influence of osmotic and oncotic stimuli. On the other hand, the parvocellular CRH and AVP travel, via axonal transport, to median eminence (ME) at the lower part of hypothalamus from where they are secreted into the vascular connection between hypothalamus and anterior pituitary, the portal circulation. Multiple neural signals regulate the synthesis of CRF and AVP as well as their secretion from ME. CRH reaching the anterior pituitary corticotrophs binds to the CRH-R1 receptors. The corticotrophs represent approximately 10% of anterior pituitary cells. Their main product, POMC is a 260 AA protein, which is post-translationally cleaved into several bioactive peptides that are secreted from the corticotrophs along with ACTH, including β-lipotropin, the endogenous opioid peptide beta-endorphin and melanocyte stimulating hormones (MSH). Glucocorticoids exert their negative feedback control on both levels i.e. hypothalamus and anterior pituitary corticotrophs suppressing POMC synthesis and ACTH secretion. High levels of glucocorticoids cause characteristic corticotropic cell degeneration. The immune system participates in the regulation of ACTH production via interleukins (IL)-1, IL-6, tumor necrosis factor (TNF)-alpha and interferons alpha and gamma, which affect the axis at all levels i.e. hypothalamus, pituitary, and adrenal cortex.

Mechanism of ACTH action on adrenal cortical cells

ACTH enters the systemic circulation and binds to specific high affinity receptors located on the surface of adrenal cortical cells and the skin. The adrenal cortex is composed of three zones. The outermost zona glomerulosa produces aldosterone, the middle zona fasciculata produces cortisol, and the innermost zona reticularis produces androgens. The steroid hormones produced by the adrenal cortex are classified as 21-carbon (the glucocorticoids, mineralocorticoids), 19-carbon (adrenal androgens) and 18-carbon (adrenal estrogens). Cortisol, the main endogenous glucocorticoid, is synthesized in the adrenal cortex under the exclusive regulation of ACTH. The adrenal cortex produces approximately 25 mg cortisol per day, 0.1 mg aldosterone and 10 mg of the adrenal androgen dehydroepiandrosterone (DHEA). ACTH is the principal regulator of cortisol production by zona fasciculata while it is of secondary importance in aldosterone and adrenal androgen production. The mechanism of ACTH action follows the classical peptide hormone rules. Indeed, ACTH binds to its receptors located on adrenal cell membranes activating a Gs-protein resulting in an increase of intracellular cyclic adenosine monophosphate (cAMP). ACTH stimulates cortisol synthesis and secretion by affecting several steps in the steroidogenesis pathway: (a) ACTH increases the number of low-density lipoprotein (LDL) receptors resulting in increased cholesterol uptake, the precursor for the biosynthesis of all steroid hormones. Indeed, while the adrenal cortex can synthesize cholesterol, almost 80% of the cholesterol used in steroid synthesis derives from sources outside the adrenals. (b) Recent studies have shown an additional level of regulation: ACTH controls the formation of specialized plasma membrane compartments, called microvillar channels, which retain HDL particles and contain high numbers of the HDL receptor SR-BI. HDL is then taken up and readily utilized for the synthesis of Glucocorticoids (1). A feedback mechanism is then initiated in which Glucocorticoids suppress SR-BI expression (2) (c)ACTH stimulates the cleavage of the side-chain of cholesterol converting it to pregnenolone, the first and rate-limiting step in cortisol production. The CYP11A1 gene encodes the cholesterol side-chain cleavage enzyme, cytochrome P450(scc). Expression of CYP11A1 is controlled by ACTH and the steroidogenic factor 1, SF-1 (3). (d) ACTH hydroxylates pregnenolone to give 17-OH-pregnenolone, which then travels to the endoplasmic reticulum for conversion to 11-deoxycortisol. 11-deoxycortisol moves back to mitochondria where another hydroxylation takes place at position 21 to produce the final product, cortisol. Cortisol is not stored in the adrenal cortex but is promptly secreted. The adrenal cortex synthesizes cortisol to maintain its normal serum levels for only few minutes. Thus, the effect of ACTH on adrenal cortisol production can be measured in the serum within minutes from its induction.

The melanocortin receptor family (MC-R)

The ACTH receptor is a seven transmembrane domain protein coupled to a guanine nucleotide binding protein (Gs), which activates adenyl cyclase. The human ACTH receptor gene has been cloned and it belongs to the melanocortin receptor family (MC-R) classified as melanocortin receptor 2 (MC2-R). The family of melanocortin receptors includes five members (4). Each receptor subtype has characteristic size, tissue distribution and biological significance. The melanocortin system and its receptors regulate skin pigmentation, glucocorticoid production, and energy balance. The melanocortin receptors are as follows:

MC1-R is a 315 amino acid transmembrane protein. In humans it maps to 16q24 (5). It is the principal melanocortin receptor in the skin where it regulates its pigmentation (6). It exhibits high affinity for most MSH isoforms and for ACTH. MC1-R exhibits the highest affinity towards alpha–MSH (Ki = 0.033 nmol/l). It is also present in the adrenals, leukocytes, lung, lymph node, ovary, testis, pituitary, placenta, spleen and uterus. The agouti protein is an endogenous antagonist of the MC1R in the skin (7). Over-expression of the agouti protein results in fair skin, reddish hair and disturbances of energy balance.

MC2-R is the primary ACTH receptor. The ACTH / MC2 receptor is a 297 amino acid transmembrane G-protein coupled receptor (8). In humans it maps to 18p11.2 (5). Activation of the MC2 receptor initiates a cascade of events affecting multiple steps in corticoid steroidogenesis. Mutations in MC2-R may result in familial glucocorticoid deficiency, a group of autosomal recessive disorders characterized by resistance to ACTH. It should be noted that although the ACTH / MC2 receptor is expressed predominantly in the adrenal cortex, it is also present in skin melanocytes while its ligand ACTH binds to the MC1 receptor thus affecting skin pigmentation (6, 9, 10). Thus, chronically elevated ACTH in the circulation (chronic adrenal insufficiency, ectopic ACTH production or in Nelson's syndrome following adrenalectomy) can induce skin and gum hyper-pigmentation. MC2-R is also expressed in adipocytes and mediates stress-induced lipolysis via central ACTH release (11).

The fact that the ACTH receptor belongs to the melanocortin receptor family implies close association between several physiological processes including stress, homeostasis, regulation of food intake and regulation of energy balance, immunity and skin function. Indeed, ACTH can bind in melanocytes, adipocytes, mononuclear / macrophage cells, skin, and various areas of the central nervous system.

Direct actions of ACTH through MC2-R have been reported in peripheral tissues. ACTH inhibits leptin secretion from adipocytes via MC2-R, indirectly contributing to the regulation of energy balance (12).

MC3-R is expressed in the brain. In humans it is a 360 amino acid protein whereas in mice and rats 323 amino acid (13). In humans it maps to 20q13.2 (5). It should be noted that the MC3-R and MC4-R in the Central Nervous System regulate food intake and energy homeostasis. MC3 and MC4-R knockouts are obese. However, the MC4 receptor KO mice are hyperphagic while the MC3 receptor KO animals are not hyperphagic but still obese (14). The agouti (ag) and the agouti related protein (argp) are endogenous natural antagonists of the MC1, MC3 and MC4 receptors (15). Finally, the MC3 receptor may be involve in the mechanism turning off the inflammatory response (16, 17). Indeed, recent evidence showed that ACTH induced Heme-Oxygenase 1 (HO-1) via MC3-R in macrophages, contributing to the suppression of macrophage migration (18).

MC4-R is a 332 amino acid transmembrane protein. It is expressed in the central nervous system (mainly in the hypothalamus), the gastrointestinal tract and the placenta (19). In humans, it maps to 18q22 (5). MC4-R is the principal melanocortin receptor for food intake regulation (20). Inactivating mutations of MC4 cause obesity both in mice and humans (21, 22).

The melanocortinergic system : As it was mentioned above, the melanocortinergic system in the central nervous system consists of the endogenous agonists alpha-, beta-, and gamma-MSH (post-translational products of POMC), the naturally occurring antagonists the agouti-related protein (AGRP) produced by the arcuate nucleus neurons in hypothalamus, and the agouti protein found in the skin. The AGRP antagonizes alpha-MSH in the hypothalamus at the level of MC3 and MC4 receptors. The agouti protein and AGRP require the presence of a third protein, the Mahogany to antagonize MSH. Mahogany protein is widely expressed and it is a close relative of Attractin, an immunoregulatory protein made by human T lymphocytes. Activation of the central melanocortin receptors (MC3 and MC4) by alpha MSH inhibits feeding and alters the rate of energy consumption leading to weight loss, whereas its blockade results in obesity (23, 24). Development of MC3R and MC4R knockout mice revealed differential actions of each receptor. MC4R -/- mice were hyperphagic with partially increased metabolic efficiency while MC3R-/- animals developed obesity due to increased metabolic efficiency, thus underlying their significance in metabolism and obesity (14, 25).

The MC4 receptor is also involved in the regulation of autonomic nervous system tone and of arterial pressure at the level of the central nervous system (26). The MC4 receptor appears to be also involved in several higher learning processes. Outside the central nervous system the MC4 receptor is expressed in osteoblasts where it may be involved in bone remodeling facilitating the communication between osteoblasts and osteoclasts (21).

MC5-R is a 325 amino acid transmembrane protein. It is expressed in the adrenals, skin, stomach, lung and spleen (8). Its levels in the central nervous system are very low. In the adrenal cortex it is expressed in all three layers but predominantly in the aldosterone-producing zona glomerulosa cells. In the skin it affects the exocrine function. It is expressed in peripheral lymphocytes and in splenocytes indicating that this may be the receptor utilized by ACTH in those cells (27).Indeed, recent studies have confirmed the initial hypothesis and shown that MC-5R is expressed in articular chondrocytes mediating cytokine production in the inflamed joint in rheumatoid arthritis (28). In addition, MC5-R mediates the induction of IL-6 from adipocytes, contributing to the local metabolic inflammation (29).

Regulation of ACTH receptor gene expression

The ACTH receptor gene has one untranslated exon (exon one), an 18kb intron, and the coding exon (exon two). The existence of different ACTH-R transcripts in human adrenal cortical cells suggests the presence of multiple transcription initiation sites. Recent evidence indicated that an alternate exon 1 (exon1f) is transcribed in adipose tissue but not in the adrenals. This exon appears to be transcribed by a different promoter region from that reported in the adrenal, thus conferring tissue specificity (30). Studies on ACTH promoter polymorphisms revealed a single nucleotide polymorphism close to the transcriptional initiation site (-2C/T) resulted in inhibition of ACTH transcription and accounted for reduced ACTHR levels even in the heterozygous state. This allele is present in 10% of the population. The relevance of this and other polymorphisms in disease remains to be evaluated (31). Recent studies have shown association of ACTH receptor polymorphisms with heroin addiction (32), and responsiveness to ACTH therapy in infantile spasms (33).

The ACTH receptor promoter contains binding sites for several transcription factors. Transcription factors are nuclear proteins modifying the expression of genes by binding to specific DNA sequences usually located upstream of gene promoters. Phosphorylation of a transcription factor results in its activation and modulation of the transcriptional activity of a promoter containing response elements for the specific factor. The most important transcription factors affecting the expression of ACTH receptor gene are the following:

SF-1 (Steroidogenic Factor-1 binding sites): SF-1 is an orphan nuclear receptor regulating the transcription of genes involved in steroidogenesis. It also plays a role in adrenal organogenesis. Indeed, SF-1 knockout mice lack adrenal glands and gonads. SF-1 is also essential for the compensatory adrenal growth following unilateral adrenalectomy (34). SF-1 plays a key role in steroidogenesis in both adrenal cortical and gonadal cells. Thus, the transcription of CYP11A1, a gene that encodes the P450scc cholesterol side-chain cleavage enzyme, the first step in steroidogenesis, has several SF-1-binding sites modulating its transcription rate (3). As for the ACTH receptor gene, it has been shown that it contains three SF-1 binding sites in the proximity of the transcription initiation site. It should be noted that the nuclear receptor Dax-1 (dosage-sensitive sex reversal adrenal hypoplasia congenita critical region on the X chromosome gene-1) inhibits SF-1-mediated steroidogenesis. Absence of Dax-1 results in an increased adrenal responsiveness to ACTH most probably mediated by up-regulation of the ACTH receptor via SF-1 (35). Furthermore, cAMP-dependent PKA augments the SF-1-mediated stimulation of steroidogenic enzymes (36). It should be noted however, that it has been recently reported that during ovine late-gestation the ACTH ligand does not appear to affect the expression of either SF-1 or the ACTH receptor genes in fetal adrenals (37).

DAX-1 (Dosage-sensitive sex reversal, Adrenal hypoplasia congenital critical region on the X chromosome, gene 1): DAX-1 is a transcription factor expressed in the adrenal gland and in the gonads. In fact, DAX-1 encodes an orphan member of the nuclear hormone receptor super family. DAX-1 is a suppressor of the transcription of several genes involved in the steroidogenic pathway. However, the physiological roles of DAX-1 are far from being elucidated. Thus, while DAX-1 inhibits SF-1-mediated induction of the steroidogenic genes including MIS, inactivating mutations of DAX-1 results in the X-linked form of adrenal hypoplasia congenital (AHC) with associated hypogonadotropic hypogonadism. AHC usually reveals itself as adrenal failure in early infancy, although a wide range of phenotypic expression has been reported. Interestingly, the ACTH-R promoter contains DAX-1 sites (35). DAX-1 represses basal ACTH-R levels when transfected in adrenocortical Y-1 cells. In adrenocortical tumors there is a definite negative correlation between DAX-1 and ACTH-R (35).

StAR (steroidogenic acute regulatory protein): StAR, which promotes intra-mitochondrial cholesterol transfer in the adrenal cortical cells, is the only major adrenal transcription factor, which has not been associated to the expression of the ACTH-R gene. StAR is induced by ACTH via the ACTH-R to regulate steroidogenesis but no direct effect or binding element on the ACTH-R promoter has been described (38).

AP-1 (Activator Protein-1 regulatory element): Activation of several signaling pathways, including that of PKA and PKC, causes the hetero-dimerization of the proto-oncogenes Fos and Jun to form the AP-1 transcription factor. Two AP-1 binding sites have been identified upstream

of the ACTH-R gene modulating its response to cAMP. Thus, deletion of the AP-1 binding sites on the ACTH-R gene abolishes the effect of cAMP. The effect of glucocorticoids and Angiotensin II on the expression of ACTH receptor may be accomplished via glucocorticoid-mediated inhibition of AP-1 binding sites on the ACTH receptor promoter (39).

ACTH: Several studies have shown that the ACTH-receptor gene is up regulated by its own ligand, ACTH (40). Indeed, ligand-induced up-regulation of ACTH-receptor expression may be an important adaptive process directed towards optimizing adrenal responsiveness to ACTH. The effect of ACTH on ACTH-receptor expression is dependent on cAMP, probably mediated through AP-1. SF-1 plays an important role in ACTH-induced up-regulation of ACTH-R expression. Indeed, the ACTH receptor promoter has three SF-1-binding sites. Suppression of ACTH secretion by endogenous or exogenous glucocorticoids results in reduction of the ACTH-R gene expression (41). On the other hand, DAX-1 suppresses the expression of the ACTH receptor gene. The mRNA for MC2R and SF-1 do not appear to be regulated by ACTH in the late-gestation ovine fetus, although a pituitary-dependent factor may be involved in the regulation of SF-1 mRNA abundance (37).

Glucocorticoids: Six glucocorticoid regulatory elements (GRE) in the ACTH receptor gene indicate that glucocorticoids are major regulators of its expression. Glucocorticoids exert an enhancing effect on basal, ACTH- and cAMP-induced ACTH-R expression (42).

Angiotensin II : Angiotensin II stimulates the expression of ACTH receptor gene in the adrenal cortex (43, 44). Promoter deletion studies revealed that the two AP1 binding elements on the ACTH-R (MC2-R) promoter mediate the Angiotensin II stimulatory signals. Indeed, Angiotensin II rapidly activates Fos and Jun to promote ACTH-R transcription (39).

Distribution of ACTH receptors in normal adrenals

The ACTH-R is localized in all three zones of the adrenal cortex (45). Results from binding studies indicate that in the adrenal cortex the ACTH receptors can be subdivided into a type with a KD of 1 nM, but with only 60 binding sites per cell and into a second type with a KD of 300 nM, but with several orders of magnitude more binding sites (about 600,000) per cell. The presence of high and low affinity receptors for ACTH means that the adrenal cortex is highly sensitive to the concentration of ACTH in the systemic circulation.

The ACTH receptor in adrenal tumors

The ACTH receptor is functional in adrenal adenomas. However, the level of ACTH receptor transcript and protein are highly variable in neoplastic adrenals and does not allow for a clear differentiation between benign and malignant tumors (46). Recent studies suggest that blockade of ACTH receptor could be a potential treatment for congenital adrenal hyperplasia, allowing the use of lower doses of Glucocorticoids (47).

ACTH receptor signaling

ACTH receptors are G-protein coupled receptors. Among the G proteins Gs and Gi2 are implicated in ACTH signaling. ACTH also increases the transcription of Galpha q and G alpha 11 which couple the ACTH receptor (48). Mutations of the alpha subunits of Gs and Gi2 are associated with adrenocortical tumor formation (49). Signals that initiate from the ACTH receptor and the G-proteins lead to cAMP formation and activation of PKA and PKC. As a result several intermediate molecules are involved including kinases and transcription factors that orchestrate the ACTH actions on adrenal cells.

SAPK and JNK: The ACTH receptor is a weak activator of MAP Kinases ERK1 and ERK2. Nevertheless, ERK1 and ERK2 activation is important in ACTH-triggered mitogenic effects (50). In normal adrenal cortical cells, ACTH-R signals lead to activation of the Stress Activated Protein Kinase (SAPK) JNK. Activation of JNK depends on PKC activity and mobilization of intracellular Ca++ implying that both PKC activation and Ca++ influx result from the binding of ACTH to its receptor (51).

Akt/PKB: In tissue culture experiments using the Y1 adrenocortical tumor cell line ACTH exerts antiproliferative effect, mediated by cAMP. ACTH signals result in dephosphorylation and inactivation of Akt/PKB kinase thus inhibiting the proliferation of adrenocortical tumor cells (52). Such anti-proliferative effect is most likely associated with increased steroidogenesis and suppression of the malignant phenotype of this particular cell line.

CREM and CREB: The ACTH / MC2 receptor effects are mediated via activation of the cAMP pathway, which includes the cAMP-dependent transcription factors CREM (cAMP responsive element modulator) and CREB (cAMP responsive element binding protein) that result in transcriptional activation of steroidogenic enzymes, cell proliferation and differentiation (53).

AP-1: Activation of the ACTH receptor leads to stimulation of Fos and Jun transcription, which by heterodimerizing form the AP1 complex. It should be noted here that the Fos gene family consists of four members, c-Fos, FosB, Fra1 and Fra2 while the Jun family consists of three members, c-Jun, JunB and JunD. These proteins form hetero- or homo- dimers inducing transcription through binding to AP1- binding sites. Activation of AP1-dependent transcriptions leads to the production of several pro-mitotic proteins while its inhibition results in a blockade of cell cycle to the G1 to S phase transition.

ACTH-resistance syndromes

The ACTH insensitivity syndromes are rare disorders. In the majority of cases they are inherited but they can be acquired due to the development of auto-antibodies blocking the ACTH receptor. All patients with the ACTH insensitivity syndromes exhibit low or undetectable serum cortisol levels, high plasma ACTH, and absent or markedly impaired adrenal response to exogenous ACTH. The patients develop early primary adrenal insufficiency, but characteristically have no fluid, and electrolyte disturbances, which are typically present in primary adrenal insufficiency of Addison’s syndrome. These disorders can be fatal if proper treatment is not given.

ACTH resistance consists of two distinct genetic syndromes that are both inherited as autosomal recessive traits: the isolated ACTH resistance and the Allgrove syndrome (triple-A syndrome i.e. alacrimia – achalasia – adrenal insufficiency plus neurologic disorders) (54). Inactivating mutations of the ACTH receptor usually cause isolated ACTH resistance now termed as Familial Glucocorticoid Deficiency (FGD). Introduction of stop codons within the coding region of the ACTH receptor, frameshift mutations and mutations that cause single amino acid substitutions and structural disruption of the ACTH receptor affecting the ligand-binding domain resulting in loss of the ligand-binding capability. On the other hand, mutations in the intracellular portion of the receptor may result in loss of the signal transduction properties of the receptor. Absence of a biological response to ACTH may thus be due to impaired binding of ACTH to its receptors or inability of the bound ACTH to initiate its post-receptor effects.

Effect on the receptor	**Associated mutations**
Structural disruption	S120R,Y254C, C251F, P273H, A233P
Truncated receptor	R201X, L192fs, G217fs, F119fs,
Loss of ligand affinity	S74I, I44M, D103N, D107N
Loss of signal transduction	R146H, R128C, R137W, V142L

Table I: Mutations of the ACTH receptor identified to date and their probable functional effects.

The Allgrove (triple A) syndrome is characterized by ACTH unresponsiveness and adrenal insufficiency as well as alacrimia, achalasia, and several neurological defects (55). There is a significant clinical variability between patients with the triple A syndrome (54). ACTH-R gene mutations have been identified in some families with the syndrome (56). However, it should be emphasized that most kindreds with the triple A syndrome have no ACTH-R mutations (54, 56, 57). It is possible that the disease is due to defects in molecules that affect the ACTH receptor signaling pathways, conditions that are now designated as FGD type 2.

Indeed, it now appears that FGD associated to ACTHR mutations in approximately 25% of the cases while the remaining 75% are not. Recent work revealed a novel gene encoding a single trans-membrane domain protein termed “melanocortin 2 receptor accessory protein” (MRAP) as one of the other genes underlying FGD type 2 (58). MRAP had previously been identified as a protein induced when NIH3T3-L1 cells differentiated into adipocytes. In the effort to identify additional genetic loci for FGD type 2, microarray-based SNP genotyping identified a further disease locus on chromosome 21. Fine mapping of this locus led to the identification of MRAP as a candidate for FGD type 2, and several mutations of MRAP were identified in FGD type 2 patients. These mutations cluster around the first coding exon (exon 3), especially at the splice donor site. The same mutation has been found in genetically unrelated individuals suggesting that this is a true ‘hot spot’ area for mutation. The other common site for mis-sense mutations is in the initiator methionine. This mutation prevents translation of the full-length protein. The next in-frame methionine is at position 60 which, if translated, would result in a severely truncated protein (59).

Mutations in MRAP account for approximately 20% of all FGD cases (59, 60), implying that at least half of all FGD cases result from other genes yet to be identified. The identification of a novel genetic cause of this disorder allows one to ask whether there are any phenotypic

features that associate particularly with MRAP mutations. However, based on current genotype–phenotype information there seem to be no clearly defined clinical entity. Features such as increased height are also seen in FGD type 2. Adrenal histology of FGD type 2 is typical of other cases of FGD resulting from MC2R defects, showing a relatively preserved glomerulosa cell layer with highly atrophic and disorganized fasciculata and reticularis cell layers. It, thus, remains to be evaluated whether mutations in additional GPCR accessory proteins are also associated with FGD.

ACTH action on adrenal neoplasias

Chronic exposure of adrenocortical cells to high levels of ACTH (from entopic or ectopic production) results in the development of adrenal nodules and finally neoplasias. Activation of ACTH receptor and PKA are considered vital for maintaining the highly differentiated cellular phenotype of adrenal cells and the subsequent activation of ERK is of low importance for cell proliferation. In addition, ACTH signals inactivate Akt, a kinase that promotes survival and proliferation. On the other hand, ACTH receptors are up-regulated in adrenocortical adenomas of patients with ACTH-dependent hyper-cortisolemias intensifying the adrenal response to the already elevated ACTH, aggravating their disease. ACTH also up-regulates the human homolog of Diminuto/Dwarf1 gene, which is associated with benign adrenocortical adenomas. Low expression of this gene correlates with apoptosis, indicating that its intensified expression may contribute to cell survival (61). The role of ACTH in adrenocortical tumors remains to be elucidated. It may depend on the state of differentiation of the particular cell or the presence of additional events that may decide the direction of the ACTH signal towards cell survival or inhibition of proliferation.

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