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Gene Section
Review

NR3C1 (nuclear receptor subfamily 3, group C, member 1/glucocorticoid receptor)

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Abstract

NR3C1 gene encodes the human glucocorticoid receptor(hGR), which is a ligand-dependent transcription factor and activates transcription of glucocorticoid-responsive genes through binding directly to glucocorticoid response elements(GREs) in their promoter region, or modulating transcriptional activity of other transcription factors through protein-protein interactions. hGR is implicated in a broad spectrum of biochemical physiologic functions, which are essential for life, and has also a key role in the maintenance of basal and stress-related homeostasis. Almost 20% of the genes expressed in human leukocytes are regulated positively or negatively by the hGR. Approximately every cellular, molecular and other physiologic network in the human body are influenced by this receptor and more specifically growth, reproduction, intermediary metabolism, immune and inflammatory reactions, as well as central nervous system and cardiovascular functions and lymphoproliferative disorders, cellular proliferation and differentiation in target tissues and normal renal tubular function and thus water and electrolyte homeostasis are only some of the examples where hGR is implicated(Nicolaides, Galata, Kino, Chrousos, and Charmandari, 2010).

Identity

Other names: GCCR, GCR, GR, GRL

HGNC (Hugo): NR3C1

Location: 5q31.3

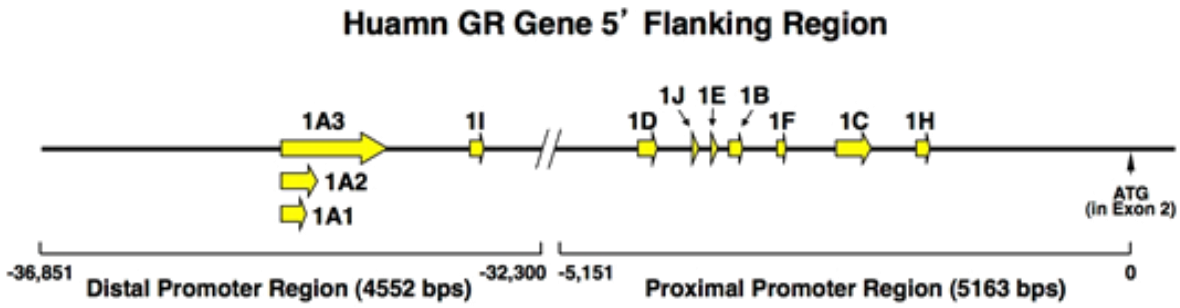

Figure 1. Human hGR/NR3C1 gene 5' Flanking Region

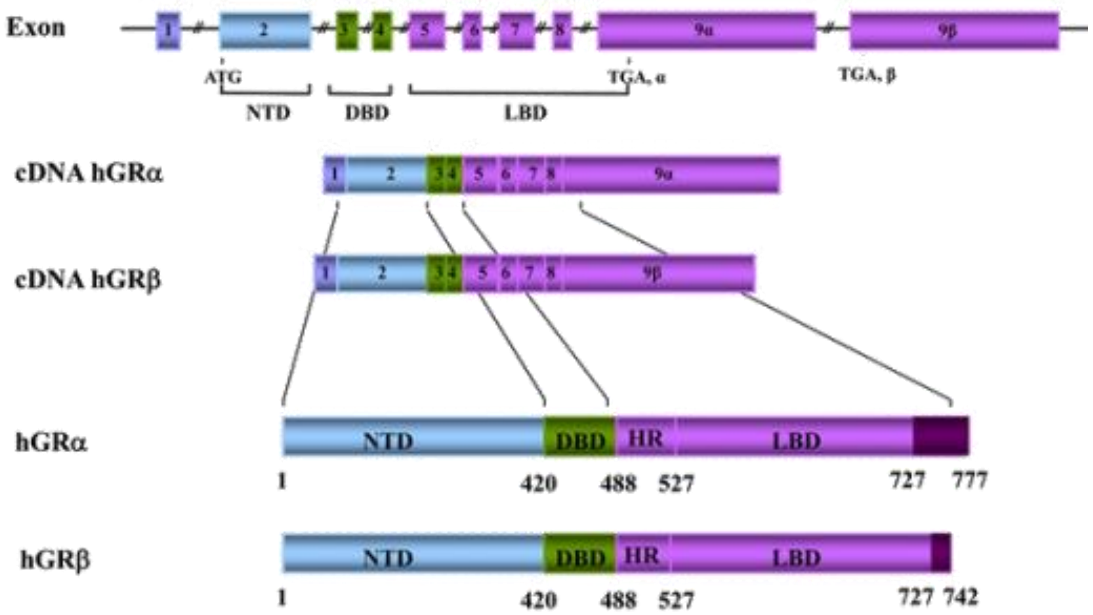

Fig. 2A. Genomic structure of the human glucocorticoid receptor (hGR/NR3C1) gene. It is composed of 9 exons. Alternative splicing of the primary transcript leads to the consequent two mRNA and proteins isoforms, hGRalpha and hGRbeta.

DNA/RNA

Description

The human NR3C1 gene spans a length of 157,582 bases. The NR3C1 structural gene is composed of nine exons and is located in chromosome 5 (5q31.3)(Hollenberg et al., 1985)(Figure 2A).

Transcription

The NR3C1 gene expresses mainly two mRNAs through alternative use of exons 9alpha and 9beta, producing two highly homologous receptor isoforms, termed alpha and beta(N. Z. Lu and Cidlowski, 2005). They are identical through amino acid 727, with hGRalpha having an additional 50 amino acids and hGRbeta having an extra no homologous 15 amino acids (Fig. 2A). Their molecular weights of hGR9alpha and hGR9beta are 97 and 94 kDa, respectively. Except these products, the NR3C1 gene expresses GR? (gamma), which has one amino acid insertion due to splicing variation at exon 3-4 boundary,(Meijsing et al., 2009) and GR-P isoform, which has only 676 amino acids and is encoded by an mRNA expressed from exons 1-7, but lacking exons 8 and 9 and unknown biologic significance(Hagendorf et al., 2005). The human GR gene has eleven different promoters with their alternative first exons (1A1, 1A2, 1A3, 1B, 1C, 1D, 1E, 1F, 1H, 1I and 1J) (Figure 1). Therefore, the human GR gene can produce eleven different transcripts alternating the different promoters that encode the same GR proteins having a common exon 2, which contains the translating ATG codon. 1A1, 1A2, 1A3 and 1I are located in the distal promoter region spanning ~32,000-36,000 bps upstream of the translation initiation site, while 1B, 1C, 1D, 1E, 1F, 1H and 1J position in the proximal promoter region located upstream up to ~5,000 bps. Alternate use of these promoters, differentiate the levels of GR protein isoforms in various tissues(Presul, Schmidt, Kofler, and Helmberg, 2007). Different splicing and translational GR isoforms originating from alternate promoters constitute up to 256 different combinations of homo- and hetero-dimers with different expression levels and transcriptional activities.

This marked diversity in the transcription/translation of the GR gene allows cells/tissues to accommodate appropriately to the circulating concentrations of glucocorticoids depending on their needs(Chrousos and Kino, 2005a) and is responsible for the highly stochastic nature of the glucocorticoid-signaling pathway (Chrousos and Kino, 2005b).

Pseudogene

The NR3C1 gene has a pseudogene (NC3C1P1) in chromosome 16q (provided by RefSep 2012)

Protein

Description

The human NR3C1 protein sequence (NP_000167.1)consists of 777 amino acids and has a MW of 85659 Da. Without the presence of the ligand, hGRalpha takes part in a heteromultimeric cytoplasmic complex with chaperone Heat Shock Proteins (HSP)90,70,50 immunophilins and other proteins.

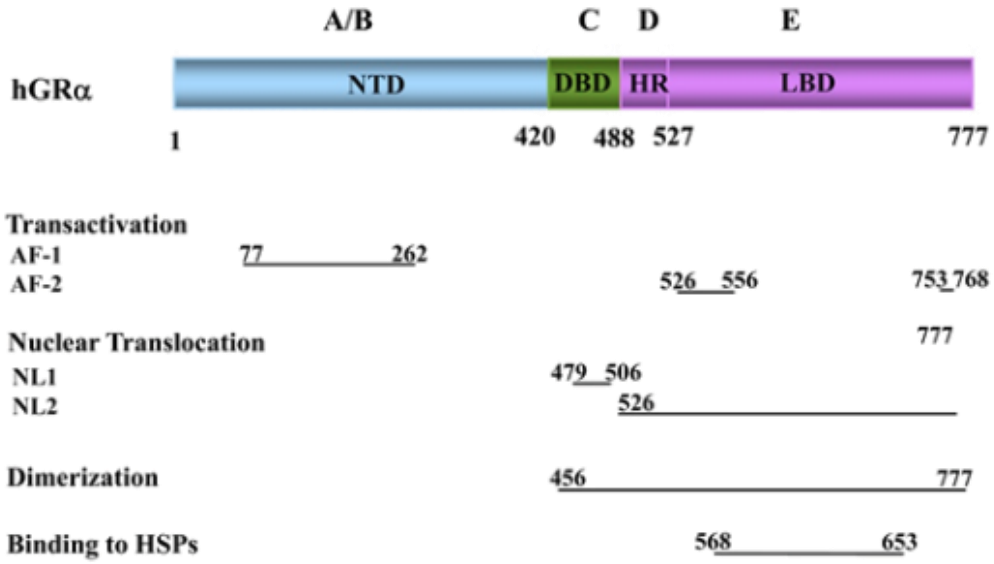

Fig 2B. Functional domains of the NR3C1/hGRalpha. AF, activation function; DBD, DNA-binding domain; HSPs, heat shock proteins; LBD, ligand-binding domains; NLS, nuclear localization signal.

As soon as it binds to the ligand, dissociates from the previous complex and FK506-binding immunophilin heat shock protein 56 takes its place, thereby connecting to dynein and mediating the transportation to the nucleus, where it dissociates (Czar, Lyons, Welsh, Renoir, and Pratt, 1995). When it reaches the nucleus, the receptor binds as a homodimer to various Glucocorticoid Response Elements(GREs) sequences in the promoter region of many genes, and as a heterodimer with NR3C2 or the retinoid X receptor, thus regulating their expression either positively or negatively depending on GRE sequence and promoter context. The ligand-activated hGRalpha modulates gene expression without binding to GREs, by interacting also with other transcription factors, such as activator protein-1(AP-1), nuclear factor-kB (NF-kB), p53 and signal transducers and activators of transcription (STATs). For the transcription when hGRalpha uses its transcriptional activation domains, AF-1 and AF-2, as surfaces to interact with specific nuclear receptor coactivators and chromatin-remodeling complexes, then these coactivators form a bridge between DNA-bound hGRalpha and the transcription initiation complex, conveying the transmission of the glucocorticoid signal to the RNA polymerase II and its ancillary components leading to initiation and promotion of the transcription. As a member of the nuclear receptor superfamily, hGR has 3 major domains: the N-terminal domain (NTD), middle DNA-binding domain (DBD) and the C-terminal ligand-binding domain (LBD) as illustrated in (Fig. 2B). Using the typical nomenclature for NR subdomains, hGR consists of the amino-terminal A/B region (corresponding to NTD), C (DBD), D (hinge region) and E (LBD) regions, without having the F region. The N-terminal domain (NTD) consist of transactivation domain, termed activation function (AF)-1, located between amino acids 77 and 262, activated when is ligand-independent. It has an important role in the interaction of the receptor with molecules necessary for stimulation of transcription, such as coactivators, chromatin modulators and basal transcription factors. The DNA-binding domain (DBD) consists of amino acids 420-480, contains two zinc finger motifs through which binds to specific DNA sequences, such as the glucocorticoid response elements (GREs) in the promoter region(s) of specific genes. The DBD also contains sequences important for receptor dimerization and nuclear translocation. The hinge region gives flexibility connecting DBD with LBD by conferring structural flexibility in the receptor dimers, allowing single receptor dimmer to interact with multiple GREs and different sequences. The ligand-binding domain (LBD) consist of amino acids 481-777, binds ligand glucocorticoid with its ligand-binding pocket and contains a second transactivation domain, the ligand-depended AF-2 which plays an important role in the glucocorticoid-induced stimulation of hGR transcriptional activity, by interacting with coactivators containing LxxLL motifs. LBD takes part in the complex formation with heat shock proteins, in the process of nuclear translocation and receptor dimerization (Nicolaides, et al., 2010).

Expression

Ubiquitous. Almost all human tissues and cells are expressing the hGRalpha. The GR expression has been reported in the Bone Marrow, Monocytes, Dendritic Cells, NK Cells, T Cells (CD4+), T Cells (CD8+), B Lymphoblasts, B Cells, Lymph Node, Spleen, Thymus, Retina, Heart, Cardiac Myocytes,

Atrioventricular Node, Smooth Muscle, Skeletal Muscle, Appendix, Pancreatic Islet, Small Intestine, Colon, Adipocyte, Kidney, Liver, Lung, Trachea, Bronchial Epithelium, Tongue, Thyroid, Salivary Gland, Adrenal Gland, Breast, Skin, Ovary, Uterus Corpus, Uterin Cervix, Placenta, Fetal Brain, Liver, Lung and thyroid, Tonsil, Prefrontal Cortex, Cingulate Cortex, Parietal Lobe, Temporal Lobe, Occipital Lobe, Ciliary Ganglion, Globus Pallidus, Olfactory Bulb, Thalamus, Hypothalamus, Subthalamic Nucleus, Caudate Nucleus, Amygdala, Pons, Medulla Oblongata, SupCervical Ganglion, Dorsal Root Ganglion, Trigeminal Ganglion, Spinal Cord, Pineal (Day)and Pineal (Night), Pituitary, Prostate, Testis Germ, Testis Intersitial, Testis Leydig cells.

Localisation

In the absence of ligand, hGRalpha resides mostly in the cell cytoplasm, but upon ligand-induced activation, the receptor dissociates from the multiprotein complex and translocate into the nucleus. After binding to specific DNA responsive elements remains within the nucleus for a considerable length of time and is then exported to the cytoplasm. It is also present in the Mitochondrion and Plasma membrane. The isoform Beta is mainly expressed in the nucleus.

Function

hGR has a dual mode of transcriptional activity: acting either as a glucocorticoid-dependent transcription factor, binding mainly to glucocorticoid response elements (GRE) or functioning as a modulator of other transcription factors through protein-protein interaction. Post-translational modifications (PTMs), such as phosphorylation, acetylation, ubiqutilation and nitrosylation, play also an important role in the regulation of GR activity, affecting the receptor stability, subcellular localization, and also interaction between GR and other proteins, influencing finally the transcriptional activity. Recent studies have demonstrated that the circadian rhythm transcription factors CLOCK and BMAL1 repress GR-induced transcriptional activity by acetylating several lysine residues (Kino and Chrousos, 2011).

Homology

Is a member of the nuclear hormone receptor family, NR3 subfamily.

Mutations

Mutations or polymorphisms in the hGR gene impair one or more of the molecular mechanisms of hGRalpha action and as a final consequence alter the tissue sensitivity to glucocorticoids. Reduced affinity of the mutant receptors for the ligand, altered subcellular localization, delayed nuclear translocation after binding to the ligand, reduced ability to bind with GREs and decreased transcriptional activity, altering the exertion of a dominant negative effect upon the wild-type receptor, reduced interaction with other coactivators and reduced motility within the nucleus are some of the mechanisms of mutant hGR (Charmandari, Chrousos, and Kino, 2009). Although, most mutations of the NR3C1 gene exert generalized glucocorticoid resistance there is one mutation reported to date in the hGRalpha NTD region that replaces aspartic acid at amino acid 401 by histidine (D401H) facilitating the mediated gene expression (Charmandari et al., 2008). Interindividual variations in tissue sensitivity to glucocorticoids have been described within the normal population and are mainly attributed to polymorphisms in the hGR gene. A heterozygous polymorphism replacing aspartic acid to serine at amino acid 363 mildly increases transcriptional activity, and arginine to lysine replacement at amino acid 23 is associated with relative glucocorticoid resistance. A single nucleotide polymorphism that replaces A with G at the nucleotide 3669 (A3669G) located in the 3' end of exon 9beta increases the stability of GRbeta mRNA, leading to greater inhibition of GRalpha-induced transcriptional activity and thus glucocorticoid resistance (Syed et al., 2006).
It is worth mentioning also the fact that there is a plethora of laboratory generated mutated GR proteins, which provides an interesting tool for exploring hGR structure-function relationships. (Beck, De Bosscher, and Haegeman, 2011)

Implicated in

Normal physiology and homeostasis

The stochastic nature of glucocorticoid signaling pathways(Chrousos and Kino, 2005b), and the variable effect that hGR gene mutations/polymorphisms exert on glucocorticoid signal transduction, suggest that alterations in hGR action affect many critical biological processes including the behavioural and physiologic responses to stress, the immune and inflammatory reaction, the process of sleep, growth and reproduction. It is an extremely important component of many cellular and molecular signaling pathways in maintaining homeostasis and preserving normal physiology (Charmandari and Kino, 2010)

Primary MyeloFibrosis(PMF)

The frequency of A3669G single nucleotide polymorphism (SNP) of human glucocorticoid receptor is increased in patients with polycythemia vera compared to normal population.

Author	Mutation Position		Resistance or Increased Sensitivity
	cDNA	Amino Acid	
1. Chrousos et al. Hurley et al.	1922(A→T)	641 (D → V)	Resistance
2. Karl et al.	4 bp Deletion in exon–intron 6		Resistance
3. Malchoff et al.	2185(G→A)	729 (V → I)	Resistance
4. Karl et al. Kino et al.	1676(T→A)	559 (I → N)	Resistance
5. Ruiz et al. Charmandari et al.	1430(G→A)	477 (R → H)	Resistance
6. Ruiz et al. Charmandari et al.	2035(G→A)	679 (G → S)	Resistance
7. Mendonca et al.	1712(T→C)	571 (V → A)	Resistance
8. Vottero et al.	2241(T→G)	747 (I → M)	Resistance
9. Charmandari et al.	2318(T→C)	773 (L → P)	Resistance
10. Charmandari et al.	2209(T→C)	737 (F → L)	Resistance
11. Nader et al	2141(G>A)	R714Q	Resistance
12. McMashon et al	2-bp deletion at nt 2318-9	773	Resistance
13. Zhu et al	1667G>T	T556I	Not studied yet
14. Charmandari et al	1201G>C	D401H	Increased sensitivity

Table 1: Reported mutations in the hGR/NR3C1 gene causing either generalized glucocorticoid resistance or increased sensitivity.

This variant allele at the homozygous state (G/G) is considered also a susceptibility allele to PMF. Especially, in cooperation with other mutated genes such as JAK2V617F, the glucocorticoid receptor A3669G SNP contributes to the phenotype of excess myeloproliferation, and determination of Blast Transformation (Poletto et al., 2012).

Acute Lymphoblastic Leukemia (ALL)

Glucocorticoids (GC) are pivotal in the treatment of acute lymphoblastic leukemia (ALL) and other lymphoid malignancies, since they induce apoptosis in lymphoblasts. Although research studies delineated the transcriptional response to GCs in two ALL cell lines (precursor B-ALL and T-childhood ALL), forming mainly the basis for the molecular understanding of their antileukemic (and perhaps other) effects; questions on their induction of apoptosis and cell cycle arrest in leukemic cell lines studied still exists. Although a wide range of possible interacting genes were analysed (c-myc and Cyclin D3, BMF, MCL1, Bcl-XL, PMAIP1/Noxa, ZBTB16, SLA, PFKFB2, TNFAIP8, GPR65/TDAG8,DDIT4/Dig2, MAP2K3, MYC, mir17~92, TXNIP) indications were that they had only moderate influence if any, on GC-induced apoptosis in the experimental systems mentioned with the only exception of members of the BCL2 gene family. Could it be a single critical gene downstream responsible for the GR apoptosis induction or rather a GC-regulated network of genes; this is still under investigation (Rainer et al., 2012).

However, GC-resistance is major therapeutic problem without yet a clear molecular mechanism. In two key models of acute lymphoblastic leukemia the GCs resistance was associated with mutations at the level of the glucocorticoid receptor (some of which were newly identified; previously not associated with GC resistance, such as: A484D, P515H, L756N, Y663H, L680P, and R714W0 (Schmidt et al., 2006). The survival probabilities in children with ALL were associated with homozygocity of G allele of the NR3C1 BcII polymorphism, presenting a worse progression and prognosis of the disease (Fleury et al., 2004), and also three other NR3C1 SNPs polymorphism; ?627A/G, intron2 +646)C/T and 9bT/C were associated with dismal childhood cALL outcome with reduced event-free and overall survival (Labuda et al., 2010)

Multiple Myeloma

Downregulation of GR mRNA in a glucocorticoid resistant Multiple Myeloma cell line is in partly explained by the transcriptional block at intron B of NR3C1 (Sanchez-Vega and Gandhi, 2009). Novel Glucocorticoid-based therapy based on combination of selective glucocorticoid receptor (GR) activators (SEGRA) and proteasome inhibitors are effective in the treatment of Multiple Myeoloma, circumventing the undesired effects of chronic use of glucocorticosteroids. The novel non-steroidal GR modulator Compound A (CpdA) retains glucocorticoid-like anti-inflammatory and anti-

cancer activity and has fewer side effects compared to glucocorticoids. (Sommer and Ray, 2008) CpdA strongly inhibits growth and viability of multiple myeloma cells in GR-dependent manner. There is evidence for an important GR-dependent cooperation between CpdA and proteasome-inhibitor Bortezomib in eliminating survival of multiple myeloma cells (Lesovaya et al., 2013).

Osteosarcoma (OS)

Osteoblasts are highly sensitive to glucocorticoids, which reduce their proliferation and show apoptosis upon glucocorticoid treatment. In contrast to normal osteoblasts, OS cells express 11beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD2), which converts cortisol (active) to cortisone (inactive), and thus, expression of 11beta-HSD2 renders OS cells resistant to glucocorticoids and subsequent apoptosis. High 11beta-HSD2 expression is correlated with a poor response to GCs treatment in Osteosarcoma (Patel et al., 2012).

Prostate Cancer

Glucocorticoids are used in clinical practise for patients with hormone-refractory prostate cancer. They inhibit tumour angiogenesis and subsequent tumour growth, possibly by down-regulating vascular endothelial growth factor (VEGF) and interleukin-8 and additionally supressing tumour-associated lymphangiogenesis by down-regulating VEGF-C through glucocorticoid receptor (Yano et al., 2006).

Ectopic ACTH-producing tumours

Non-pituitary (ectopic) ACTH secretion generally is not responding to exogenous glucocorticoid administration. DMS-79 small-cell lung carcinoma cells derived from these ectopic ACTH-producing tumours express an abnormal GR mRNA which encodes a protein lacking the steroids-binding domain leading to misfunctional characteristics of this ligand-activated transcription factor. The abnormal transcripts in these cells arrived from normal GR genes by aberrant splicing of intron G (between exons 7 and 8). Although GR signalling defects seem likely to cause glucocorticoid resistance of non-pituitary tumours, the suppression at high doses of exogenous glucocorticoids as is appeared particularly in bronchial carcinoids implicates other potential mechanisms are also possible(Parks, Turney, Detera-Wadleigh, and Kovacs, 1998).

Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). High levels of hGR in patients with advanced NSCLC are associated with better outcome (Y. S. Lu et al., 2006). GR expression causes activation of the apoptotic pathway as evidenced by marked induction of caspase-3 activity. On the other hand methylation analysis revealed that there was significantly increased DNA methylation in the 1C promoter of the NR3C1, which was negatively correlated with GR protein expression in tested human SCLC cells (Kay et al., 2011).

Pituitary Adenoma and Adrenocortical tumours

The expression of the GR is an essential element of the negative closed feedback loop formed by corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol in the context of the hypothalamic-pituitary-adrenal (HPA) axis. The variability in expression and function of the GR in pituitary and adrenocortical cells is responsible for the considerable differences in function of this loop. Some of the variation can be ascribed to functional GR polymorphism, which may also predispose to adrenocortical tumour formation (Majnik et al., 2006). This variability may explain why it is so difficult to interpret (or reproduce) results regarding the analysis of diagnostic testing of the HPA axis in patients with pituitary adenomas (Cushing disease) or adrenocortical tumours (Cushing syndrome). (Briassoulis, Damjanovic, Xekouki, Lefebvre, and Stratakis, 2011)

Astrocytoma

Glial tumour cells are sensitive to glucocorticoids (GC), which cross the blood-brain barrier and are used for certain glial tumours treatment. Although low-grade malignant human astrocytoma cells did not present a significant hGRalpha expression they did endogenously express the Cortisol Binding Globulin (CBG). Upon GCs treatment CBG is immediately released (possibly in a nongenomic way) suggesting the apoptosis of certain glial tumours is partly associated with this phenomenon of CBG-release and not through hGR (Pusch, Wegmann, Caldwell, and Jirikowski, 2009)

Sarkoma Kaposi (KS)

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS)-KS cells expressed unusually high levels of glucocorticoid receptor protein and at the same time were significantly stimulated by glucocorticoids (Enwonwu, 1996). The increased expression of functional GRs was associated with four cytokines, namely interleukin-1beta, interleukin-6, tumour necrosis factor-alpha, and oncostatin M, all of which are known autocrine growth factors for AIDS-KS cells. The high levels of GR expression in these cells and the up-regulation of GRs by KS-growth-promoting factors are associated with the enhanced and sustained sensitivity to the actions of glucocorticoids (Guo et al., 1996).

Cancers of the Digestive System

GR is strongly expressed in oesophageal squamous epithelia, pancreatic islet cells and hepatocytes, but generally it has a weak or negative expression in non-squamous epithelia (gastric and colorectal adenocarcinomas). Chemotherapy resistance in tumours originating from the above mentioned tumour-cells induced by the use of Dexamethasone (DEX) is suggesting that GR expression may be biologically important in some GR-expressing carcinomas (Lien et al., 2008). In Gastric Carcinoma, NR3C1 methylation was a useful marker for identifying distinct type-subsets of these carcinomas (Kang et al., 2008). Analysis of tissues sections in well differentiated pancreatic adenocarcinomas revealed a strong positivity (mainly cytoplasmic) for Glucocorticoid receptor, but interestingly the liver metastasis of these tumours was completely negative(Bekasi and Zalatnai, 2009).

Colorectal cancer

A significant difference in mRNA expression (reduced) of hGRalpha, 11beta-HSD-1(overexpressed) and other glucocorticoid metabolism-related genes was observed in colorectal adenocarcinomas which were associated with the downregulation of E-cadherin mRNA, a critical required step in the progress of tumor invasiveness, connecting these genes to carcinogenesis and progression of colorectal cancer(Storkson et al., 2012). Cancer-specific hypermethylation of the NR3C1 gene was identified in colorectal tumors (Lind et al., 2006) and FK506-binding proteins (FKBPS) suppressed the proliferation of colorectal adenocarcinoma possibly due to the suppression of function of the glucocorticoid receptor (Mukaide et al., 2008).

Cervical Cancer

GR expression is observed in cervical low and high-grade intraepithelial neoplasia and in invasive cervical squamous cell carcinoma. Since glucocorticoids act also as cofactor with human papillomaviruses in the etiology of cervical cancer, and inhibit chemotherapy or radiation-induced apoptosis, the persistence of GR in cervix cancer cells questions the combined use of glucocorticosteroids with antineoplastic drugs or other agents in clinical practise settings for women presenting with cervix cancer. (Buxant, Bucella, Anaf, Simon, and Noel, 2009)

Breast cancer

Glucocorticoid receptor (GR) is playing an important role in mammary gland development and differentiation, and has been implicated in breast tumourigenesis without actually knowing the exact biochemical pathways or consequence of this unique expression of GR in terms of progression of Breast Cancer. It is strongly expressed in metaplastic carcinomas and malignant phyllodes tumour but there is lack of important GR expression in great majority of non-metaplastic carcinomas (Lien et al., 2006). Glucocorticoid Receptor and Nuclear Factor Nf?BETA signaling pathways appears to be an important phenomenon in the initiation, progression and recurrence of inflammatory Breast Cancer (BC), wherein NFkB and glucocorticoid receptor (GR) are critical transcription factors in regulating inflammation. NFkB is generally pro-inflammatory, while GR is anti-inflammatory. It is the crosstalk between these two transcription factors that exert a crucial function in determining the survival or apoptosis of BC cells. However, the use of Glucocorticosteroids (GCs) and their biological effects through GR unexpectedly promote cancer cell survival and induce chemo-resistance in BC (Ling and Kumar, 2012). Curcumin which exerts a wide spectrum of anti-inflammatory, anti-oxidant and anti-cancer activities is under investigation as chemopreventive and chemotherapeutic agent which main action is through GR and NFkB modificatory expressions (Sinha, Biswas, Sung, Aggarwal, and Bishayee, 2012).

Coronary Artery Disease

Development of Epicardial Adipose Tissue is not augmented by glucocorticoids, as does the Subcutaneous Adipose Tissue. The decreased total GR mRNA expression and reduced associated transcripts in promoter B and C into this specific tissue; suggest a protective role for Coronary physiology (Silaghi, Silaghi, Scridon, Pais, and Achard, 2012)

Bronchial asthma

The N363S single nucleotide polymorphisms (SNPs) of the hGR/NR3C1 gene are supposed to play an important role in the development of bronchial asthma and in the alteration of sensitivity to Glucocorticosteroids in severe bronchial asthma (Panek et al., 2012). At the cellular level the impairment of GR-Ser211 phosphorylation in Airway Smooth Muscle cells by proasthmatic cytokines drastically reduced their responsiveness to glucocorticoids (Bouazza et al., 2012) and the use of glucocorticoid Dexamethasone repressed the production of mucin glycoproteins in lung epithelial cancer cells. This repression is induced by lower expression of mucin genes, which is mediated by the glucocorticoid receptor (GR) and two glucocorticoid response elements (GREs) in the mucin gene promoter region (Chen et al., 2012).

Adult Onset Chronic Diseases

Extreme maternal psychosocial stressors and early life experiences in utero and in newborns modify locus-specific epigenetic marks in the newborn

correlating these events with the newborn methylation in the promoter of the glucocorticoid receptor NR3C1.
Increased methylation impairs plasticity in subsequent NR3C1 gene expression and accordingly the range of future stress adaptation responses, resulting possibly in increased risk for adult-onset diseases (Mulligan, D'Errico, Stees, and Hughes, 2012).

Rheumatic Diseases

The specific actions of the hGR appear to play an important role in the regulation of the immune system and consequently play a specific role in diseases such as Rheumatoid arthritis, Systemic Lupus erythematosus, and ankylosing spondylitis. It is the splicing isoform GRbeta which is highly expressed in these patients that exert a negative effect on GRalpha and leads to resistance to glucocorticoids. Proinflammatory cytokines and the presence of a single nucleotide polymorphism in the 3' untranslated region of the hGRbeta mRNA (rs6198G allele) are responsible for the increased presence of the splicing variant GRbeta (Kino, Charmandari, and Chrousos, 2011).

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