The Physiology of Human Glucocorticoid Receptor β (hGRβ) and Glucocorticoid Resistance

LAURA J. LEWIS-TUFFIN[a,b] AND JOHN A. CIDLOWSKI[a]

[a]*Laboratory of Signal Transduction, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, 27709, USA*

[b]*Department of Cancer Cell Biology, Mayo Clinic, Jacksonville, Florida 32224, USA*

ABSTRACT: The development of glucocorticoid (GC) resistance is a serious problem that complicates the treatment of immune-related diseases, such as asthma, ulcerative colitis, and hematologic cancers. hGRα and hGRβ are two isoforms of the human glucocorticoid receptor, which differ in the structural composition of the carboxy-terminal end of the ligand-binding domain and therefore in their ability to bind glucocorticoid ligand and in their physiological function. hGRα is the classically functional GR, while hGRβ seems to act mainly as a dominant negative to the function of hGRα. Because of the ability of hGRβ to antagonize the action of hGRα, it has been hypothesized that changes in the expression of hGRβ may underlie the development of glucocorticoid resistance. In this article we review what is known about the expression and physiological action of hGRβ in normal cells and tissue as well as in several disease states. Taken together, the evidence suggests that the ratio of hGRα:hGRβ expression is indeed critical to the glucocorticoid responsiveness of various cells. This ratio can be altered by changing the expression level of hGRα, hGRβ, or both receptors simultaneously. Higher ratios correlate with glucocorticoid sensitivity, while lower ratios correlate with glucocorticoid resistance. Thus hGRβ can be an important modulator of glucocorticoid responsiveness.

KEYWORDS: glucocorticoid receptor beta (GRβ); glucocorticoid resistance; insensitivity; asthma; ulcerative colitis; leukemia; nasal polyps

INTRODUCTION

Glucocorticoids (GC) are a class of naturally occurring and synthetic steroid hormones that affect virtually every aspect of human physiology. Their actions

Address for correspondence: John A. Cidlowski, Laboratory of Signal Transduction, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, 111 TW Alexander Drive, P.O. Box 12233, Research Triangle Park, NC 27709, USA. Voice: 919-541-1564; fax: 919-541-1367.
e-mail: cidlowski@niehs.nih.gov

Ann. N.Y. Acad. Sci. 1069: 1–9 (2006).
doi: 10.1196/annals.1351.001

include important roles in the development of the lung and nervous system,[1–3] the modulation of skeletal metabolism,[4] the maintenance of homeostasis,[5–7] and the modulation/regulation of behavior.[8–12] Perhaps their most important effects, however, are highly effective anti-inflammatory and immunomodulatory actions that are exploited in the treatment of such diseases as arthritis, asthma, allergic rhinitis, and leukemia/lymphoma.[13–18] The broad involvement of glucocorticoids in both normal and pathologic physiological processes makes them one of the most important and commonly prescribed classes of drugs available,[19] but also underlies the side effects commonly experienced with glucocorticoid treatment.[20,21] In particular, the development of glucocorticoid resistance is a serious complication that can occur during chemotherapy regimens for hematologic cancers and chronic asthma therapy, making treatment of those conditions more difficult.[22,23] The mechanisms that underlie the development of glucocorticoid resistance are poorly understood and likely vary with disease type, treatment regimen, and the genetic background of the patient. However, an increasing number of reports indicate that changes in the relative expression of the glucocorticoid receptor (GR) isoforms hGRα and hGRβ are associated with glucocorticoid resistance, and may contribute to its development. Here, we review what is known about hGRβ and its relationship to glucocorticoid resistance.

GLUCOCORTICOID RECEPTOR α AND β: STRUCTURAL DIFFERENCES

Glucocorticoid actions are mediated by the glucocorticoid receptor, which is a member of the large steroid/thyroid/retinoic acid receptor superfamily that regulates gene transcription in a ligand-dependent manner. The gene for human GR (hGR) was originally cloned in 1985.[24] It is located on chromosome 5 (region 5q31)[25,26] and consists of nine exons.[24,27] Through alternative splicing of exon 9, two isoforms of the hGR gene, hGRα and hGRβ, are produced.[28]

The nuclear receptor superfamily has a common, modular domain structure that includes a variable-length amino terminus, a centrally located, zinc-finger DNA-binding domain (DBD), and a carboxy terminus ligand-binding domain (LBD).[19,29] In addition to these domains, GR has two transcription-activating regions, one in the amino terminal domain of the protein (AF-1 or τ1) that appears to act somewhat independently of ligand binding, and a second in the ligand-binding domain (AF-2 or τ2) whose function is dependent on ligand binding.[30,31] Additionally, the hGR LBD contains nuclear localization signals and sites for interaction with other transcription factors, cofactors, and protein chaperones.[32–34] Analysis of the crystal structure of the hGRα LBD indicates that it is a 12-helix bundle consisting of three layers, with the ligand-binding pocket located in the center.[35] Comparison of the GR LBD structure with the LBD structures of other nuclear receptors suggests that the ligand-dependent

conformation of the final, 12th helix is critical to the AF-2 transactivation function of GR.[36,37]

The alternately spliced exon 9 of the hGR coding sequence encodes the extreme carboxy terminal end of the GR ligand-binding domain, as well as the 3′ UTR. Thus the hGRα and β isoforms are identical proteins up through amino acid 727 corresponding to the C-terminal end of helix 10 of the LBD, but the remainder of the ligand-binding domain differs between the two receptors. hGRα has an additional 50 amino acids that encode helices 11 and 12 to complete a functional domain capable of binding ligand and transactivating gene expression. In contrast, hGRβ has only an additional 15 distinct amino acids. Consequently, hGRβ is missing helix 12 of the ligand-binding domain and possesses a unique sequence in helix 11 when compared to hGRα. The shortened, distinct LBD of hGRβ is reported to be unable to bind ligand,[24,28,30] resulting in a receptor that is unable to directly activate glucocorticoid responsive promoters.[24,30] Sequential mutation of the 15 unique amino acids within the hGRβ LBD suggests that amino acids 733 and 734 (unique amino acids 6 and 7) play an important role in determining the biological activity of hGRβ.[38]

GLUCOCORTICOID RECEPTOR α AND β: FUNCTIONAL DIFFERENCES

Because the α isoform of hGR binds ligand and affects gene expression, while the β isoform does not, far more is known about the mechanisms of hGRα than hGRβ action. In the absence of ligand, hGRα is maintained in the cytoplasm in a multiprotein complex that includes heat-shock protein 90 and several immunophilins. Upon ligand binding, this complex dissociates, exposing the nuclear localization signal of hGRα and allowing it to translocate to the nucleus. Once in the nucleus, hGRα affects gene transcription, either by binding to specific DNA elements known as glucocorticoid response elements (GRE), or by protein–protein interactions with other transcription factors, such as AP-1, NF-κB, or STAT family members.

In contrast, hGRβ is found constitutively in the nucleus and is not thought to bind ligand. [28,39] In addition, hGRβ cannot affect gene expression by itself. Instead, evidence suggests that hGRβ may act as a dominant negative to repress the transcriptional activity of hGRα. Reporter gene experiments carried out using exogenously expressed hGRα and hGRβ in cells that do not express endogenous GR have shown that (1) hGRβ is not able to activate reporter gene expression by itself[28,40] and (2) when hGRβ is overexpressed relative to hGRα, hGRβ represses the transcriptional activity of hGRα.[40,41] In addition, exogenous expression of hGRβ can repress the activity of transiently transfected reporter genes driven by endogenous hGRα expression.[28] It is believed that hGRβ's dominant negative activity is the combined result of (1) differences in the identity of amino acid residues 733 and 734 between the hGRα

and hGRβ LBDs, which cause hGRβ's Helix 11 to be disordered, and (2) the constitutively nuclear localization of the hGRβ receptor.[38]

The dominant negative activity of hGRβ in cell culture has led to the hypothesis that changes in hGRβ expression relative to hGRα could underlie the development of glucocorticoid (GC) resistance in several human diseases. This hypothesis has been partially tested in cell culture using HeLa S_3 cells that express endogenous hGR. It has been demonstrated in these cells that hGRβ protein levels increase in response to treatment with the proinflammatory cytokine tumor necrosis factor α (TNF-α).[42] This increase was correlated with the development of GC resistance in these cells, as measured by reporter gene assay. A more direct test of the idea that hGRβ expression underlies GC resistance comes from a study in which mouse hybridoma cells, which are naturally devoid of the GRβ isoform, were virally transduced with cDNA for hGRβ.[43] The proliferation of these cells was then compared to nontransduced cells in the presence of hydrocortisone. In contrast to the nontransduced cells, the cells that expressed hGRβ were resistant to the antiproliferative effects of hydrocortisone. Although these studies do not prove that increased expression of hGRβ directly underlies glucocorticoid resistance in humans, they do provide evidence that such expression could contribute to this desensitized state of hormone responsiveness. Consequently, there have been a number of investigations into the expression of hGRβ in disease states that have become GC resistant.

EXPRESSION OF HGRβ IN NORMAL AND DISEASED CELLS AND TISSUE

The distribution of hGRβ has been examined in both normal and diseased human cells and tissues, as well as in a number of human cell lines. However, direct comparisons of the levels of the hGRα and hGRβ isoforms, especially for protein expression in normal tissues, have not been done as often or as rigorously as one would like. In addition, few attempts have been made to analyze the expression of hGRβ in different cell types within the same organ (e.g., neurons vs. glia in brain tissue). Therefore, the actual extent of hGRα versus β expression in both normal and diseased cells and tissues is in many cases still unclear. Having said that, the mRNA for hGRβ has been found in almost every normal human tissue and cell type examined, including adult brain, lung, liver, heart, placenta, skeletal muscle, kidney, pituitary, pancreas, thymus, spleen, bone marrow, nasal mucosa, abdominal fat, leukocytes, eosinophils, peripheral blood mononuclear cells (PBMCs), macrophages, and neutrophils, as well as fetal brain, lung, and liver.[28,40,44] In contrast, hGRβ protein has been shown to have a more restricted distribution. Most frequently, hGRβ protein has been found in normal T lymphocytes, macrophages, neutrophils, eosinophils, and PBMCs.[45–47] In addition, hGRβ protein has been reported in brain, lung, and

heart tissue, [39] although there is a contradictory report. [44] Finally, human lung carcinoma, breast carcinoma, endometrial carcinoma, and bladder carcinoma cell lines, as well as HeLa S_3 cervical carcinoma cells, CEM-C7 leukemia cells, JAR choriocarcinoma cells, HEK-293 embryonic kidney cells, and normal lung epithelial cells have all been shown to express hGRβ protein.[39]

The expression of hGRβ in diseased tissue has been studied primarily in the context of GC-resistant forms of asthma, ulcerative colitis, nasal polyposis, and leukemia, including chronic lymphocytic and acute lymphoblastic leukemias. Of these, GC-resistant chronic asthma has been the most extensively studied. Increased numbers of hGRβ immunoreactive PBMCs and CD3+ T cells from the airways of patients with GC-resistant versus GC-sensitive asthma have been reported.[45,48] Extending these findings, greater numbers of hGRβ immunoreactive cells, primarily CD3+ T cells, have also been found in the lungs of fatal asthma cases as compared to cases of emphysema, mild asthma, or normal subjects.[49] Furthermore, using a cutaneous tuberculin inflammation model, the expression of hGRβ was greater in T cells and macrophages from GC-resistant versus GC-sensitive asthma patients.[50] Taken together, these reports suggest that increased expression of hGRβ in inflammatory cells, especially T cells, may be related to the development of GC-insensitive asthma.

Three studies have examined the expression of hGRβ in GC-resistant forms of ulcerative colitis. Two of these studies, examining hGRα and β mRNA expression in PBMCs from patients with ulcerative colitis versus normal subjects, found that PBMCs from patients with active ulcerative colitis were more likely to express hGRβ mRNA.[51,52] In addition, quantitative comparison of hGRβ mRNA levels in PBMCs from patients with GC-resistant versus GC-sensitive ulcerative colitis revealed higher expression of hGRβ mRNA in the GC-resistant cases. Furthermore, examination of hGRβ mRNA levels longitudinally in patients whose ulcerative colitis relapsed revealed increased hGRβ levels during the relapse.[52] There was no difference in the expression of hGRα mRNA between normal subjects and any of the ulcerative colitis patients in these studies. Finally, examination of hGRβ protein levels in PBMCs by Western blot and in colonic mucosal cells by immunocytochemistry confirmed increased expression of hGRβ in GC-resistant versus GC-sensitive ulcerative colitis.[51,53] Taken together, these studies suggest that increased expression of hGRβ in inflammatory cells is predictive of GC resistance, which is reduced patient response to GC treatment, in ulcerative colitis.

The expression of hGRβ protein in inflammatory cells found in nasal polyps as opposed to normal middle olfactory turbinate tissue has also been examined.[47] This study found increased hGRβ expression in nasal polyp inflammatory cells, particularly in T cells, eosinophils, and macrophages. Furthermore, although the number of subjects was small, an inverse correlation was noted between the baseline level of hGRβ expression and the response to the glucocorticoid fluticasone propionate. High levels of hGRβ expression correlated with a poor response to treatment with fluticasone propionate.

Finally, hGRβ expression associated with GC resistance has been examined in several cases of leukemia. The first such report concerned the relative expression of hGRα and β isoforms in a single case of GC-resistant chronic lymphocytic leukemia.[54] In cultured lymphocytes from this patient, the level of hGRα protein was found to be severely reduced and the level of hGRβ protein was elevated, resulting in a 20-fold excess of hGRβ compared to hGRα. A second report examined the relative levels of hGRα and β in 13 cases of acute lymphoblastic leukemia (ALL), including 8 ALL cases with pre-B cell lineage and 5 ALL cases with T cell lineage versus EBV-transformed lymphocytes from normal controls.[55] This study found no changes in the expression of hGRβ protein in ALL versus normal controls, but did find significant decreases in the expression of hGRα protein, especially in the T cell lineage ALL cells. As a result, the ratio of hGRα:hGRβ expression was reduced, from 1.4 in controls to 0.86 in ALL with pre-B lineage, and to 0.09 in ALL with T cell lineage. Interestingly, lymphoblasts of the T cell lineage are known to have reduced GC sensitivity.[56] A similar study also correlated the ratio of hGRβ:hGRα to ALL-phenotype and GC sensitivity.[57] In that study, hGRβ:hGRα ratios were lower in cases of pre-B ALL, which responds well to GC treatment, compared to other types of ALL, which have with a poorer prognostic phenotype and response to GC treatment. Taken together, the results of these studies indicate that the relative expression of hGRα to hGRβ in leukemia cells correlates with their sensitivity to GCs. Lymphoblasts/lymphocytes with lower hGRα:hGRβ ratios are less sensitive to the apoptosis-inducing effects of GC treatment and are associated with a poorer prognosis.

When the results of all these studies on hGRβ expression in different disease states are taken together, a picture begins to emerge in which a reduction in the relative expression of hGRα:hGRβ protein is associated with a poor response to GC treatment. Thus decreased expression of hGRα and/or increased expression of hGRβ in inflammatory cells appears to be a common mechanism for the development of glucocorticoid resistance in multiple organs.

CONCLUSIONS

There is general agreement that the expression of hGRα is much greater than the expression of hGRβ in most cells and tissues, in both normal and diseased states. Consequently, there is some disagreement as to whether hGRβ makes an important contribution to either normal or disease physiology. Some authors have argued that, with such low starting levels, small increases in hGRβ expression are unlikely to be physiologically relevant because they cannot substantially affect the hGRα:hGRβ ratio. However, it has been demonstrated for a growing number of immune-related disease states that decreases in the expression of hGRα and/or increases in the expression of hGRβ do result in substantial changes to the hGRα:hGRβ ratio and are correlated with the

development of GC resistance. When taken together, these results suggest that hGRβ does have an important role to play in the development of GC resistance. Thus, even if we do not currently understand the mechanistic details, hGRβ is potentially a key modulator of the progression of certain immune-related diseases. It is up to future investigators to determine the mechanisms of hGRβ function in both normal and disease states.

REFERENCES

1. JOBE, A.H. 2001. Glucocorticoids, inflammation and the perinatal lung. Sem. Neonatol. **6:** 331–342.
2. KOENIG, J.I., B. KIRKPATRICK & P. LEE. 2002. Glucocorticoid hormones and early brain development in schizophrenia. Neuropsychopharmacology. **27:** 309–318.
3. MATTHEWS, S.G. *et al*. 2002. Glucocorticoids, hypothalamo-pituitary-adrenal (HPA) development, and life after birth. Endocr. Res. **28:** 709–718.
4. CANALIS, E., R.C. PEREIRA & A.M. DELANY. 2002. Effects of glucocorticoids on the skeleton. J. Pediat Endocrinol. Metab. **15:** 1341–1345.
5. DALLMAN, M.F. *et al*. 2000. Bottomed out: metabolic significance of the circadian trough in glucocorticoid concentrations. Int. J. Obes. Rel. Metab. Disord: J. Int. Assoc. Study Obes. **24:** S40–S46.
6. JEANRENAUD, B. & F. ROHNER-JEANRENAUD. 2000. CNS-periphery relationships and body weight homeostasis: influence of the glucocorticoid status. Int. J. Obes. Rel. Metab. Disord: J. Int. Assoc. Study Obes. **24:** S74–S76.
7. RABER, J. 1998. Detrimental effects of chronic hypothalamic-pituitary-adrenal axis activation: from obesity to memory deficits. Mol. Neurobiol. **18:** 1–22.
8. FUCHS, E. *et al*. 2001. Psychosocial stress, glucocorticoids, and structural alterations in the tree shrew hippocampus. Physiol. Behav. **73:** 285–291.
9. MACCARI, S. *et al*. 2003. Prenatal stress and long-term consequences: implications of glucocorticoid hormones. Neurosci. Biobehav. Rev. **27:** 119–127.
10. MARINELLI, M. & P.V. PIAZZA. 2002. Interaction between glucocorticoid hormones, stress and psychostimulant drugs. Eur. J.Neurosci. **16:** 387–394.
11. REUS, V.I. & O.M. WOLKOWITZ. 2001. Antiglucocorticoid drugs in the treatment of depression. Exp. Opin. Invest. Drugs **10:** 1789–1796.
12. STECKLER, T., F. HOLSBOER & J.M. REUL. 1999. Glucocorticoids and depression. Best Prac. Res. Clin. Endocrinol. Metab. **13:** 597–614.
13. ALMAWI, W.Y., M.M. ABOU JAOUDE & X.C. LI. 2002. Transcriptional and post-transcriptional mechanisms of glucocorticoid antiproliferative effects. Hem. Oncol. **20:** 17–32.
14. BARNES, P.J. 1998. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. Clin. Sci. **94:** 557–572.
15. NACLERIO, R.M. 1988. The pathophysiology of allergic rhinitis: impact of therapeutic intervention. J. Allergy Clin. Immunol. **82:** 927–934.
16. RICCARDI, C., S. BRUSCOLI & G. MIGLIORATI. 2002. Molecular mechanisms of immunomodulatory activity of glucocorticoids. Pharmacol. Res. **45:** 361–368.
17. PERRETTI, M. & A. AHLUWALIA. 2000. The microcirculation and inflammation: site of action for glucocorticoids. Microcirculation **7:** 147–161.
18. SZEFLER, S.J. 2000. Asthma: the new advances. Advan. Pediat. **47:** 273–308.

19. EVANS, R.M. 1988. The steroid and thyroid hormone receptor superfamily. Science **240:** 889–895.
20. SCHACKE, H., W.D. DOCKE & K. ASADULLAH. 2002. Mechanisms involved in the side effects of glucocorticoids. Pharm. Therap. **96:** 23–43.
21. WHELAN, C.J. 2003. Will non-steroid approaches to the treatment of inflammation replace our need for glucocorticoids? Curr. Opin. Invest. Drugs **4:** 536–543.
22. SCHAAF, M.J. & J.A. CIDLOWSKI. 2002. Molecular mechanisms of glucocorticoid action and resistance. J. Steroid Biochem. Mol. Biol. **83:** 37–48.
23. KINO, T. *et al*. 2003. Tissue glucocorticoid resistance/hypersensitivity syndromes. J. Steroid Biochem. Mol. Biol. **85:** 457–467.
24. HOLLENBERG, S.M. *et al*. 1985. Primary structure and expression of a functional human glucocorticoid receptor cDNA. Nature **318:** 635–641.
25. FRANCKE, U. & B.E. FOELLMER. 1989. The glucocorticoid receptor gene is in 5q31-q32 [erratum appears in Genomics 1989 5(2):388]. Genomics **4:** 610–612.
26. THERIAULT, A. *et al*. 1989. Regional chromosomal assignment of the human glucocorticoid receptor gene to 5q31. Hum. Gen. **83:** 289–291.
27. ENCIO, I.J. & S.D. DETERA-WADLEIGH. 1991. The genomic structure of the human glucocorticoid receptor. J. Biol. Chem. **256:** 7182–7188.
28. OAKLEY, R.H., M. SAR & J.A. CIDLOWSKI. 1996. The human glucocorticoid receptor beta isoform: expression, biochemical properties, and putative function. J. Biol. Chem. **271:** 9550–9559.
29. KUMAR, R. & E.B. THOMPSON. 1999. The structure of the nuclear hormone receptors. Steroids **64:** 310–319.
30. GIGUERE, V. *et al*. 1986. Functional domains of the human glucocorticoid receptor. Cell **46:** 645–652.
31. HOLLENBERG, S.M. & R.M. EVANS. 1988. Multiple and cooperative *trans*-activation domains of the human glucocorticoid receptor. Cell **55:** 899–906.
32. DEFRANCO, D.B. 1999. Regulation of steroid receptor subcellular trafficking. Cell Biochem. Biophys. **30:** 1–24.
33. JENKINS, B.D., C.B. PULLEN & B.D. DARIMONT. 2001. Novel glucocorticoid receptor coactivator effector mechanisms. Trends Endocrinol. Metab. **12:** 122–126.
34. PRATT, W.B. 1993. The role of heat shock proteins in regulating the function, folding, and trafficking of the glucocorticoid receptor. J. Biol. Chem. **268:** 21455–21458.
35. BLEDSOE, R.K. *et al*. 2002. Crystal structure of the glucocorticoid receptor ligand binding domain reveals a novel mode of receptor dimerization and coactivator recognition. Cell **110:** 93–105.
36. WEATHERMAN, R.V., R.J. FLETTERICK & T.S. SCANLAN. 1999. Nuclear-receptor ligands and ligand-binding domains. Annu. Rev. Biochem. **68:** 559–581.
37. STEINMETZ, A.C.U., J.-P. RENAUD & D. MORAS. 2001. Binding of ligands and activation of transcription by nuclear receptors. Annu. Rev. Biophys. Biomol. Struct. **30:** 329–359.
38. YUDT, M.R. *et al*. 2003. Molecular origins for the dominant negative function of human glucocorticoid receptor beta. Mol. Cell Biol. **23:** 4319–4330.
39. OAKLEY, R.H. *et al*. 1997. Expression and subcellular distribution of the beta-isoform of the human glucocorticoid receptor. Endocrinology **138:** 5028–5038.
40. BAMBERGER, C.M. *et al*. 1995. Glucocorticoid receptor β, a potential endogenous inhibitor of glucocorticoid action in humans. J. Clin. Invest. **95:** 2435–2441.

41. OAKLEY, R.H. *et al*. 1999. The dominant negative activity of the human glucocorticoid receptor beta isoform: specificity and mechanisms of action. J. Biol. Chem. **274:** 27857–27866.
42. WEBSTER, J.C. *et al*. 2001. Proinflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative beta isoform: a mechanism for the generation of glucocorticoid resistance. Proc. Natl. Acad. Sci. USA. **98:** 6865–6870.
43. HAUK, P.J. *et al*. 2002. Increased glucocorticoid receptor β expression converts mouse hybridoma cells to a corticosteroid-insensitive phenotype. Am. J. Resp. Cell Mol. Biol. **27:** 361–367.
44. PUJOLS, L. *et al*. 2002. Expression of glucocorticoid receptor alpha- and beta-isoforms in human cells and tissues. Am. J. Physiol. Cell Physiol. **283:** C1324–C1331.
45. HAMID, Q. *et al*. 1999. Increased glucocorticoid receptor β in airway cells of glucocorticoid-insensitive asthma. Am. J. Resp. Crit. Care Med. **159:** 1600–1604.
46. STRICKLAND, I. *et al*. 2001. High constitutive glucocorticoid receptor β in human neutrophils enables them to reduce their spontaneous rate of cell death in response to corticosteroids. J. Exp. Med. **193:** 585–593.
47. HAMILOS, D.L. *et al*. 2001. GRβ expression in nasal polyp inflammatory cells and its relationship to the anti-inflammatory effects of intranasal fluticasone. J. Allergy Clin. Immunol. **108:** 59–68.
48. LEUNG, D.Y.M. *et al*. 1997. Association of glucocorticoid insensitivity with increased expression of glucocorticoid receptor β. J. Exp. Med. **186:** 1567–1574.
49. CHRISTODOULOPOULOS, P. *et al*. 2000. Increased number of glucocorticoid receptor-β-expressing cells in the airways in fatal asthma. J. Allergy Clin. Immunol. **106:** 479–484.
50. SOUSA, A.R. *et al*. 2000. Glucocorticoid resistance in asthma is associated with elevated in vivo expression of the glucocorticoid receptor β-isoform. J. Allergy Clin. Immunol. **105:** 943–950.
51. HONDA, M. *et al*. 2000. Expression of glucocorticoid receptor β in lymphocytes of patients with glucocorticoid-resistant ulcerative colitis. Gastroenterology **118:** 859–866.
52. ORII, F. *et al*. 2002. Quantitative analysis for human glucocorticoid receptor α/β mRNA in IBD. Biochem. Biophys. Res. Commun. **296:** 1286–1294.
53. ZHANG, H. *et al*. 2005. Significance of glucocorticoid receptor expression in colonic mucosal cells of patients with ulcerative colitis. World J. Gastroenterol. **11:** 1775–1778.
54. SHAHIDI, H. *et al*. 1999. Imbalanced expression of the glucocorticoid receptor isoforms in cultured lymphocytes from a patient with systemic glucocorticoid resistance and chronic lymphocytic leukemia. Biochem. Biophys. Res. Commun. **254:** 559–565.
55. LONGUI, C.A. *et al*. 2000. Low glucocorticoid receptor alpha/beta ratio in T-cell lymphoblastic leukemia. Horm. Metab. Res. **32:** 401–406.
56. PIETERS, R. *et al*. 1998. Relation between age, immunophenotype and in vitro drug resistance in 395 children with acute lymphoblastic leukemia: implications for treatment of infants. Leukemia **12:** 1344–1348.
57. KOGA, Y. *et al*. 2005. Differential mRNA expression of glucocorticoid receptor alpha and beta is associated with glucocorticoid sensitivity of acute lymphoblastic leukemia in children. Pediat. Blood Cancer **45:** 121–127.