

Steroid resistance in leukemia

Darshan S Shah, Raj Kumar

Darshan S Shah, Raj Kumar, Department of Basic Sciences, The Commonwealth Medical College, Scranton, PA 18509, United States

Author contributions: Both authors contributed to this paper.
Correspondence to: Raj Kumar, PhD, Department of Basic Sciences, The Commonwealth Medical College, Scranton, 525 Pine Street, Scranton, PA 18509, United States. rkumar@tcmedc.org
Telephone: +1-570-5049675 Fax: +1-570-5049660
Received: April 10, 2013 Revised: May 2, 2013
Accepted: May 19, 2013
Published online: May 20, 2013

levels and steroid-resistance in patients has been found. In recent years, several other mechanisms of action have been reported that could play an important role in the development of such drug resistances in leukemia.

Shah DS, Kumar R. Steroid resistance in leukemia. *World J Exp Med* 2013; 3(2): 21-25 Available from: URL: <http://www.wjgnet.com/2220-315X/full/v3/i2/21.htm> DOI: <http://dx.doi.org/10.5493/wjem.v3.i2.21>

Abstract

There are several types of leukemia which are characterized by the abnormal growth of cells from the myeloid or lymphoid lineage. Because of their lympholytic actions, glucocorticoids (GCs) are included in many therapeutic regimens for the treatment of various forms of leukemia. Although a significant number of acute lymphoblastic leukemia patients respond well to GC treatment during initial phases; prolonged treatments sometimes results in steroid-resistance. The exact mechanism of this resistance has yet not been completely elucidated, but a correlation between functional GC receptor expression levels and steroid-resistance in patients has been found. In recent years, several other mechanisms of action have been reported that could play an important role in the development of such drug resistances in leukemia. Therefore, a better understanding of how leukemic patients develop drug resistance should result in drugs designed appropriately to treat these patients.

© 2013 Baishideng. All rights reserved.

Key words: Leukemia; Glucocorticoid; Steroid resistant; Mutations; Genes

Core tip: The exact mechanism of this resistance has yet not been completely elucidated, but a correlation between functional glucocorticoid receptor expression

INTRODUCTION

Leukemia affects a large population of individuals, both young and old; however, those over the age of 60 years are more at risk of developing the disease. Leukemia is characterized by the abnormal growth of cells of the myeloid or lymphoid lineage that can arise due to several factors including chromosomal abnormalities, transcription factor alterations, and/or chromosomal hyperploidy^[1]. In addition to affecting either the myeloid or lymphoid lineage, leukemia can be classified as either acute or chronic. In acute leukemia, the white blood cells multiply very rapidly and are very immature, and therefore cannot function properly. In chronic leukemia, the blasts form more slowly, allowing the body to continue to producing normal, functional cells. This causes fewer symptoms for the patient but often results in splenomegaly. In all major forms of leukemia, as the leukemic bone marrow cells divide, they crowd the marrow and suppress production and function of other healthy cells. The rate of progression and replacement of normal bone marrow cells with cancerous ones is different with each type of leukemia^[1].

TYPES OF LEUKEMIA

There are four major types of leukemia: chronic lymphoblastic leukemia (CLL), chronic myeloid leukemia (CML), acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL). CLL is mainly caused by unregulated

proliferation of developing B-cells. The lack of growth regulation can be related to the developmental process where B-cells interact with T-cells in the germinal centers of lymph nodes to receive proliferative signaling. In CLL the B-cells express CD19, CD5, and CD23 and have lower levels of IgM, IgD, and CD79b. This phenotype is indicative of an activated mature B-cells^[2]. CML is a cancer of the hematopoietic stem cell, in which 95% of cases arise from the formation of the Philadelphia chromosome. The Philadelphia chromosome is the result of a reciprocal translocation between chromosome 9 and 22, specifically t(9;22)(q34;q11)^[3-5]. Currently, Imatinib or interferon α are used as the primary treatment for standard risk CML^[6].

In AML, the hematopoietic progenitor cells lose their ability to differentiate normally due to a heterogeneous clonal disorder. The specific mutations associated in AML are very diverse but some common mutations are related to the *FLT3*, *NPM1*, *CEBPA*, *MLL*, *BAALC*, or *EV11* genes^[7-12]. Regardless of the mutation(s), patients diagnosed with AML have difficulty producing mature erythrocytes, neutrophils, monocytes, and platelets. This is usually noticed in the patient by the inability to fight infections^[13]. Induction therapy for AML includes a course of cytarabine following a course of anthracycline daunorubicin^[14]. Due to different biological and clinical features compared to younger patients, treatment of older patients with AML has been hampered by uncertainties. There are suggestions that cytogenetic information is critical in order to facilitate treatment decisions for older AML patients. Such patients with adverse-risk cytogenetics derive little benefit from standard induction therapy, and an assessment of the percentage of bone marrow blasts may guide treatment decisions. Over the last few years large-scale genomic studies of patients with AML have also unveiled recurrent somatic mutations in genes involved in epigenetic regulation and the spliceosomal machinery. The identification of these mutations and their impact on prognostication has led to improvements in risk-stratification strategies and provided new potential targets for the treatment of these myeloid malignancies.

The causes of ALL include chromosomal translocations, hyperploidy of more than 50 chromosomes, and altered transcription factors. These alterations contribute to changes the cellular function of the hematopoietic stem cells^[15]. The possible cellular processes damaged in ALL are the regulation of differentiation, proliferation, and cell programmed death^[1]. Some of the pathways affected include the expression of *FLT3*, a tyrosine receptor kinase, which regulates the retinoblastoma pathway and cells entrance into mitosis cycle^[16]. Another mutation that commonly occurs in ALL is the formation of the *TEM-AML1* fusion protein which causes deacetylation of histones. By deacetylating the histones, this inhibits differentiation of the hematopoietic stem cells by inhibiting gene transcription^[17,18]. Regardless of the type of ALL, the standard induction therapy for all cases is the administration of glucocorticoids (GCs). The most commonly

used steroids are dexamethasone and prednisolone. Unlike AML, and CML, ALL has a higher incidence rate in children than in adults giving it a median age of incidence of 39 years^[19]. Given the younger median age of these patients, they tend to be very resilient to the treatment over the course of therapy, and in over 80% of cases go into full remission^[1,20]. Because they are unable to tolerate chemotherapy regimens as intense as those administered to children, adult ALL patients present with higher-risk features, and therefore, the overall treatment plan for adult ALL is modeled after the pediatric paradigm. This includes multi-agent chemotherapy in the forms of induction, consolidation, and maintenance. Most patients will go into complete remission but often relapse. Wealth of new information regarding the genetic alterations involved in the development of lymphoid leukemias is likely to have a significant impact on patient care as well present several important challenges and opportunities. It is likely that some genetic alterations may have a complex and unexpected role in the development of malignancies. Further, different genetic lesions can affect the same cellular pathway in different cases. Proper understanding of these genetic variations may not only provide a framework for basic research but also could convert these results into a meaningful clinical outcome.

ROLE OF GLUCOCORTICOIDS IN LEUKEMIA

Most of the biological effects of GCs are regulated *via* the glucocorticoid receptor (GR) at the level of second messengers such as cAMP^[20]. The two major GR-protein isoforms of interest in pro-inflammatory responses are the GR- α and GR- β . The GR- α is typically associated with steroid sensitivity and acts in an agonistic manner whereas the GR- β seems to be associated with GC mediated GR resistance and seems to act as an antagonist when bound to GC^[21,22]. The GR gene lies on chromosome 5 (5q31). The GR protein contains four major functional domains: the N-terminal transactivation domain for AF1, A DNA binding domain (DBD) that contains two zinc fingers, and the C-terminal ligand binding domain (LBD)^[23]. The N-terminal transactivation domain contains the AF1 domain and is responsible for transcriptional activation of target genes^[24]. The first zinc finger binding domain contains the AF1 and nuclear factor κ B binding domains and is involved in the transrepression of the receptor^[25]. The second zinc finger domain contains the genes that regulate receptor dimerization and glucocorticoid response element mediated transactivation^[26-29]. The LBD contains a pocket for steroid binding, a nuclear localization signal, and small but potent ligand-dependent transactivation region (AF2), which interacts with a specific set of co-activators or co-repressors. The determination of AF2 co-activation/co-repression activation depends on the orientation of the AF2 binding, which is based on whether the LBD is activated by an agonist or an antagonist to LBD^[30,31]. Due to their lympholytic actions, GCs are included in many therapeutic regimens for

the treatment of various forms of leukemia and lymphoma^[32,33]. It is clear that the presence of adequate quantities of properly functioning GR is a necessary but not solely sufficient component for lymphocytolysis^[34,35]. In chronic lymphocytic leukemia, certain types of childhood ALL, and malignant lymphomas, a correlation between response to GC therapy and functional GR levels assayed by ligand binding has been found^[36,37]. However due to the diversity of these diseases, coupled with their relative individual rarity, no simple overall correlation was found between GC activity and activation of lymphocytolysis.

STEROID-RESISTANCE

Although a significant number of ALL patients respond well to GCs, some reveal primary GC resistance, and those sensitive to GCs almost exclusively develop secondary resistance after prolonged GC therapy^[38]. There are two forms of resistance, primary and secondary. Primary resistance is due to an inherent GC resistance. This can be related to the level of GR expression and the regulation of intracellular substrate availability^[39]. The second form of steroid resistance is developed over the course of treatment and can take multiple forms. Within the developed resistance, B-cell lineages and T-cell lineages seem to have divergent mechanisms of resistance. Though the mechanism of this resistance has not been completely elucidated, it was once thought that the resistance was due to an alteration in GR expression that is induced by GC treatment. However, later studies found this not to be the sole cause of the resistance^[40]. Another proposed mechanism of resistance involves the B-cell lymphoma family of proteins^[41]. Large clinical surveys suggest a correlation between functional GR expression levels and primary GC sensitivity and prognosis^[42,43]. GC-resistance is either a familial or sporadic condition that can be characterized by generalized end-organ inability to respond to normal GC levels^[44]. Thus, steroid resistance in leukemia is a major problem in ALL as it is the primary induction therapy in childhood. Without GC sensitivity the leukemic cells are no longer induced into apoptosis by the treatment.

The BCL2 family of proteins is critical in the regulation of apoptosis induced by cellular stress. BCL2 family of proteins can have either pro-apoptotic or pro-survival properties. Though the signals control opposing functions, they are related through conserved sequence motifs. These motifs are the BCL2 homology domains (BH). The high affinity BH1 and BH2 domains, a pro-survival specific motif, interacts with the pro-apoptotic BH3 domains, inhibits the death signaling pathway allowing for cell survival^[45]. The opposing pathway, induced by BH3, induces cell death *via* the BCL2 pathway. It is induced by the activation of the BCL2-associated X protein (BAX) and BCL2 homologous antagonist/killer (BAK). The activation of the BAX/BAK pathway leads to apoptosis *via* permeation of the mitochondrial membrane^[46]. However, when BCL2 and BCL2 extra-large (*MCL-1*) knockdowns

were induced, GC administration showed no effect on cell viability when cells from a child ALL patient were used. This indicated that the mechanism of GC resistance lies downstream of BCL2 and MCL-1 pathways^[47].

Another possible cause of resistance in ALL patients could be due to an over expression of 11 β -HSD. The function of this protein is to inactivate GC as they enter the cell. In rats that have been undergoing dexamethasone therapy and are sensitive to GCs, it has been found that their circulating levels of 11 β -HSD1 are elevated. However, once they become resistant to GCs, their levels of 11 β -HSD1 are significantly decreased even in the presence of dexamethasone^[48]. As a result, inhibitors of 11 β -HSD, such as carbenoxolone, have been shown to improve cell death in the T-cell leukemic cell line, CCRF-CEM^[49]. This suggests that 11 β -HSD inhibitor could be used as part of a combination therapy in ALL.

SUMMARY AND PERSPECTIVES

It has been reported that several point mutations in the LBD of the human GR develop in steroid-resistant leukemic patients, which interferes with GR's ability to bind GCs and subsequently interferes with gene regulation. GC-based therapy is still the most commonly used treatment to combat chronic and acute inflammation. Due to multiple physiological actions of GC/GR, a chronic exposure to pharmacological GC doses becomes a problem in therapeutic settings, causing undesirable, yet on-target effects. Therefore the real challenge is not only to develop more specific GR-ligands, but to change the spectrum of GR-mediated events and try to skew it more towards desired pathways. Therefore, the mainstay of research efforts must be focused on further characterizing the mechanisms of GR actions in detail and developing new therapeutic strategies to fight leukemia with a better benefit-to-risk-ratio. We must aim to dissect certain important determinants of GC/GR signaling in clinical contexts that can be applied for designing of more specific and better targeted therapies to combat leukemia.

REFERENCES

- 1 Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. *N Engl J Med* 2004; **350**: 1535-1548 [PMID: 15071128 DOI: 10.1056/NEJMra023001]
- 2 Chiorazzi N, Rai KR, Ferrarini M. Chronic lymphocytic leukemia. *N Engl J Med* 2005; **352**: 804-815 [PMID: 15728813 DOI: 10.1056/NEJMra041720]
- 3 Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. *Science* 1990; **247**: 824-830 [PMID: 2406902 DOI: 10.1126/science.2406902]
- 4 Heisterkamp N, Groffen J, Stephenson JR, Spurr NK, Goodfellow PN, Solomon E, Carritt B, Bodmer WF. Chromosomal localization of human cellular homologues of two viral oncogenes. *Nature* 1982; **299**: 747-749 [PMID: 7121606 DOI: 10.1038/299747a0]
- 5 Ren R. Mechanisms of BCR-ABL in the pathogenesis of chronic myelogenous leukaemia. *Nat Rev Cancer* 2005; **5**: 172-183 [PMID: 15719031 DOI: 10.1038/nrc1567]

- 6 **Hehlmann R**, Hochhaus A, Baccarani M. Chronic myeloid leukaemia. *Lancet* 2007; **370**: 342-350 [PMID: 17662883 DOI: 10.1016/S0140-6736(07)61165-9]
- 7 **Baldus CD**, Tanner SM, Ruppert AS, Whitman SP, Archer KJ, Marcucci G, Caligiuri MA, Carroll AJ, Vardiman JW, Powell BL, Allen SL, Moore JO, Larson RA, Kolitz JE, de la Chapelle A, Bloomfield CD. BAALC expression predicts clinical outcome of de novo acute myeloid leukemia patients with normal cytogenetics: a Cancer and Leukemia Group B Study. *Blood* 2003; **102**: 1613-1618 [PMID: 12750167 DOI: 10.1182/blood-2003-02-0359]
- 8 **Barjesteh van Waalwijk van Doorn-Khosrovani S**, Erpelinck C, van Putten WL, Valk PJ, van der Poel-van de Luytgaarde S, Hack R, Slater R, Smit EM, Beverloo HB, Verhoef G, Verdonck LF, Ossenkoppele GJ, Sonneveld P, de Greef GE, Löwenberg B, Delwel R. High EVI1 expression predicts poor survival in acute myeloid leukemia: a study of 319 de novo AML patients. *Blood* 2003; **101**: 837-845 [PMID: 12393383 DOI: 10.1182/blood-2002-05-1459]
- 9 **Caligiuri MA**, Strout MP, Lawrence D, Arthur DC, Baer MR, Yu F, Knuutila S, Mrózek K, Oberkircher AR, Marcucci G, de la Chapelle A, Elonen E, Block AW, Rao PN, Herzig GP, Powell BL, Ruutu T, Schiffer CA, Bloomfield CD. Rearrangement of ALL1 (MLL) in acute myeloid leukemia with normal cytogenetics. *Cancer Res* 1998; **58**: 55-59 [PMID: 9426057]
- 10 **Fröhling S**, Schlenk RF, Stolze I, Bihlmayr J, Benner A, Kreitmeier S, Tobis K, Döhner H, Döhner K. CEBPA mutations in younger adults with acute myeloid leukemia and normal cytogenetics: prognostic relevance and analysis of cooperating mutations. *J Clin Oncol* 2004; **22**: 624-633 [PMID: 14726504 DOI: 10.1200/JCO.2004.06.060]
- 11 **Verhaak RG**, Goudswaard CS, van Putten W, Bijl MA, Sanders MA, Hagens W, Uitterlinden AG, Erpelinck CA, Delwel R, Löwenberg B, Valk PJ. Mutations in nucleophosmin (NPM1) in acute myeloid leukemia (AML): association with other gene abnormalities and previously established gene expression signatures and their favorable prognostic significance. *Blood* 2005; **106**: 3747-3754 [PMID: 16109776 DOI: 10.1182/blood-2005-05-2168]
- 12 **Yokota S**, Kiyoi H, Nakao M, Iwai T, Misawa S, Okuda T, Sonoda Y, Abe T, Kahsima K, Matsuo Y, Naoe T. Internal tandem duplication of the FLT3 gene is preferentially seen in acute myeloid leukemia and myelodysplastic syndrome among various hematological malignancies. A study on a large series of patients and cell lines. *Leukemia* 1997; **11**: 1605-1609 [PMID: 9324277]
- 13 **Anderlini P**, Luna M, Kantarjian HM, O'Brien S, Pierce S, Keating MJ, Estey EH. Causes of initial remission induction failure in patients with acute myeloid leukemia and myelodysplastic syndromes. *Leukemia* 1996; **10**: 600-608 [PMID: 8618434]
- 14 **Estey E**, Döhner H. Acute myeloid leukaemia. *Lancet* 2006; **368**: 1894-1907 [PMID: 17126723 DOI: 10.1016/S0140-6736(06)69780-8]
- 15 **Hanahan D**, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100**: 57-70 [PMID: 10647931 DOI: 10.1016/S0092-8674(00)81683-9]
- 16 **Armstrong SA**, Kung AL, Mabon ME, Silverman LB, Stam RW, Den Boer ML, Pieters R, Kersey JH, Sallan SE, Fletcher JA, Golub TR, Griffin JD, Korsmeyer SJ. Inhibition of FLT3 in MLL. Validation of a therapeutic target identified by gene expression based classification. *Cancer Cell* 2003; **3**: 173-183 [PMID: 12620411 DOI: 10.1016/S1535-6108(03)00003-5]
- 17 **Downing JR**. The core-binding factor leukemias: lessons learned from murine models. *Curr Opin Genet Dev* 2003; **13**: 48-54 [PMID: 12573435 DOI: 10.1016/S0959-437X(02)00018-7]
- 18 **Speck NA**, Stacy T, Wang Q, North T, Gu TL, Miller J, Binder M, Marín-Padilla M. Core-binding factor: a central player in hematopoiesis and leukemia. *Cancer Res* 1999; **59**: 1789s-1793s [PMID: 10197598]
- 19 **Soslow RA**, Baergen RN, Warnke RA. B-lineage lymphoblastic lymphoma is a clinicopathologic entity distinct from other histologically similar aggressive lymphomas with blastoid morphology. *Cancer* 1999; **85**: 2648-2654 [PMID: 10375114 DOI: 10.1002/(SICI)1097-0142(19990615)85:12<2648::AID-CNCR22>3.0.CO;2-R]
- 20 **Hepler JR**, Gilman AG. G proteins. *Trends Biochem Sci* 1992; **17**: 383-387 [PMID: 1455506 DOI: 10.1016/0968-0004(92)90005-T]
- 21 **Goecke A**, Guerrero J. Glucocorticoid receptor beta in acute and chronic inflammatory conditions: clinical implications. *Immunobiology* 2006; **211**: 85-96 [PMID: 16446173 DOI: 10.1016/j.imbio.2005.11.002]
- 22 **Leung DY**, Hamid Q, Vottero A, Szefer SJ, Surs W, Minshall E, Chrousos GP, Klemm DJ. Association of glucocorticoid insensitivity with increased expression of glucocorticoid receptor beta. *J Exp Med* 1997; **186**: 1567-1574 [PMID: 9348314 DOI: 10.1084/jem.186.9.1567]
- 23 **Theriault A**, Boyd E, Harrap SB, Hollenberg SM, Connor JM. Regional chromosomal assignment of the human glucocorticoid receptor gene to 5q31. *Hum Genet* 1989; **83**: 289-291 [PMID: 2793174 DOI: 10.1007/BF00285175]
- 24 **Hollenberg SM**, Evans RM. Multiple and cooperative transactivation domains of the human glucocorticoid receptor. *Cell* 1988; **55**: 899-906 [PMID: 3191531 DOI: 10.1016/0092-8674(88)90145-6]
- 25 **Tao Y**, Williams-Skipp C, Scheinman RI. Mapping of glucocorticoid receptor DNA binding domain surfaces contributing to transrepression of NF-kappa B and induction of apoptosis. *J Biol Chem* 2001; **276**: 2329-2332 [PMID: 11106637 DOI: 10.1074/jbc.C000526200]
- 26 **Dahlmann-Wright K**, Wright A, Gustafsson JA, Carlstedt-Duke J. Interaction of the glucocorticoid receptor DNA-binding domain with DNA as a dimer is mediated by a short segment of five amino acids. *J Biol Chem* 1991; **266**: 3107-3112 [PMID: 1993683]
- 27 **Hollenberg SM**, Giguere V, Segui P, Evans RM. Colocalization of DNA-binding and transcriptional activation functions in the human glucocorticoid receptor. *Cell* 1987; **49**: 39-46 [PMID: 3829127 DOI: 10.1016/0092-8674(87)90753-7]
- 28 **Picard D**, Yamamoto KR. Two signals mediate hormone-dependent nuclear localization of the glucocorticoid receptor. *EMBO J* 1987; **6**: 3333-3340 [PMID: 3123217]
- 29 **Zilliucius J**, Wright AP, Carlstedt-Duke J, Gustafsson JA. Structural determinants of DNA-binding specificity by steroid receptors. *Mol Endocrinol* 1995; **9**: 389-400 [PMID: 7659083 DOI: 10.1210/me.9.4.389]
- 30 **Heitzer MD**, Wolf IM, Sanchez ER, Witchel SF, DeFranco DB. Glucocorticoid receptor physiology. *Rev Endocr Metab Disord* 2007; **8**: 321-330 [PMID: 18049904 DOI: 10.1007/s11154-007-9059-8]
- 31 **Tissing WJ**, Meijerink JP, den Boer ML, Pieters R. Molecular determinants of glucocorticoid sensitivity and resistance in acute lymphoblastic leukemia. *Leukemia* 2003; **17**: 17-25 [PMID: 12529655 DOI: 10.1038/sj.leu.2402733]
- 32 **Ahmad N**, Kumar R. Steroid hormone receptors in cancer development: a target for cancer therapeutics. *Cancer Lett* 2011; **300**: 1-9 [PMID: 20926181 DOI: 10.1016/j.canlet.2010.09.008]
- 33 **Inaba H**, Pui CH. Glucocorticoid use in acute lymphoblastic leukaemia. *Lancet Oncol* 2010; **11**: 1096-1106 [PMID: 20947430 DOI: 10.1016/S1470-2045(10)70114-5]
- 34 **Yamagishi S**, Fukami K, Ueda S, Okuda S. Molecular mechanisms of diabetic nephropathy and its therapeutic intervention. *Curr Drug Targets* 2007; **8**: 952-959 [PMID: 17691932]
- 35 **Thompson EB**, Johnson BH. Regulation of a distinctive set of genes in glucocorticoid-evoked apoptosis in CEM human lymphoid cells. *Recent Prog Horm Res* 2003; **58**: 175-197 [PMID: 12795419 DOI: 10.1210/rp.58.1.175]
- 36 **Hillmann AG**, Ramdas J, Multanen K, Norman MR, Harmon JM. Glucocorticoid receptor gene mutations in leukemic cells acquired in vitro and in vivo. *Cancer Res* 2000; **60**:

- 2056-2062 [PMID: 10766198]
- 37 **Ramdas J**, Liu W, Harmon JM. Glucocorticoid-induced cell death requires autoinduction of glucocorticoid receptor expression in human leukemic T cells. *Cancer Res* 1999; **59**: 1378-1385 [PMID: 10096574]
 - 38 **Roychowdhury S**, Talpaz M. Managing resistance in chronic myeloid leukemia. *Blood Rev* 2011; **25**: 279-290 [PMID: 21982419 DOI: 10.1016/j.blre.2011.09.001]
 - 39 **Kaspers GJ**, Pieters R, Klumper E, De Waal FC, Veerman AJ. Glucocorticoid resistance in childhood leukemia. *Leuk Lymphoma* 1994; **13**: 187-201 [PMID: 8049644]
 - 40 **Bachmann PS**, Gorman R, Mackenzie KL, Lutze-Mann L, Lock RB. Dexamethasone resistance in B-cell precursor childhood acute lymphoblastic leukemia occurs downstream of ligand-induced nuclear translocation of the glucocorticoid receptor. *Blood* 2005; **105**: 2519-2526 [PMID: 15572593 DOI: 10.1182/blood-2004-05-2023]
 - 41 **Bhadri VA**, Trahair TN, Lock RB. Glucocorticoid resistance in paediatric acute lymphoblastic leukaemia. *J Paediatr Child Health* 2012; **48**: 634-640 [PMID: 22050419 DOI: 10.1111/j.1440-1754.2011.02212.x]
 - 42 **Thompson EB**, Harmon JM. Glucocorticoid receptors and glucocorticoid resistance in human leukemia in vivo and in vitro. *Adv Exp Med Biol* 1986; **196**: 111-127 [PMID: 3521219]
 - 43 **Stevens J**, Stevens YW. Glucocorticoid Receptors in human Leukemia and Lymphoma: quantification and clinical significance. In: Hollander VP, editor. Hormonally responsive tumors. New York: Academic Press, 1985: 155-181
 - 44 **Bloomfield CD**, Munck AU, Smith KA. Glucocorticoid receptor levels predict response to treatment in human lymphoma. *Prog Clin Biol Res* 1984; **142**: 223-233 [PMID: 6608734]
 - 45 **Kelekar A**, Thompson CB. Bcl-2-family proteins: the role of the BH3 domain in apoptosis. *Trends Cell Biol* 1998; **8**: 324-330 [PMID: 9704409 DOI: 10.1016/S0962-8924(98)01321-X]
 - 46 **Chipuk JE**, Kuwana T, Bouchier-Hayes L, Droin NM, Newmeyer DD, Schuler M, Green DR. Direct activation of Bax by p53 mediates mitochondrial membrane permeabilization and apoptosis. *Science* 2004; **303**: 1010-1014 [PMID: 14963330 DOI: 10.1126/science.1092734]
 - 47 **Ploner C**, Schmidt S, Presul E, Renner K, Schröcksnadel K, Rainer J, Riml S, Kofler R. Glucocorticoid-induced apoptosis and glucocorticoid resistance in acute lymphoblastic leukemia. *J Steroid Biochem Mol Biol* 2005; **93**: 153-160 [PMID: 15860257 DOI: 10.1016/j.jsbmb.2004.12.017]
 - 48 **Sai S**, Nakagawa Y, Sakaguchi K, Okada S, Takahashi H, Hongo T, Seckl JR, Chapman KE, Ohzeki T. Differential regulation of 11beta-hydroxysteroid dehydrogenase-1 by dexamethasone in glucocorticoid-sensitive and -resistant childhood lymphoblastic leukemia. *Leuk Res* 2009; **33**: 1696-1698 [PMID: 19446331 DOI: 10.1016/j.leukres.2009.04.016]
 - 49 **Sai S**, Nakagawa Y, Yamaguchi R, Suzuki M, Sakaguchi K, Okada S, Seckl JR, Ohzeki T, Chapman KE. Expression of 11beta-hydroxysteroid dehydrogenase 2 contributes to glucocorticoid resistance in lymphoblastic leukemia cells. *Leuk Res* 2011; **35**: 1644-1648 [PMID: 21794917 DOI: 10.1016/j.leukres.2011.07.002]

P- Reviewers Anagnou NP, Chen SS, Thomas X
S- Editor Zhai HH **L- Editor** A **E- Editor** Zheng XM





Published by **Baishideng Publishing Group Co., Limited**

Flat C, 23/F., Lucky Plaza, 315-321 Lockhart Road,

Wan Chai, Hong Kong, China

Fax: +852-65557188

Telephone: +852-31779906

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>

