Commentary

The kinome and glucocorticoid-induced apoptosis

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Key words: apoptosis, glucocorticoids, GSK3, protein kinases, lymphoid malignancies

In this perspective, I discuss the complex interplay between GC signaling and the kinome that ultimately determines the cell fate after GC treatment. Apoptosis ensues when the cell expresses sufficient levels of GR and Bim together with a kinome favoring GSK3 activation. Protein kinases that prevent Bim upregulation and/or inhibit GSK3, confer GC-resistance on the cell. GC-resistance may be overcome in T and B lymphoid malignancies by inhibiting the JNK, Src, PI3K, Akt or mTOR survival pathways. Both staurosporine and rapamycin have recently been proved efficient to sensitize resistant T and B malignant cells to GC-induced apoptosis. This is a proof-of-principle that it is possible to improve GC therapy by altering the cell’s kinome.

Glucocorticoids (GCs) are central components in the treatment of various hematological malignancies owing to their ability to induce apoptosis of these cancerous cells. Whereas some lymphomas and leukemias readily respond to this treatment, others are refractory. The emergence of GC resistant cells during treatment is a major cause for therapy failure. Therefore it is crucial to know how GC-induced apoptosis is regulated and how to overcome the GC resistance obstacle. Although GC-induced apoptosis has been the focus for intensive studies since the phenomenon was described the first time for more than half a century ago, the mechanisms involved have remained a mystery. It is well known that the effects of GCs are mediated through the glucocorticoid receptor (GR), which has to be expressed above a threshold level that the effects of GCs are mediated through the glucocorticoid mechanisms involved have remained a mystery. It is well known that the effects of GCs are mediated through the glucocorticoid receptor (GR), which has to be expressed above a threshold level for achieving the pro-apoptotic effect.1-3 Some lymphoma cells innately express sufficient high GR levels, while in others GR has to be upregulated in order to reach apoptotic competence. The latter may explain the requirement for gene transcription for GC-induced apoptosis in some lymphoid cells, which usually belong to the delayed response group, i.e. cells that show apoptotic response only after 48-72 hrs.1 The upregulation of GR is auto-induced by activated GR through interaction with a glucocorticoid response element (GRE) located within the GR gene.5 In myelogenic leukemia cells, GR is frequently downregulated in response to GC, which may be one reason for their GC-resistant phenotype.5 Thus, the resulting GR expression level after GC treatment is a better parameter than the basal GR level for predicting the cellular response to GCs. Long-term exposure of lymphoma cells to GCs may lead to permanent downregulation of GR with subsequent emergence of GC-resistance in originally GC-sensitive cells.3 Reintroduction of GR in such cells restores GC sensitivity, with a direct correlation between the GR expression level and the susceptibility of the cell to GC-induced apoptosis.3 These findings underscore the need for sufficient GR expression for executing this cell death process. Nevertheless, the mere expression of GR is insufficient for achieving an apoptotic response. Most primary lymphoblastic leukemias are GR positive irrespectively to their GC sensitive phenotype, indicating that GC-resistance is often caused by factors downstream to GR activation.

GR is well known to act as a transcription factor. In the absence of ligand, the receptor is sequestered in the cytosol to heat-shock protein (Hsp) complexes7 or to 14-3-3.8 Upon ligand binding, GR becomes hyperphosphorylated and dissociates from the Hsp complex. The released GR dimerizes and rapidly translocates to the nucleus where it regulates the expression of a large number of genes through transactivation and transrepression.9 These nuclear effects occur both in GC-sensitive and GC-resistant cells. Some cell type-specific patterns of affected genes have been described.2 Also, the phosphorylation status of GR may modulate the repertoire of GC-induced genes.9 The most relevant gene alteration related to apoptosis is the upregulation of the pro-apoptotic Bim protein, an essential mediator of GC-induced apoptosis.10-12 Upregulation of Bim is essential for achieving apoptotic competence in lymphoid cells expressing low basal Bim expression,12 which may explain the delayed onset of apoptosis in these cells. On the other hand, lymphoid cells harboring high basal Bim levels are more prone for a rapid apoptotic response, unless co-expressing anti-apoptotic proteins of the Bcl-2 family that counteract the pro-apoptotic function of Bim.12 Bim upregulation was shown to be more profound in GC-sensitive than in GC-resistant primary lymphoblastic leukemia samples.6 This may be explained by the
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observation that Bim is apparently an indirect target of GCs and depends on adequate activation of the FoxO3 transcription factor. The activity of FoxO3 is inhibited through phosphorylation by Akt/PKB, a protein kinase frequently activated in GC-resistant cells. The mere upregulation of Bim expression is insufficient for triggering apoptosis. This pro-apoptotic protein, which is frequently expressed at high basal levels in various hematological malignancies, has to undergo activation by post-translational modifications and protein-protein interactions. Thus, the genomic effects of GR only contribute to alter the composition of the proteome toward a more apoptosis-prone phenotype, but per se are insufficient to trigger apoptosis. Rather the simultaneous elicitation of non-genomic signals is required for initiating the apoptotic cascade.

Several rapid effects have been described to occur immediately after exposure to GCs that have been attributed to signaling pathways activated by GCs independently of their nuclear effects. In thymocytes which are highly sensitive to GC-induced apoptosis, GCs lead to transient calcium mobilization to the cytosol, and rapid production of ceramide and reactive oxygen species (ROS) in the mitochondria. These effects of GCs are believed to be important for GC-induced apoptosis. For instance, GC-induced apoptosis could be prevented by chelating calcium or by the Calmodulin inhibitor calmidazolium. Calcium mobilization is also important for the GC-induced phosphorylation of GR. Anti-oxidants neutralizing ROS also attenuate this cell death process. The anti-oxidant N-acetyl L-cysteine prevented GC-induced elevation in cytosolic calcium levels, suggesting that oxygen radical production is upstream to Ca2+ mobilization. The major source of ROS production induced by GCs is the mitochondrial electron transport chain, NAD(P)H oxidase and xanthine oxidase. GCs have also been shown to induce mitochondrial proton leak. Intriguingly, GCs induce GR translocation to the mitochondria in GC-sensitive, but not in GC-resistant, lymphoma cells, which may be responsible for at least some of the above-described, immediate mitochondrial effects of GCs.

Recent data suggest that the kinome has a major impact on GC-induced apoptosis. It has long been known that T cell receptor (TCR) activation antagonizes GC-induced apoptosis in T cells through activation of the pro-survival MAP kinase ERK. Also various cytokines (e.g., IL-2 and IL-6) and the growth factor IGF-1 counteract the pro-apoptotic function of GCs through activation of ERK and PI3K/Akt survival pathways, with subsequent activation of sphingosine kinase. Sphingosine kinase phosphorylates the pro-apoptotic sphingosine and converts it into sphingosine-1-phosphate that stimulates growth and suppresses apoptosis. Overexpression of sphingosine kinase in multiple myeloma cells induces Mcl-1 expression with subsequent blockade of GC-mediated apoptosis. Thus, the sphingolipid rheostat may modulate the apoptotic process.

IL-6 production by multiple myeloma cells or by bone marrow stroma cells in the tumor microenvironment is a common cause for GC-resistance. Prevention of IL-6 secretion by thalidomide or lenalidomide could reverse GC-resistance in multiple myeloma cells. These drugs are currently common components in the combinatory GC-based treatment of multiple myeloma. Also, blocking endogenous IGF-1 leads to the sensitization of multiple myeloma cells to GCs. Similarly, inhibition of either the fibroblast growth factor receptor 3 (FGF3) or the epidermal growth factor receptor (EGFR/ErbB) is sufficient for potentiating GC-induced apoptosis of multiple myeloma cells. Inhibition of these growth factor receptors was associated with alteration in Akt and ERK activities.

Vice versa, prolonged exposure to GCs may lead to inactivation of ERK due to upregulation of Dual specificity phosphatase-1 (DUSP-1)/Mitogen-activated phosphatase-1 (MKP1). This may be one mechanism by which GCs control osteoblast proliferation and induce growth arrest in certain solid cancers. Thus, a mutual antagonism prevails between GCs and the pro-survival ERK. Besides ERK, MKP1 inactivates p38 and JNK which may account for the immunosuppressive effects of GCs. Also, GC-induced chemoresistance is associated with the induction of MKP1 as well as of serum and glucocorticoid-inducible protein kinase-1 (SGK1). Inhibition of MKP1 restores paclitaxel (Taxol)-induced apoptosis in GC-protected cancer cells. The chemoprotective effect of GCs may be explained by the requirement for JNK in mediating paclitaxel-induced apoptosis. Also, SGK1 antagonizes JNK signaling by inactivating stress-signaling kinase SEK1/MKK4, which acts upstream to JNK. In contrast to the antagonistic effects of MKP1 on chemotherapy-induced apoptosis, MKP1 had no effect on GC-induced apoptosis. Thymocytes from MKP1 knockout mice were as sensitive to GC-induced apoptosis as the respective unmodified cells. On the other hand, the ability of GCs to affect MAPK activities through DUSP/MKP is regulated by the cellular kinome. For instance, a positive cross-talk exists between the PI3K/Akt/mTOR and MEK/ERK pathways through mTOR-mediated phosphorylation and degradation of DUSP6. This cross-talk may explain the prevention of GC-induced downregulation of MAPK and p70 ribosomal S6 kinase (p70S6K) activities by IL-6 in multiple myeloma cells.

PKB/Akt is frequently activated in Notch1-expressing T-acute lymphoblastic leukemia (T-ALL) and various lymphomas. Overexpression of intracellular active Notch1 (ICN-Notch1) in 2B4 T cells leads to GC-resistance through activation of Akt and induction of McI-1 expression. Also, the overexpression of an active Akt in 2B4 T cells induces Mcl-1 expression and blocks Dex-induced apoptosis. Akt inhibits apoptosis through several mechanisms. Among others, Akt phosphorylates and inactivates the pro-apoptotic Bad protein and the transcription factor FoxO3 essential for transcriptional induction of Bim. Akt further antagonizes GC-induced apoptosis by inhibiting Glycogen synthase kinase 3 (GSK3), a kinase essential for promoting this cell death process. Inhibition of Akt or its upstream regulator PI3K overcomes GC-resistance in follicular lymphoma, thymic lymphoma cells and multiple myeloma cells. Arsenic trioxide sensitizes T-ALL cells to GC-induced apoptosis through inhibition of Akt.

An upstream activator of Akt is the Src tyrosine kinase. GC treatment has been shown to lead to the release of Src from...
Hsp90 complexes,\(^62,63\) which may contribute to cell survival rather than cell death.\(^{17,59}\) Inhibition of Src may sensitize resistant lymphoid cells to GC-induced apoptosis.\(^{17,59}\) Intriguingly, the highly GC-sensitive PD1.6 thymic lymphoma cells exhibit high Csk activity (unpublished data), which antagonizes Src-dependent signaling pathways. These observations suggest that Csk may modulate the sensitivity of the cell to GC-induced apoptosis. In the A549 lung epithelial cell line, Src mediates the rapid GR-dependent phosphorylation of Caveolin.\(^64\) GR and Src were co-localized to Caveolin-containing membrane fractions.\(^64\) Caveolin-1 phosphorylation is required for activation of the Akt/mTOR survival pathways.\(^64\) The Src kinases Fyn and Lck were similarly shown to dissociate from T cell receptor (TCR)/Hsp90 complexes upon GC treatment, leading to the disruption of TCR-dependent signals with consequent depression of T cell function.\(^{65}\) Regulation of Src activity seems thus to be a nodal point in controlling the cell's susceptibility to GC-induced apoptosis.

Activation of mTOR downstream to Akt is believed to have a major contribution to GC-resistance, as rapamycin, a mTOR inhibitor, could sensitize resistant T-ALL and multiple myeloma cells to GC-induced apoptosis.\(^{66-68}\) Inhibition of mTOR by rapamycin in ALK-positive anaplastic large cell lymphoma cells leads to down-regulation of Mcl-1 and Bcl-2,\(^69\) suggesting that the expression of these anti-apoptotic proteins are regulated by the Akt/mTOR pathway. This is supported by the observation that Akt overexpression induces Mcl-1 expression in 2B4 T cells.\(^60\) mTOR also regulates apoptosis by phosphorylating p70S6K and 4E-BP1 translational repressor required for cap-dependent translation of cell cycle proteins. When cap-dependent translation was prevented by transfection with a mutant 4E-BP1 construct that can not be phosphorylated by mTOR, multiple myeloma cells responded to GCs with enhanced apoptosis.\(^60\) Rapamycin also prevents the translation of several anti-apoptotic proteins, such as XIAP, CIAP1, Hsp27, and BAG-3.\(^68\) Interestingly GCs can antagonize the mTOR pathway through upregulation of Dig2/REDD1, a repressor of the mTORC1 complex.\(^70\) This mutual antagonism may explain why prolonged GC exposure may ultimately lead to apoptosis of T-ALL cells harboring active mTOR. Thus, mTOR activation leads to delayed GC response, but does not confer complete GC resistance. Similar observation has been made for Bcl-2-overexpressing T lymphoid cells, which shows delayed apoptosis rather than a complete GC resistance phenotype.\(^71\) Also, Notch1 expressing cells show delayed apoptotic response, suggesting that prolonged GC exposure may overcome Notch1-induced GC resistance.\(^71\) This can be reconciled by the observation that Notch1 requires Akt to be functional active.\(^72\) Thus, GCs may in the long term overcome some kinds of GC resistance through slow-acting antagonistic pressure on survival kinases. The additions of drugs that antagonize the resistant mechanisms are expected to accelerate the apoptotic process, and are of clinical importance for improving GC therapy.

GC resistance of several leukemia cell lines can be overcome by increasing the intracellular levels of cAMP.\(^73\) PKA activation can lead to potent inhibition of Akt/PKB\(^74,75\) and reduction in Mcl-1 expression.\(^74\) The potentiation of GC-induced apoptosis by cAMP was recently shown to be mediated by the PKA RIIb isoform,\(^74\) and cAMP analogs that selectively activate type II PKA (e.g., forskolin), promote apoptosis and antagonize Akt/PKB activity in CCRF-CEM T-ALL cells.\(^74\) Down-regulation of RIIb leads to increased Akt/PKB activation and enhanced GC resistance in CCRF-CEM cells.\(^74\) One mechanism by which cAMP inhibits Akt is through preventing PDK1 translocation to the plasma membrane.\(^76\) PDK1 activates PKB/Akt, p70S6K and SGK. Increase in intracellular cAMP leads to the induction of the pro-apoptotic Bim,\(^77\) inhibition of the Hedgehog (Hh) pathway,\(^78\) reduction in c-Myc expression level,\(^73\) inhibition of JNK\(^66,68\) and activation of p38 MAPK.\(^79\) These versatile effects of cAMP modulate the cellular kinome in a way that facilitates GCs to transmit the pro-apoptotic signals.

JNK inhibition is as effective as Akt/mTOR inhibition in sensitizing resistant CCRF-CEM T-ALL and S49 T lymphoma cells to GC-induced apoptosis.\(^17,66\) This observation suggests that there is a cross-talk between Akt and JNK. Indeed, the mTOR inhibitor rapamycin leads to a concomitant inhibition of JNK\(^66,80\) suggesting that JNK is regulated by mTOR. Also, JNK has been shown to regulate Akt.\(^81\) Akt is inactivated by interaction with the JNK-interacting protein JIP1. Phosphorylation of JIP1 by JNK leads to the dissociation of Akt from JIP1, thereby restoring Akt1 activity.\(^81\) The JNK pathway plays a dual role in regulating cell survival and apoptosis depending on the cell type and the cellular context.\(^82\) While in some settings JNK-mediated phosphorylation of Bim increases its pro-apoptotic function,\(^83,84\) in T-ALL cells the same phosphorylation promotes degradation of Bim.\(^85\) JNK may further prevent apoptosis by phosphorylating the pro-apoptotic Bad protein, leading to its inactivation.\(^86\) The antagonistic effect of JNK on GC-induced apoptosis is compatible with data showing that c-Jun and JNK are required for survival of T cells\(^87\) and transformed B lymphoblasts.\(^88\) JNK may also reduce GR transcriptional activity through phosphorylating GR at Ser246.\(^89\) This phosphorylation of GR facilitates subsequent GR sumoylation at Lys297 and Lys313, which further deactivates GR.\(^89\) JNK also impairs the nuclear translocation of GR\(^90\) and promotes its nuclear export.\(^91\) Vice versa, GCs may antagonize JNK by upregulating MKP1,\(^92\) and through direct interaction of GR with JNK.\(^93\) Thus, a mutual antagonism prevails between JNK and GR that may explain the delayed apoptotic response to GCs in JNK-positive lymphoid malignancies.

In contrast to the above-described protein kinases that antagonize GC-induced apoptosis, MAP kinase p38 activation was shown to be essential for GC-induced apoptosis of partially resistant S49 T lymphoma and CCRF-CEM T-ALL cells.\(^13,17,94,95\) However, p38 activation was not required for GC-induced apoptosis of the highly sensitive thymocytes or CD4+8+ PD1.6 thymic lymphoma cells,\(^17\) or the intermediate sensitive multiple myeloma cells or eosinophils.\(^57,96,97\) p38 inhibition even improves the response of multiple myeloma cells to GCs.\(^98\) The latter may be explained by the finding that p38 may phosphorylate GSK3 at its C-terminus, leading to its inactivation.\(^79\) The cell-type specific effect of p38 inhibition on GC-induced apoptosis, suggests that p38 is specifically required for overcoming GC resistance in S49 and CCRF-CEM cells. These cells are characterized by elevated levels...
of intracellular active Notch1 and high basal Bcl-2 expression.\textsuperscript{1,17} p38 activity was required for Bim upregulation in these cells,\textsuperscript{13} which may be related to the positive effect of p38 on FoxO3 nuclear translocation.\textsuperscript{100} p38 may further promote apoptosis by phosphorylating Bim and Bcl-2. Whereas p38-mediated Bim phosphorylation enhances its pro-apoptotic effect,\textsuperscript{101} the phosphorylation of Bcl-2 leads to its inactivation.\textsuperscript{102} p38 phosphorylation and Bim expression are innately high in PD1.6 thymic lymphoma cells,\textsuperscript{17} which may explain why p38 inhibition did not affect GC-induced apoptosis in these cells. Interestingly, in neutrophils GCs induce survival through PI3K- and p38-dependent upregulation of Mcl-1.\textsuperscript{103} Thus, the p38 signaling may exert opposite effects depending on the cell type.

Another protein kinase proposed to positively regulate GC-induced apoptosis is the Related adhesion focal tyrosine kinase RAFTK/Pyk2.\textsuperscript{104} RAFTK is activated by increases in intracellular calcium levels. GC-induced apoptosis in multiple myeloma cells is associated with activation of RAFTK.\textsuperscript{104} Overexpression of wild-type RAFTK induced apoptosis, whereas overexpression of a kinase-inactive RAFTK blocked GC-induced apoptosis in both multiple myeloma cells\textsuperscript{104} and osteocytes.\textsuperscript{24} On the other hand, activation of the RAFTK-related Focal adhesion kinase (FAK) prevents GC-induced apoptosis of osteocytes.\textsuperscript{24} IL-6 protects multiple myeloma cells against GCs by inducing Shp2 phosphatase that negatively regulates RAFTK.\textsuperscript{105} Overexpression of a dominant negative Shp2 blocked the protective effect of IL-6 against GC-induced apoptosis.\textsuperscript{105} Shp2 is highly expressed in complete GC-resistant NB4 promyelocytic leukemia cells\textsuperscript{17} and primary leukemia samples.\textsuperscript{106} Shp2 can be downregulated upon retinoic acid-induced differentiation of myelogenic leukemia.\textsuperscript{106} It is thus inquiring to study whether retinoic acid pretreatment of myelogenic leukemia would alter the cell’s susceptibility to GCs. A recent study using various GR mutants showed that GC-induced apoptosis in multiple myeloma cells may also proceed through a RAFTK-independent pathway.\textsuperscript{107}

We recently observed that GSK3\textgreekalpha controls a central role in promoting GC-induced apoptosis.\textsuperscript{17} GSK3\textgreekalpha was found to be associated with GR in the absence of ligand, but becomes immediately released upon ligand binding. Inhibition of GSK3\textgreekalpha activity prevented the apoptotic process in all lymphoid cell lines tested, suggesting that GSK3\textgreekalpha is important for propagating the pro-apoptotic signals. Further studies showed that the released GSK3\textgreekalpha interacts with Bim,\textsuperscript{17} which is an essential upstream mediator of the intrinsic apoptotic pathway. A further look at the mechanisms leading to GC-resistance reveals a common denominator that converges on GSK3 inhibition. For instance, Akt inhibits GSK3\textgreekalpha/\textgreekbeta by phosphorylating Ser21 and Ser9, respectively.\textsuperscript{108} ERK interacts with and phosphorylates GSK3\textgreekbeta at Thr43, which primes it for subsequent phosphorylation at Ser9 by p90\textgreekRsk, resulting in its inactivation.\textsuperscript{109} Src and JNK indirectly activate Akt with consequent inhibition of GSK3.

Similarly to RAFTK, GSK3 is activated by elevations in intracellular calcium concentration.\textsuperscript{108} Intriguingly, RAFTK/Pyk2 may phosphorylate and activate GSK3,\textsuperscript{110} suggesting that the RAFTK activation seen in GC-treated multiple myeloma cells\textsuperscript{104} may be important for activating the GSK3\textgreekalpha released from GR after GC exposure.\textsuperscript{17} GC-induced ceramide production in the mitochondria\textsuperscript{111} may also activate GSK3 through phosphatase 2A (PP2A)-mediated dephosphorylation of GSK3\textgreekbeta.\textsuperscript{112} As mitochondrial translocation of GR occurs in sensitive, but not in resistant, lymphoma cells,\textsuperscript{31} it is likely that the rapid elevation of GR in the mitochondria is responsible for the GC-induced mitochondrial production of ceramide and reactive oxygen species (ROS), as well as the transient calcium mobilization. As these non-genomic effects of GCs are important for full GSK3 activation, I propose a model were mitochondrial GR cooperates with GSK3 in promoting GC-induced apoptosis (Fig. 1).

In a search for a drug that may overcome GC-resistance, we found that subtoxic concentrations of the broad-acting kinase inhibitor staurosporine sensitize several GC-resistant lymphoma cell lines to GCs.\textsuperscript{3} Staurosporine has a broader spectrum of cells that could be sensitized to GCs than rapamycin (unpublished data), indicating that staurosporine does not only prevent the Akt/mTOR pathway. In this study, Kfir et al.\textsuperscript{3} shed light on the mechanisms by which staurosporine overcomes GC-resistance. Staurosporine was shown to act at multiple levels. It did not affect
GR expression level and had only a minor effect on mitochondrial GR translocation. However, staurosporine had a profound effect on Bim expression. Staurosporine induced ERK-dependent phosphorylation of Bim. This modification of Bim resulted in elevated Bim level in lymphoma cells responding to staurosporine sensitization, while leading to a reduction in Bim expression in myelogenic leukemia cells that are resistant to even the combined treatment of staurosporine and GCs. Moreover, Kfir et al. observed that staurosporine may overcome GC-resistance caused by Bcl-2, Bcl-XL, and/or Notch1. One mechanism is the elevation in GSK3 activity by staurosporine due to inhibition of Akt/PKB. GSK3 phosphorylates Notch1 and downregulates its activity. In addition, staurosporine leads to the induction of the orphan receptor Nur77 that may prompt apoptosis also in the presence of Bcl-2. Even Nur77 may convert the anti-apoptotic Bcl-2 into a pro-apoptotic molecule. Dominant negative Nur77 abolished staurosporine sensitization to the apoptotic effects of GCs, indicating that the concomitant presence of Nur77 signaling cooperates with GCs in triggering apoptosis of otherwise GC-resistant cells. The staurosporine sensitization to GC-mediated apoptosis was cell-type specific. The drug couldn't overcome GC-resistance in myelogenic leukemia cells, excluding a general cytotoxic effect of staurosporine. In these cells, GCs reduce GR expression that can not be prevented by staurosporine, and staurosporine enhances the degradation of Bim. Both effects enforce the GR-resistant phenotype. In addition, the myelogenic leukemia cells showed elevated ERK activity, that antagonizes GSK3 required for this apoptotic process. The specific sensitization effect of staurosporine on GC-induced apoptosis in lymphoid malignancies makes its clinical analogs 7-hydroxystaurosporine (UCN-01) and 4'-N-benzoyl-staurosporine (PKC412) potential drugs in improving GC therapy of these cancerous cells. It should be noted that the sensitization is achieved at low concentrations of staurosporine, which would enable the use of non-toxic staurosporine dosages in combination with GCs.

In this perspective, I have tried to present data showing the complexity of the kinase network that determine the susceptibility of hematopoietic malignancies to GC-induced apoptosis. The concept has turned from a simple model where GR acts as a transcription factor that modulates gene expression, into a complex model where GR-binding to GR leads to the activation of GSK3, p38 and RAFTK that promote apoptosis, and to the release of Src together with the induction of SGK1 that favor cell survival (Fig. 1). In addition, activated GR induces the transcription of MKP1 that inactivates MAPKs, thereby inhibiting cell growth as well as preventing apoptosis induced by chemotherapeutic drugs. Some of these GC-mediated effects are cell-type specific, and the balance between the activation of pro-apoptotic versus pro-survival kinases are detrimental for the cell fate. The cellular outcome is also determined by factors affecting GR and Bim expression. GC resistance is usually caused by elevated activities of JNK, Src, PI3K, Akt, mTOR and/or ERK, which ultimately leads to the inhibition of GSK3, prevention of Bim expression and upregulation of anti-apoptotic proteins of the Bcl-2 family. Early intervention of these resistance mechanisms would accelerate the apoptotic response to GCs, and would be important to prevent secondary resistance, which is frequently caused by downregulation of GR due to prolonged exposure to GCs.

Acknowledgements
This work was supported by The Israel Cancer Research Fund, The Israel Cancer Association and The Concern Foundation. I want to thank Prof. Eitan Yefenof for have letting me studying this interesting cell death process in his laboratory.

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