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Review

Latest perspectives on glucocorticoid-induced apoptosis and resistance in lymphoid malignancies

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ABSTRACT

Glucocorticoids are essential drugs in the treatment protocols of lymphoid malignancies. These steroidal hormones trigger apoptosis of the malignant cells by binding to the glucocorticoid receptor (GR), which is a member of the nuclear receptor superfamily. Long term glucocorticoid treatment is limited by two major problems: the development of glucocorticoid-related side effects, which hampers patient quality of life, and the emergence of glucocorticoid resistance, which is a gradual process that is inevitable in many patients. This emphasizes the need to reevaluate and optimize the widespread use of glucocorticoids in lymphoid malignancies. To achieve this goal, a deep understanding of the mechanisms governing glucocorticoid responsiveness is required, yet, a recent comprehensive overview is currently lacking. In this review, we examine how glucocorticoids mediate apoptosis by detailing GR's genomic and non-genomic action mechanisms in lymphoid malignancies. We continue with a discussion of the glucocorticoid-related problems and how these are intertwined with one another. We further zoom in on glucocorticoid resistance by critically analyzing the plethora of proposed mechanisms and highlighting therapeutic opportunities that emerge from these studies. In conclusion, early detection of glucocorticoid resistance in patients remains an important challenge as this would result in a timelier treatment reorientation and reduced glucocorticoid-instigated side effects.

1. Introduction

Synthetic glucocorticoids (GCs), such as dexamethasone and prednisone, are an integral part of the treatment of multiple myeloma (MM), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL)[1,2]. GCs are steroidal hormones exerting pro-apoptotic and anti-proliferative actions on lymphoid malignant cells[1,3–5]by binding to the glucocorticoid receptor (GR), a transcription factor of the nuclear receptor superfamily[6]. In the absence of ligand, GR is predominantly localized in the cytoplasm and part of a multiprotein complex that includes chaperones (e.g. Hsp90) and immunophilins (e.g. FK506-binding protein 51, FKBP51), which help maturing the receptor into a high-affinity state for GC binding[7,8]. Upon GC stimulation, GR undergoes a conformational change together with a reshuffling of the multiprotein complex to mediate GR translocation into the nucleus[9]. Following translocation, GC-bound GR exerts genomic mechanisms including both GR-mediated activation of target genes (e.g. GILZ) and GR-mediated repression of transcription factor-driven (e.g. NF-κB, AP-1) gene expression (e.g. IL-6) [10]. The plethora of mechanisms by which GR mediates these genomic actions where extensively reviewed elsewhere [11,12]. Two of many possible mechanisms are the binding of GR homodimers to glucocorticoid response elements (GRE) on the DNA of target genes (gene activation) [13] and GR monomer binding to a DNA-bound transcription factor without contacting DNA itself (tethering, gene repression) [14].

Besides the genomic mechanisms, which typically take place over the course of hours, GCs also rely on fast (seconds, minutes) non-genomic mechanisms to trigger the apoptotic cascade. The latter mechanisms, independent of transcription, may include cytosolic GR that translocates into mitochondria, interactions of GCs with a membrane-bound GR, GR-independent actions of GCs on e.g. cellular membranes and interaction of cytosolic GR with signaling pathway molecules[15,16,4]. Nevertheless, GR can also use its transcriptional activity to modulate downstream effects in

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signaling pathways.

In this review, we will give an extensive overview of the currently known mechanisms governing GC-mediated apoptosis and present the major problems associated with prolonged GC treatment, being the GC-related side effects and the emergence of GC resistance. Despite the plethora of studies that have been undertaken to resolve the underlying mechanisms governing GC resistance, all patients receiving long-term GC treatment are still becoming GC resistant over time. In this review, we therefore also summarize a wealth of data on GC resistance mechanisms in lymphoid malignancies and link them to novel treatment strategies that should emerge from these insights.

2. GC-induced apoptosis in lymphoid malignancies

Although the mechanisms underlying GC-induced apoptosis remain incompletely resolved to this day, it was established that GCs rely primarily on the intrinsic mitochondrial apoptotic pathway for their lympholytic actions, rather than on the extrinsic apoptotic pathway[4,17–21]. Briefly, the intrinsic pathway is activated by external stimuli (e.g. GCs, toxins, radiation) and is characterized by the disruption of the mitochondrial membrane, mediated by pro-apoptotic Bcl-2 family members. This results in the release of cytochrome C and apoptotic peptidase-activating factor 1 (Apaf-1) from the mitochondria, thereby activating the initiator caspase 9 and the formation of the apoptosome[22–24]. The extrinsic pathway, however, involves extrinsic ligands (e.g. FasL, TRAIL) that stimulate membrane-bound death receptors of the TNF superfamily, leading to the formation of the death-induced signaling complex (DISC) and the activation of the initiator caspase 8[22–24]. Both pathways converge at the execution stage, characterized by the activation of executioner or effector caspases (3, 6 and 7). The latter caspases activate endonucleases, which degrade chromosomal DNA and cause chromatin condensation, and proteases, to degrade nuclear and cytoskeletal proteins, ultimately leading to disruption of the cytoskeleton, cell shrinkage and disintegration of the cell into apoptotic bodies[22,24]. Finally, phosphatidylserines, which are normally present on the inner plasma membrane, will externalize on the surface of apoptotic cells, which facilitates phagocytic uptake. GCs rely both on their genomic and non-genomic action mechanisms as well as on crosstalk with signaling pathway molecules to induce apoptotic cell death (Fig. 1), which are discussed in the following sections. Although a plethora of studies are centered around mitochondrial apoptosis, we will also briefly discuss the involvement of autophagy and necroptosis[25]in GC-induced cell killing as mechanisms that are increasingly gaining attention. Note that we refer to MM cell lines as MM cells, while studies or experiments with primary cells are explicitly mentioned as such. We apologize to all authors whose work we could not include due to space constraints.

2.1. Genomic mechanisms of GC-induced apoptosis

GR-mediated gene activationis essential for the initiation of GC-induced apoptosis, as the latter was blocked in the presence of actinomycin D and cycloheximide, thereby showing the need for *de novo* transcription and translation[19]. The expression of the pro-apoptotic Bcl2 family member Bim was upregulated by GCs in both MM, ALL, CLL and lymphoma cell lines and in primary CLL and ALL patient samples[26–33], although there was no GRE in the promoter of the Bim gene[34,35]. Rather, GCs were shown to upregulate the expression of the transcription factor (TF) FOXO3a, which in turn induces the expression of Bim[36,37]. In addition, a role for the TFs Runx2 and c-Jun in Bim transcription was suggested, as Bim expression and subsequent apoptosis of ALL cells were decreased in cells harboring dysfunctional c-Jun and in cells in which Runx2 was knocked down[30]. As another indirect mechanism, GC treatment upregulated miR-103 expression in GC-sensitive ALL cells, which reduced c-myc expression, in turn decreasing the miR-18a and miR-20a levels and ultimately leading to elevated GR and Bim expression, respectively[38]. Still, in support of GR as a direct regulator, Jing *et al.* reported a novel GR binding site in an intronic region of the Bim gene. Hereto, GR was only recruited in the GC-sensitive ALL patient-derived xenografts (PDX) [29].

To trigger apoptosis, Bim needs to be activated via phosphorylation, which is mediated by GSK3 via non-genomic mechanisms (seesection 2.2). Activated Bim promotes oligomerization of the pro-apoptotic Bax and Bak proteins, either through direct interaction or by inhibiting the association between Bak and the anti-apoptotic Bcl-2 protein by downregulation of Bcl-2 (Fig. 1,Table 1) [39,40]. Yet, GC-induced apoptosis in primary CLL cells was shown to result from increased association between Bim and Bcl-2, leading to activation of Bax and Bak, rather than from a direct interaction of Bim with Bax and Bak[32]. Bax/Bak oligomers are essential for inducing mitochondrial permeability through the formation of a mitochondrial pore that enables the release of cytochrome C and Smac/DIABLO, which in turn triggers apoptosis [39,41]. In 2016, Smac mimetics were found to be effective against different ALL subtypes, and their addition to conventional therapies including Dex improved the *in vivo* efficacy of the latter[42,43].

The direct GR target gene GILZ, which harbors 6 GRE elements in its promoter[44], is also involved in GC-mediated apoptosis [2,19,45–47]. Transgenic mice overexpressing GILZ in the T-cell lineage, showed a reduced number of double positive thymocytes [47]. Moreover, primary thymocytes from these GILZ transgenic mice showed augmented apoptosis, which was due to reduced levels of anti-apoptotic Bcl-XL and increased caspase 8 and 3 activation[47]. In primary mouse spleen T cells and thymocytes, GILZ was also shown to directly interact with Ras, thereby forming a trimeric complex that also includes Raf [45]. In this way, GILZ diminished Ras/Raf signaling and thus decreased the activation of downstream ERK1/2 and Akt signaling, and of retinoblastoma (Rb) phosphorylation and cyclin D1 gene transcription, together supporting the anti-proliferative actions of GILZ[45]. Furthermore, GILZ overexpression in neutrophil-like cells enhanced apoptosis by increasing caspase 3, 9 and 8 activation, by decreasing the mitochondrial membrane potential and by inducing phosphorylation and subsequent proteasomal degradation of the anti-apoptotic protein Mcl-1[48]. GILZ expression was also increased by GCs in MM cell lines and primary MM cells, while GILZ knockdown decreased GC-induced apoptosis in MM cells[46]. Moreover, the combination of PI3K/Akt inhibitors and GCs augmented GILZ expression levels and enhanced MM cell apoptosis[46]. Kervoëlen *et al.* further showed that GR expression is crucial for GC-induced apoptosis in (primary) MM cells and that GR and GILZ levels are strongly correlated[49]. Silencing GILZ in MM cells strongly attenuated Dex-induced apoptosis and impaired Bim upregulation and blocked Bcl-XL downregulation[49].

In addition to Bim and GILZ, several other GC-responsive genes were linked to GC-mediated cell killing. These comprise amongst others the suppressor of AP-1 regulated by interferon (SARI)[50], the redox-regulating tumor suppressor thioredoxin-interacting protein (TXNIP)[51,52], the tumor suppressor zinc finger and BTB domain containing 16 (ZBTB16)[52], the pro-apoptotic Noxa[53], the pro-apoptotic Bcl-2 modifying factor (Bmf)[54], the serine protease granzyme A[55,56]and the G-protein coupled receptor T cell death-associated gene 8 (TDAG8)[57]. Besides direct (immediately regulated) GR target genes, a plethora of late GC responsive genes have been identified to contribute to GC-induced cell killing[58].

GR-mediated gene repressioncan also contribute to GC-induced cell death (Fig. 1). Indeed, GCs inhibit TF-driven (e.g. NF-κB,

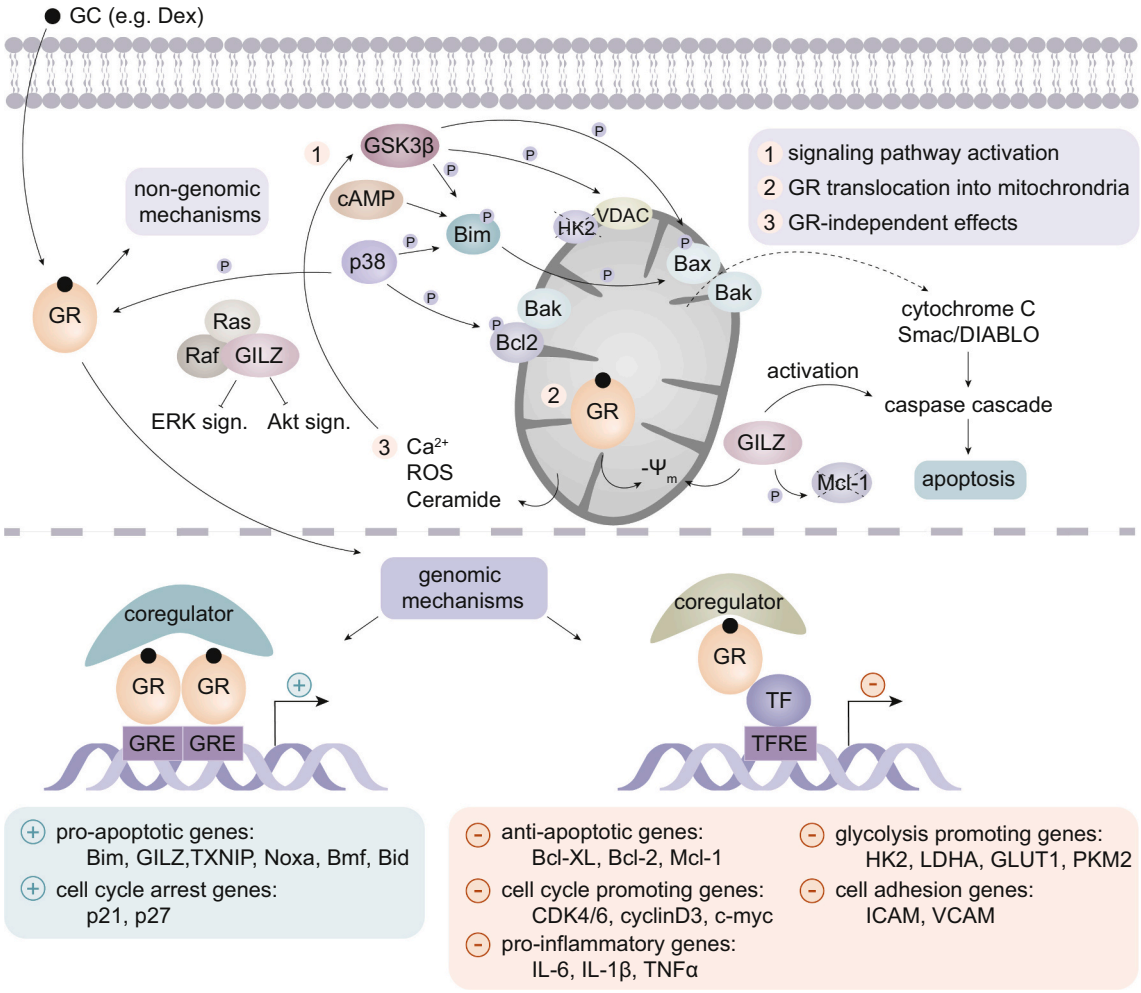

Fig. 1. Mechanisms of GC-induced apoptosis in lymphoid malignancies. Upon GC treatment, GR becomes activated, undergoes a conformational change and translocates to the nucleus to fulfill the genomic mechanisms. On the one hand, GC-activated GR can promote the transcription of pro-apoptotic genes (e.g. Bim, GILZ) and genes involved in G1-S cell cycle arrest (e.g. p27). On its turn, GILZ can form a cytosolic trimeric complex with the Ras and Raf oncogenes, herby blocking ERK1/2 and Akt signaling. GILZ also promotes the phosphorylation of anti-apoptotic Mcl-1, which triggers its proteasomal degradation, and contributes to a lowering of the mitochondrial membrane potential and activation of the caspase cascade. On the other hand, GR can inhibit transcription factor (TF)-driven (NF-κB, AP-1) gene expression of survival (e.g. Bcl-XL) and cell cycle promoting genes (e.g. cyclin D3), pro-inflammatory genes (e.g. IL-6), glycolysis genes (e.g. LDHA) and cell adhesion molecules (e.g. ICAM). GC-bound GR modulating signaling pathways also contributes to cell killing and is mediated amongst others by p38, cAMP and GSK3. GR can activate p38, which in turn can phosphorylate GR at Ser 211. p38 also stimulates the activitation of Bim and inhibits Bcl-2 via phosphorylation. cAMP and GSK3β both upregulate Bim expression, while GSK3β can also promote Bim activation. In turn, activated Bim promotes heterodimerization of Bax and Bak and inhibits interaction of Bak with Bcl-2. GSK3β can also phosphorylate VDAC, which disturbs its interaction with hexokinase 2 (HK2), and phosphorylate Bax, which leads to its activation. Non-genomic mechanisms include e.g. translocation of GR into mitochondria. Ensuing, mitochondrial GR can decrease the mitochondrial membrane potential. Together, these signals induce the release of cytochrome C and Smac/DIABLO from the mitochondria, triggering the caspase cascade which ultimately results in apoptosis of the cell.

Table 1
Bcl-2 family members and their action mechanism.

Action	Mechanism	Members
Pro-apoptotic[40,210]	Executioners; oligomerize and permeabilize the mitochondrial outer membrane by pore formation	Bax, Bak
	Activators; bind executioners and stimulate their activation	Bim, Bid, Puma
	Sensitizers; bind to anti-apoptotic proteins by sequestration hereby inactivating them	Bad, Noxa, Bmf
Anti-apoptotic[40,210]	Inhibit the activator and executioner pro-apoptotic proteins by sequestration	Bcl-2, Bcl-XL, Mcl-1

AP-1, c-myc) gene expression of anti-apoptotic genes, cell cycle promoting genes, pro-inflammatory cytokines, glycolysis promoting genes and adhesion molecules to mediate GC-induced apoptosis [2,17,18,59]. For instance, GCs can interfere with the expression of TNFα, IL-1β, IL-6, MCP-1, ICAM, VCAM, which are also implicated in MM pathology, as they all contain NF-κB and/or AP-1 binding sites [60,61]. Therefore, it is conceivable that GCs not only target the malignant myeloma cells, but also affect the stromal cells by interfering with the activation of pro-survival signaling pathways in bone marrow stromal cells (BMSCs) and with the adhesion of MM cells to BMSCs and the extracellular matrix. Although studies directly supporting this hypothesis are largely lacking, Salem and coworkers demonstrated that the combination of Dex and Bortezomib enhanced MM cell killing in the presence of

BMSCs and that the ionizing radiation-induced IL-6 secretion of BMSCs was inhibited [62]. Mechanistically, in MM cells, Bortezomib induced IκBα breakdown, but this was overruled by the Dex-mediated increase in IκBα protein levels, resulting in inhibition of NF-κB activity and cell killing of even Bortezomib-resistant MM cells [62].

Concerning anti-apoptotic proteins, GC treatment was shown to decrease Bcl-2 and Bcl-XL levels in 17 and 16 out of 28 ALL patients, respectively[63]. In extension, Makert *et al.* demonstrated that combined treatment of Dex with Venetoclax, a Bcl-2 inhibitor in phase I trials for MM, strongly enhanced cell death in MM cell lines and MM patient samples[64]. In line herewith, the group of Rosen identified that Bcl-XL and ribonucleotide reductase 2 (RRM2), an essential protein in nucleic acid production, DNA replication and repair, were repressed by GCs in GC-sensitive MM1.S cells[65]. In absence of treatment, knockdown of either Bcl-XL or RRM2 increased cell death in both GC-sensitive MM1.S and GC-resistant MM1.R cells, suggesting that both proteins are necessary for cell survival[65].

GCs mediate G1 arrest by decreasing the expression of c-myc, cyclin-dependent kinase 4 (CDK4), CDK6, cyclin D3 and by inducing the CDKi p21 and p27[66,67]. Kullmann and coworkers corroborated that Dex-induced cell cycle arrest resulted from p27 upregulation and cyclin D3 downregulation and preceded apoptosis in CEM ALL and murine lymphoma cells[68]. Mechanistically, Dex only modestly elevated p27 mRNA levels, yet, increased the half-life of p27, which explained the high protein levels of p27 upon Dex treatment[68]. Dex also decreased the mRNA and protein levels of Skp2, the negative regulator of p27[68]. Furthermore, in GC-sensitive ALL cells, miR-103 was upregulated and reduced the expression of CDK2 and its cyclin E1 target, hereby halting cell proliferation[38].

GCs also decrease the expression of several glycolytic genes as a mechanism that contributes to GC-induced apoptosis[69–72]. In ALL cells, GCs blocked glucose consumption, utilization and uptake, the latter by decreasing the levels of the glucose transporter GLUT1. This lead to inhibition of glycolysis, which in turn stimulated GC-induced cell death of ALL cell lines and primary ALL cells [69]. ALL cells cultured in low glucose medium were also more susceptible to GC-induced apoptosis, indicating that glucose levels may influence this process[69]. GCs were also demonstrated to decrease the expression of the glycolytic enzyme hexokinase 2 (HK2) in ALL cells[71]. This mechanism prevents HK2 binding to the mitochondrial voltage dependent anion channel (VDAC), which destabilizes the mitochondrial membrane potential and promotes apoptosis[73]. In CLL cells, GCs also decreased the levels of pyruvate by diminishing the expression and activity of the glycolytic enzyme pyruvate kinase M2 (PKM2)[70]. GCs also inhibited the anaerobic sequence of glycolysis in CEM ALL cells by decreasing the production of lactate[71]. The conversion of pyruvate to lactate by lactate dehydrogenase (LDHA) represents the final step of glycolysis under anaerobic circumstances and serves to proceed with glycolysis and ATP generation, also when mitochondrial activities decline. GCs inhibit this back-up cell survival step by reducing the mRNA levels of the glycolytic enzymes LDHA[71].

2.2. Non-genomic mechanisms of GC-induced apoptosis

GR-independent actions.GCs promote K^+efflux in thymocytes and T-ALL CEM cells[19]. K^+efflux was linked to apoptosis in lymphoma cells as this resulted in increased DNA fragmentation and caspase 3 activation[74]. GCs also elevate cytosolic Ca^{2+}concentrations in thymocytes, lymphoma cells and B lymphoblasts[19], giving rise to the activation of calmodulin (Ca^{2+}binding protein), which was reported to mediate DNA fragmentation and thus contributes to GC-induced apoptosis[75,76]. GCs also induce the production of reactive oxygen species (ROS) and thereby create oxidative stress[2,19]. For instance, in the absence of oxygen, Dex-induced apoptosis is inhibited in immature mouse thymocytes[77]. In analogy herewith, also in breast cancer cells, the levels of ROS and reactive nitrogen species (RNS) were increased upon cortisol treatment to induce DNA damage[78]. GC treatment of thymocytes also drives increased production of ceramide via a mechanism that involves protein kinase C[18,79], and inhibition of ceramide production was shown to inhibit GC-induced apoptosis[79]. Together, Ca^{2+}mobilization and the production of ROS and ceramide, which all originate from the mitochondria, may lead to the activation of GSK3[2], a key cytoplasmic protein in GC-mediated apoptosis (Fig. 1)[31,33,80].

Mitochondrial GR(mitoGR) may be responsible for mediating the mitochondrial effects of GCs[2,81], such as Ca^{2+}mobilization, ROS and ceramide production[82], as a putative mitochondrial localization signal (MLS) was identified in the N-terminal part of the GR ligand binding domain (LBD)[83]. Sionov *et al.* further proposed that heat-shock proteins assist in the translocation of GR into mitochondria[83], as the GR MLS overlaps with one of the Hsp90 binding sites and as the mitochondrial import receptor Tom70 interacts with Hsp70 and Hsp90 at the outer mitochondrial membrane[84,85]. Mitochondrial translocation of GR was further shown to depend on the cell type and GC responsiveness of the cells. In GC-sensitive thymoma cells, GR translocated to both the nucleus and the mitochondria following Dex treatment, while their GC-resistant counterparts displayed only nuclear translocation of GR upon Dex treatment[83]. Moreover, selective overexpression of mitoGR in lymphoma cells is enough to instigate apoptosis[83], yet, in an endogenous context GR translocation into mitochondria is necessary but not sufficient for GC-induced apoptosis to occur [4]. In double positive thymocytes, translocation of GR into mitochondria decreases the mitochondrial membrane potential, which results in the release of cytochrome C and Smac/DIABLO from the mitochondria, in turn fueling the apoptotic cascade[86]. Dex treatment of thymocytes from 4-week old mice resulted in Bax accumulation in mitochondria and association of mitochondrial GR with Bak, Bim and Bcl-XL. In line, elevated cytochrome C release and increased caspase 3, 8 and 9 activity were monitored in Dex-treated thymocytes[87].

2.3. GR crosstalk with signaling pathways drives GC-induced apoptosis

Crosstalk between GR and the kinome plays a prominent role in GC-induced apoptosis. Modulation of downstream effects in signaling pathways is either accomplished by cytosolic GR that directly interacts with signaling molecules (e.g. GSK3α, via non-genomic actions) or requires GR transcription regulatory activity. Because the outcome of both mechanisms is the modulation of signaling pathways, they are gathered under the same umbrella.

Burwick *et al.*, for instance, identified that Dex treatment increased the phosphorylation of eIF2α in MM1.S cells, which inhibited translation initiation [88]. Pharmacological induction of eIF2α phosphorylation using BTdCPU further induced cell death in Dex-responsive and Dex-resistant MM cell lines and primary MM cells. Even co-cultures of Dex-sensitive or Dex-resistant MM cell lines with BM stromal or endothelial cells were not able to protect the MM cells from a killing by BTdCPU [88].

Combined stimulation of GR and cAMP signaling induced more pronounced Bim expression in GC-sensitive and GC-resistant ALL cell lines. Pro-apoptotic Bad was also considerably more induced by this combination in GC-sensitive and -resistant MM cell lines, but not in GC-sensitive or -resistant ALL cells lines[89]. In line herewith, the cAMP analog, 8-CPT-cAMP increased Bim expression and enhanced GC-mediated apoptosis in GC-sensitive CEM-C7-14

and GC-resistant CEM-C1-15 ALL cell lines[28]. The cAMP-inducer forskolin in combination with Dex also synergistically enhanced cell killing of (primary) MM cells, an effect that was mediated by increased Bim levels[90].

GCs were also found to trigger p38 phosphorylation in ALL and lymphoma cells, which resulted in stimulation of GC-induced apoptosis (Fig. 1)[91]. In turn, p38-induced phosphorylation of GR Ser211 was at least in part responsible for promoting apoptosis, as mutation of Ser to Ala strongly reduced GR transcriptional activity and apoptosis[91]. Besides GR Ser211 phosphorylation, p38 further stimulates GC-induced apoptosis by additional indirect mechanisms. Indeed, p38 activation can also positively contribute to apoptosis by activation of Bim extra-long (Bim-EL), 1 out of 3 Bim isoforms, via phosphorylation of Ser65[92], or by inducing Ser87 and Thr56 phosphorylation of Bcl-2, which resulted in decreased anti-apoptotic potential of the latter[93]. Moreover, p38 activation was also reported to be necessary for Foxo activation and subsequent induction of Bim transcription[94]. Interestingly, in a lymphoma cell line, the GR and PR antagonist RU486 increased p38 and JNK phosphorylation, yet, only p38 activation was associated with RU486-induced apoptosis[95].

GSK3 was also identified as a crucial factor for mediating GC-induced apoptosis in thymocytes, lymphoma cells, ALL and MM cells, as a specific GSK3 inhibitor strongly attenuated GC-induced apoptosis in these cells[80]. GSK3 is a serine and threonine kinase that is expressed as 2 isoforms, GSK3α and GSK3β, and regulates many substrates (e.g. glycogen synthase, c-myc, cyclin D1) and TFs (e.g. NF-κB, NFAT, STATs) [2,96]. GSK3α and GSK3β can be inhibited by phosphorylation of Ser21 and Ser9, respectively, mediated amongst others by Akt, SGK1, PKC and PKA [2], while GC treatment decreased Ser9 phosphorylation as a means to keep GSK3β active [80]. Moreover, in absence of GC, GSK3α is bound to GR, while it is released from GR upon GC treatment, which concurred with GR Ser211 phosphorylation, although a GSK3 inhibitor did not affect GR Ser211 phosphorylation [80]. Once released, GSK3α and also GSK3β can interact with Bim in thymocytes and T cells, possibly leading to its activation (Fig. 1) [80]. In addition, GSK3 inhibition was shown to inhibit GC-induced Bim expression in lymphoma and CLL cells [31,33]. Besides activation and upregulation of Bim, GSK3 was also suggested to stimulate apoptosis by phosphorylation of Bax [97] and VDAC [73]. In steep contrast, depending on the cellular context, GSK3 was also shown to promote cell proliferation and survival both in lymphoid malignancies and solid cancers [98–100].

2.4. How do autophagy and necroptosis modulate GC-induced cell death?

Autophagy is a dynamic process in which damaged cellular contents (e.g. organelles, misfolded proteins) are encapsulated into autophagosomes for subsequent fusion with lysosomes, resulting in cargo degradation by lysosomal enzymes[101]. In ALL cells, Dex was shown to trigger autophagy, which preceded apoptosis[102]. Inhibition of autophagy by knockdown of Beclin1 even blocked Dex-mediated apoptosis in ALL cells[102], demonstrating the interconnection between autophagy and Dex-induced cell killing. In contrast, others demonstrated that pharmacological inhibition of autophagy sensitized GC-resistant lymphoma cell lines towards Dex-induced cell killing, hereby identifying autophagy as a contributing mechanism to GC resistance[103]. These studies illustrate that the role of autophagy in GC-mediated cell killing is ambiguous and needs further mechanistic clarifications.

Necroptosis, a form of programmed necrosis[104], was also linked to GC-induced cell killing. Indeed, the Bcl-2 antagonist obatoclax sensitized multidrug-resistant childhood ALL cells to GCs by activation of autophagy-dependent necroptosis, which was explained by reduced association of Beclin1 with anti-apoptotic Mcl-1 and reduced mTOR activity[105]. Dex combined with the mTOR inhibitor rapamycin mediated autophagy-dependent cell killing that was accompanied by expression of the necroptosis markers receptor-interacting protein (RIP-1) kinase and cylindromatosis[105]. Combining Dex with the Smac mimetic BV6 also triggered necroptosis in ALL cells in which caspase activation is blocked. Prior to cell death, this combination treatment triggered a drop in the mitochondrial membrane potential, ROS production and Bak activation[106]. Remarkably, upon knockdown of RIP-3 or MLKL, both critical proteins for necroptosis, ALL cells were protected against the above-mentioned Dex/BV6-induced mitochondrial events[106], showing that mitochondrial dysfunction may fuel necroptosis.

3. Major problems associated with prolonged GC treatment

Despite that GCs are effective mediators of lymphoid malignant cell apoptosis, prolonged GC treatment is hampered by two main problems (Fig. 2): 1) detrimental GC-mediated side effects and 2) the emergence of GC resistance. Indeed, over time the desired therapeutic effects are dampened and patients transition towards full-blown GC resistance, which is currently inevitable in many patients receiving long-term GC treatment. Paradoxically, the phenomenon of patient's malignant cells becoming resistant to GC-mediated cell killing, is not mirrored by a disappearance of the GC-related side effects. Remarkably, side effects instigated by GCs persist, confirming that GC resistance is a highly tissue-specific event[107]. In the following sections, we will briefly describe the GC-related side effects before scrutinizing the mechanisms governing GC resistance in lymphoid malignancies.

3.1. Side effects

The first major problems associated with prolonged GC treatment are the GC-associated side effects, which drastically hamper patient quality of life. These include osteoporosis, skin thinning/striae, muscle atrophy, hyperglycemia exacerbating to diabetes mellitus, disturbed wound healing, psychological disturbances (anxiety, irritability, severe mood swings, depression), hypertension, increased risk of infections, suppression of the HPA-axis, cardiovascular complications including hypertension, weight gain, abnormal fat redistribution, glaucoma, cataract, peptic ulcers and growth retardation in children[11,12,108,109]. The time of occurrence and severity of the side effects is different between individuals (Fig. 2) and is dependent on the dose, duration, the type of GC (different potencies) and the route of administration [108,109]. Mechanistically, the GC-related side effects were generally considered to arise from GR-mediated gene activation, although this is an oversimplified model. Nevertheless, while several GC-related side effects do associate with GR-mediated gene activation, e.g. diabetes and hypertension, others are solely the result of GR-mediated gene repression, e.g. HPA suppression and increased risk of infections, or even attributed to both GR gene activation and repression, e.g. osteoporosis[109–111]. An extensive overview of the mechanisms underlying the many GC-related side effects is beyond the scope of this review, hence, we will only describe the molecular basis of diabetes, osteoporosis and muscle wasting as these are prominent in e.g. multiple myeloma.

3.1.1. GC-induced hyperglycemia and diabetes

Hyperglycemia is a recognized side effect in ALL patients treated with GCs. In children with ALL, the complications associated with hyperglycemia are increased susceptibility to bacterial, viral and fungal infections[112]. Prolonged GC therapy can induce hyperglycemia in patients, which can evolve to diabetes mellitus,

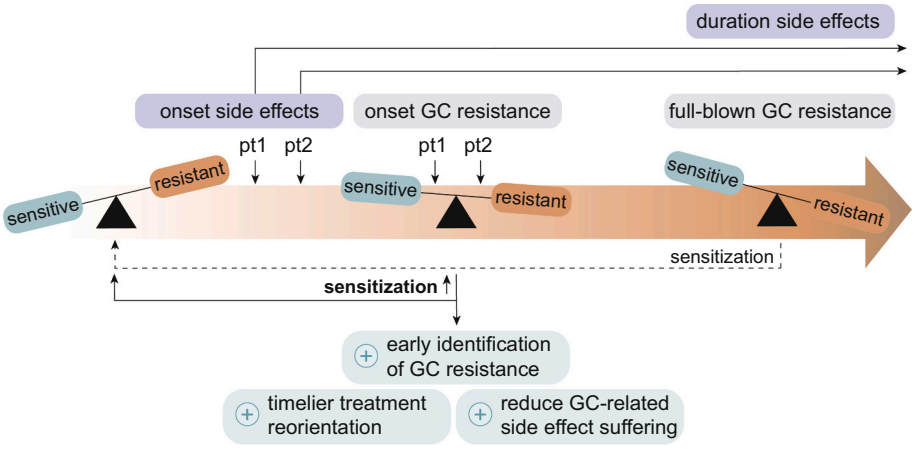

Fig. 2. Prolonged GC treatment results in side effects and GC resistance. Long-term GC treatment leads to a gradual decrease in GC responsiveness. After a while, the balance that dictates GC responsiveness starts to tip to a more GC resistant phenotype. This moment is defined as the onset of GC resistance, of which the exact time point strongly differs between patients (pt). Characterizing this intermediate phase offers the advantage of a timelier identification of when a patient is becoming GC resistant. In turn, this would enable a faster reorientation of a patient's treatment protocol and would reduce the suffering of the GC-instigated side effects. Sensitization of the cells towards GC responsiveness is likely more easily achieved at this onset stage compared to cells that have progressed to full-blown GC resistance, where the balance has completely tipped over to resistance. Moreover, GC-related side effects typically emerge early on, with interpatient variability in both the onset time and the severity of the side effects. Of note, even though the cells have become resistant to GC-induced apoptosis, side effects may persist, which argues for the tissue-specificity of GC resistance.

or can complicate maintenance of glycemic control in diabetic patients[110]. Indeed, high GC levels give rise to decreased glucose uptake in muscle and adipose tissue, to reduced pancreatic β-cell insulin production and diminish the effectiveness of insulin to limit glucose production in the liver (insulin resistance) [110,113–115]. Moreover, GCs promote gluconeogenesis in the liver by GC-induced upregulation of enzymes involved in this process, including tyrosine aminotransferase (TAT), glucose-6-phosphatase (G6P) and phosphoenolpyruvate carboxykinase (PEPCK). GC-instigated glucose production is then followed by increased glycogen storage in the liver, driven by GC-mediated activation of glycogen synthase [110,113]. Together, these GR gene activation-steered mechanisms lead to a deregulated carbohydrate metabolism.

3.1.2. GC-induced osteoporosis

GCs also exert adverse effects on bone, more specifically, bone formation is decreased by suppression of osteoblast proliferation and activity and bone resorption is increased by activation of osteoclasts[110,116,117]. Remarkably, GC-induced osteoporosis was identified as the most common type of secondary osteoporosis [116]and is linked to a high risk of bone fractures[110]. In a group of approximately 300 childhood ALL patients, a high incidence of osteonecrosis (10%) was found during GC therapy, which was significantly associated with polymorphisms in the gene coding for pro-apoptotic Bim[118].

Mechanistically, both GR-mediated gene activation and gene repression are involved in GC-induced osteoporosis. On the one hand, GCs stimulate the expression of RANKL, which promotes osteoclast differentiation and activity, and inhibits osteoclast apoptosis[117]. In addition, the expression of OPG, the soluble decoy receptor for RANKL which prevents its binding to RANK on osteoclasts, is inhibited by GCs via GR-mediated gene repression [110,116]. The effects of GCs on bone are comparable to the bone disease that is observed in MM[119], and both result in an increased RANKL/OPG ratio, which contributes to osteoporosis. GCs also increase osteoclast activity by decreasing gastrointestinal Ca^{2+}absorption and increasing urinary Ca^{2+}excretion, which triggers osteoclast-mediated bone resorption[110,117].

On the other hand, GCs suppress bone formation by triggering apoptosis of osteoblasts and osteocytes, by inhibiting growth factors (e.g. IGF-1, TGFβ) that are important in bone homeostasis, and by HPA suppression of adrenal sex hormones [110,117]. Besides their action on osteoclasts and osteoblasts, GCs also reduce the expression of bone-forming ECM proteins, including osteocalcin and collagen type I [109,110,120], the latter by promoting the synthesis of interstitial collagenase [121].

3.1.3. GC-induced muscle wasting

Excess GCs fulfill catabolic effects on skeletal muscle by stimulating proteolysis and amino acid export, and by inhibiting protein synthesis. Moreover, GCs block glucose uptake and glycogen synthesis in muscle[122]. It was demonstrated that GCs inhibit the IGF-1/insulin/PI3K/Akt signaling pathway to decrease glucose uptake, glycogen synthesis and protein synthesis in muscle[115,122,123]. In addition, studies suggest that GC-induced skeletal muscle proteolysis occurs via proteasomal degradation, more specifically, via the E3 ubiquitin ligases atrogin-1 and MuRF-1. The expression of both atrogin-1 and MuRF-1 is suppressed by Akt and stimulated by FOXO TFs and GCs are thought to indirectly affect the expression of these E3 ligases by inactivation of Akt and by upregulation of FOXO TFs[122,124,125]. GCs can also increase the expression of myostatin, a muscle growth inhibitor[126]. *In vivo* studies in skeletal muscle showed that myostatin not only inhibits protein synthesis but is also able to increase the expression of atrogenin-1 and MuRF-1[127,128]. In line herewith, GC-mediated muscle wasting did not occur in mice lacking myostatin or MuRF1[129].

3.2. GC resistance

In the context of lymphoid malignancies, GC insensitivity or resistance can be defined as the inability of malignant cells to undergo apoptosis in response to GC treatment[130], and represents the second major GC-related problem. In general, GC resistance can be caused by mutations and polymorphisms or can be acquired during treatment[131].

GR gene mutations are rarely *de novo* and are often induced by other treatments (e.g. chemotherapy) during the disease course [130,132]. A 2016 analysis of 31 relapsed ETS variant TF 6 (ETV6)/RUNX1 positive ALL samples showed that deletions in the GR gene (NR3C1) were linked to a subsequent relapse and occurred more frequently in poor responders to relapse treatment[133]. In a MM patient with multi-drug (including GCs) refractory extramedullary disease, Egan and coworkers identified a point mutation in GR (G369A) which was associated with drug resistance[134], yet, GR mutations were not reported in other MM genomes[135–137]. Although earlier studies showed that GC resistance in patient samples was generally not caused by GR gene mutations[138–140], a study from 2020 in ALL may shift this view. In a group of 103 patients with relapsed ALL, including 87 patients with B-ALL and 16 with T-ALL, 12 genes displayed relapse-specific alterations among which GR and the closely related mineralocorticoid receptor (MR). The overall prevalence of these gene mutations was 17% in very

early relapse, 65% in early relapse and 32% in late relapse[141]. Remarkably, relapse-specific GR mutations were mainly located in the DNA-binding domain (DBD) (3/7 mutations) and the N-terminal domain (NTD) (3/7 mutations) and almost completely abolished GR transcriptional activity, whilst the sole mutation in the LBD reduced GR's activity by half[141].

Besides GR gene mutations, inter-individual differences in GC sensitivity in the general population are partly attributed to **polymorphisms** in the GR gene[142]. Several single nucleotide polymorphisms (SNPs) in the GR gene are associated with either increased or decreased GC sensitivity and are present in at least 1% of the population[132,143,144]. For instance, the ER22/23EK polymorphism consists of two linked single nucleotide Arg(R) to Lys(K) mutations in codons 22 and 23 of exon 2, and was linked to decreased GC sensitivity[145]. Interestingly, ER22/23EK carriers show a favorable metabolic profile, exemplified by increased insulin sensitivity and lower cholesterol levels, and an improved cardiovascular profile, as shown by decreased C-reactive protein (CRP) levels[142,145,146]. This polymorphism was shown to result in decreased GR transactivation in PBMCs from ER22/23EK carriers that were treated with Dex[147], which was mechanistically explained by increased levels of the transcriptionally less active GRα-A isoform compared to the GRα-B isoform [148]. In contrast, the N363S polymorphism, which is present in codon 363 of exon 2 of the GR gene, is linked to increased GC sensitivity, but also to elevated body mass index and coronary heart disease and decreased bone mineral density [149]. Molecularly, N363S was linked to increased transcriptional activation upon Dex treatment [147], and it was suggested that the asparagine (N) to serine (S) substitution might contribute to improved GR coregulator interactions [142]. Other polymorphisms in the GR gene include Bcl*I*, which is also linked to increased GC sensitivity, and the allele A3669G, which is associated with increased stability of GRβ mRNA and elevated GRβ protein expression [142,150]. The Bcl*I* GR variant was reported in adult ALL patients, yet, was not found to be associated with GC responsiveness [151]. In another study, the presence of the Bcl*I* GR polymorphism in ALL patients was rather linked to more frequent GC-related side effects [152]. In addition, a GR SNP analysis (N363S, ER22/23EK, Bcl*I*) in a cohort with 346 ALL patients showed that none of the patients with a N363S, ER22/23EK or Bcl*I* SNP displayed a poor response to prednisone [153]. A study from 2018 addressed the problem that data in the past years on the relevance of GR SNPs in the GC sensitivity of ALL appear inconclusive [154], which can be partly due to differences in the type of synthetic GCs and the cell types (cell lines vs PBMCs) that were used in these studies. The same authors also identified an additional GR promoter region SNP (rs72555796, in the 5′ flanking region of exon 1A), which was markedly associated with prednisolone and Dex responsiveness [154].

Polymorphisms in genes that encode 11β-hydroxysteroid dehydrogenases (11β-HSDs), enzymes known to be involved in (in) activating GCs (see also acquired GC resistance), were also identified to regulate the intracellular availability of endogenous and certain synthetic GCs [155]. Also FKBP5 gene polymorphisms were described and were associated with differential FKBP5 upregulation upon GR activation and a subsequent altered GC responsiveness [156]. Alleles linked to increased FKBP5 expression following GR activation were described to evoke GC resistance, presumably by FKBP5-mediated inhibition of GR activation and translocation, and reduced the negative feedback of the HPA axis in healthy individuals [156]. Mulligan *et al.* further identified in tumor samples of relapsed MM patients that NRAS mutations (affecting N-Ras, a protein that regulates cell division) decreased the response rates to bortezomib, yet, not the responsiveness to high-dose Dex [157]. However, the group of Meijerink discovered in 2016 that a mutation in any of the genes of the IL-7 receptor (IL-7R) signaling pathway, including IL-7R, JAK1, JAK3, NF1, NRAS, KRAS and Akt, are associated with GC resistance and poor outcome in T-ALL patients [158]. Along the same lines involving changed kinase activities, in GC-resistant B-ALL the receptor tyrosine kinase FLT3 was shown to be constitutively activated because of a point mutation and an internal tandem duplication in FTL3, which was absent in the corresponding GC-sensitive clones [159]. Gradual GC resistance was thus shown to select for cells with a distinct oncogenic genetic background [159].

Acquired GC resistance emerges over time because the underlying disease process finds mechanisms to evade GC-induced apoptosis[160]. The mechanisms underpinning acquired GC resistance are nevertheless divergent and often cell-type specific[19], which contributes to the heterogeneity in GC responsiveness observed in patients (Fig. 2)[161,162]. Several mechanisms focus on GR itself and include decreased affinity of GR for GCs, decreased GR levels due to a negative feedback loop of GR, altered GR post-translational modifications (PTMs) and impaired GR translocation, and altered expression of the transcriptional and translational isoforms[3,19,107,130,160,163,164]. Other mechanisms that contribute to GC resistance involve inhibitory cross-modulation of TFs (e.g. NF-κB), decreased GC availability, altered expression of co-regulators, increased levels of GR (co)chaperones or immunophilins (e.g. Hsp90, FKBP5), signaling pathway interactions, a disturbed balance between pro- and anti-apoptotic proteins, metabolic changes, epigenetic changes and the BM microenvironment that confers resistance to therapy [2,20,130,160,164–166]. These mechanisms will be further discussed in-depth in the following sections and are summarized in Table 2.

3.2.1. Decreased GR levels

Although GR auto-induction upon GC treatment, via a GRE in the GR promoter, was linked to sensitivity towards apoptosis in ALL cells[19,130,167], Tissing and colleagues showed that this GC-induced GR upregulation occurred regardless of the GC sensitivity or resistance of the primary ALL patient samples[168]. Instead, a negative feedback loop of GCs and GR, which serves as *the* ubiquitous safety mechanism to prevent GC overstimulation in normal cells, is a more likely contributing mechanism to induce GC resistance over time in malignant cells[19,130]. Emphasizing its relevance, this negative feedback loop of GR can be mediated by several mechanisms, including reduced GR transcription via transcriptional initiation inhibition[150], diminished GR mRNA stability due to the presence of AU-rich elements (AREs) in the 3′UTR of the GR mRNA, and decreased GR protein stability due to targeting of GR for proteasomal degradation[19,131]. The mechanism behind transcriptional initiation inhibition involved a long-range interaction between GC-bound GR recruited to a nGRE in exon 6 of the GR gene and a GR-NCOR1-HDAC3 repression complex at the transcription start site, explaining how a constitutive GR gene repression upon prolonged GC treatment may contribute to GC resistance[150]. In line herewith, Sanchez-Vega *et al.* demonstrated in three MM cell lines, of which two parallel the emergence of GC resistance (MM1.S, MM1.RE, MM1.RL), a gradual decrease in GR mRNA levels. This mRNA decline is caused by a block in transcriptional elongation, which impaired recruitment of RNA pol II on exon 3 in the resistant variant[169].

Concerning GR activity in GC resistance, Bachmann *et al.* showed using a primary ALL xenograft mouse model that GC-resistant tumors harbor functional GR that still translocates to the nucleus, binds to GREs and induces GILZ mRNA expression upon GC treatment[139]. In contrast, prolonged Dex treatment of T-ALL-bearing mice was inseparably connected with the emergence of a GC-resistant subpopulation, of which approximately 30% displayed decreased GR protein levels[170]. A comparable proportion of human relapsed T-ALLs also showed markedly lower GR levels

Table 2
Mechanisms of GC resistance in lymphoid malignancies

Factor	Mechanism	Refs
GC availability	Increased expression levels of multidrug efflux pumps, resulting in export of GCs out of the cell	[164,177,178]
	Elevated 11β-HSD2/11β-HSD1 ratio and thus diminished GC activity	[179,180]
Affinity	Decreased affinity of GR for GCs	[20,140,176]
GR chaperones	Altered levels of Hsp90, Hsp70, FKBP51/2	[182–184]
GR levels	Auto-induction hampered	[168]
	Negative feedback loop of GR	[19,130,131,150,169–171]
	GR mutations and polymorphisms	[133,134,141,153,154]
GR PTMs	Impaired GR translocation, decreased GR stability, reduced GR transcriptional activity	[53,186–189]
GR isoforms	Altered expression levels of transcriptional or translational GR isoforms, giving rise to reduced transcriptional activity or decreased potential to induce apoptosis	[151,154,190–195,197–199]
Coregulators	Qualitative and quantitative differences in coregulators, altered availability of coregulators, giving rise to altered transcriptional activity of GR	[150,208,209]
Crosstalk with TFs	Increased levels and/or activity of pro-survival and pro-inflammatory TFs that inhibit GR's repressive action	[201,203–206]
Apoptotic proteins	Disturbed balance between pro- and anti- apoptotic proteins	[29,32,53,139,211–213]
Pathway interactions	Crosstalk with signaling pathways leading to apoptosis inhibition, e.g. increased ERK, JNK, PI3K/Akt, mTOR, CDK4, CDK6, JAK/STAT3, LCK signaling pathway activation	[26,41,46,158,214,215,217–220,222–228]
Metabolism	Deregulated metabolism that supports survival, e.g. increased glycolysis, FA oxidation and oxidative phosphorylation	[70,99,138,229–231]
Epigenetics	Aberrant miRNA expression levels which promote decreased GR levels and survival	[244–247,247,247–250]
	Altered DNA methylation and HMT activity	[234–237,239]
	Altered HDAC expression	[240,241]
Microenvironment	Soluble factor-mediated drug resistance	[254–256]
	Cell adhesion-mediated drug resistance	[257–260]

as well as an attenuated transcriptional response following Dex treatment[170]. In line herewith, GR expression in ALL cells positively correlated with GC sensitivity and clinical outcome, while vice versa, deletion of GR was associated with GC resistance, both in ALL cell lines and xenografts[171]. Heuck and colleagues further showed that at baseline, low GR expression levels further negatively impacted progression-free survival (PFS) and overall survival (OS) in myeloma patients, and that post-relapse survival was negatively affected by low GR expression[172]. This is in agreement with an *in vitro* study where a screening of approximately 9500 compounds against a GC-resistant T-ALL cell line was performed and which resulted in the discovery of compound J9[173], which was able to restore GC sensitivity in these cells by upregulation of GR[173]. In contrast, the sensitizing effect of compound J9 could not be demonstrated in a panel of Dex-resistant and Dex-sensitive ALL xenografts[174].

Together these studies indicate that it is important not to fall below a certain threshold level of GR, yet, that this factor is insufficient to reliably predict GC responsiveness. GR also needs to be transcriptionally active and even this might, at a certain time during disease progression, fall short of inducing an efficient GC-mediated apoptosis in lymphoid malignant cells. GR auto-induction, as observed in ALL, may be regarded as a positive feedback loop to support GR signaling, however, current literature suggests that this does not necessarily correlate with GC responsiveness of the cells towards cell killing and has not been reported in all lymphoid malignancies. Vice versa, the negative feedback loop of GR in, for instance, multiple myeloma cells also occurs regardless of whether the cells are susceptible to GC-mediated cell killing. Although the negative feedback loop entails a general mechanism to protect all body cells from overstimulation with (endogenous) GCs, it may be possible that certain lymphoid malignancies have been reprogrammed to have a constitutive negative feedback loop of GR.

3.2.2. Decreased affinity of GR for GCs, decreased GC availability and altered chaperone levels

GC resistance in patient-derived samples appears not widely associated with drastic mutations in the GR gene itself [139,140,175], yet, one report demonstrates that the Δ702 GR LBD mutant, which is one of the only *in vivo* confirmed acquired mutations, displayed decreased affinity for binding GCs in cells from a GC-resistant ALL patient [20,140]. Another example of this principle is in the context of asthma, as few reports in lymphoid malignancies focus on the affinity of GR for GCs. IL-2 and IL-4 treatment of PBMCs, isolated from patients with GC-resistant asthma, was shown to reduce GR's binding affinity for GCs [176].

GCs can passively diffuse across the cell membrane, however, evidence from murine T-lymphoma cells suggests that the expression of the P-glycoprotein MDR1, a multidrug efflux pomp and a member of the ATP-binding cassette (ABC) family of transporters, is increased. As such, GCs can be transported out of the cell, as such contributing to GC resistance[164,177]. In MM cell lines, MDR1 was also shown to be responsible for mediating drug resistance to GCs and natural products[178]. Beesley *et al.* further found that upregulation of the multidrug transporter ABCC9 was associated with both methylprednisone and Dex resistance in T-ALL cell lines[138].

Intracellular GC availability and activity is further regulated by 11β-HSDs [155]. Although this mainly holds true for endogenous cortisol/cortisone and not for synthetic Dex, also synthetic prednisone (inactive) and prednisolone (active) are interconverted by these enzymes [179]. Sai and colleagues reported that Dex even elevated 11β-HSD1 (GC-activating) mRNA levels in GC-sensitive ALL cells, which were diminished by Dex in GC-resistant ALL cells [180]. These authors further showed that the 11β-HSD2 (GC-inactivating) levels were higher in GC-resistant ALL cells than in GC-sensitive ALL cells [179], exemplifying the potential involvement of 11β-HSDs in GC resistance. In a 2020 follow-up study in ALL patient samples (n=37), decreased 11β-HSD1 and/or increased 11β-HSD2 expression levels were found to be associated with GC resistance at diagnosis [181]. This suggests that 11β-HSDs levels may be useful predicators of GC responsiveness, yet, studies in larger patient groups are warranted.

The proteins of the GR chaperone complex play vital roles in GR maturation, ligand binding affinity and nuclear translocation. Hence, theoretically speaking, alterations in the expression levels of the different chaperones may also indirectly contribute to GC resistance[107,130,155,164]. Out of 9 leukemic GC-resistant cell lines only 2 exhibited aberrant Hsp90 levels and very low Hsp70

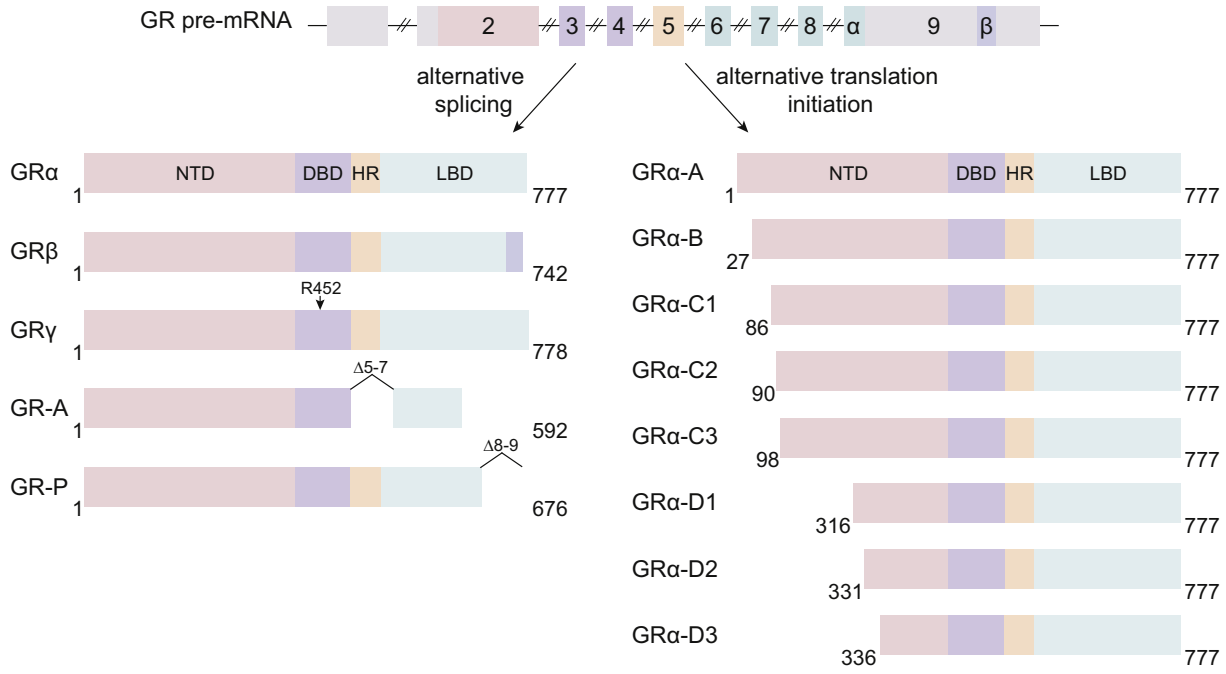

Fig. 3. Transcriptional and translational GR isoforms. Alternative splicing of the GR pre-mRNA results in 5 transcriptional isoforms: GRα, GRβ, GRγ, GR-A, GR-P. Alternative translation initiation of GRα gives rise to an additional eight translational isoforms, GRα-A, GRα-B, GRα-C1/C2/C3, GRα-D1/D2/D3 that differ in their NTD. NTD, N-terminal domain; DBD, DNA-binding domain; HR, hinge region; LBD: ligand-binding domain.

levels[182]. In another study lack of association between Hsp90 expression and GC resistance was confirmed in patient-derived ALL samples[183]. In line with these findings, Tissing *et al.* studied the levels of different GR (co)chaperones in ALL patient samples, including among others Hsp70, Hsp90, FKBP51, FKBP52 and p23, and found no significant differences in chaperone levels between *in vitro* GC-sensitive or GC-resistant ALL patients[184]. Regardless of their GR chaperoning function, Hsp70 and Hsp90 inhibitors harbor anti-myeloma activity as both proteins are survival factors in MM by acting as chaperones in the unfolded protein response and were also shown to confer resistance to Bortezomib[185].

3.2.3. Altered GR PTMs and impaired GR translocation

GR PTMs influence different aspects of GR action, including subcellular localization, GR stability and transcriptional activity, and hereby represent likely mediators of GC resistance. As a negative feedback loop of GR is implicated in decreased GC responsiveness (seesection 3.2.1)[19,131], GC-induced GR ubiquitination, which targets GR for proteasomal degradation[186], is equally likely involved in GC resistance. In addition, in a study from 2020, the ubiquitin ligase RNF6 was demonstrated to induce atypical K63-linked polyubiquitination of GR in myeloma cells[187]. Instead of hampering GR functionality, this modification unexpectedly promoted GR's transcriptional activity and increased, unexpectedly, the expression levels of the anti-apoptotic genes Bcl-XL and Mcl-1. In extension, RNF6 overexpression promoted MM cell survival and induced resistance to GC-induced MM cell killing [187].

Concerning phosphorylation, Lynch and coworkers showed that GR Ser211 phosphorylation is predominant in GC-sensitive CEM-C7-14 ALL cells, while GR Ser226 phosphorylation, mediated by JNK and which enhances nuclear export of GR[188], is more frequent in GC-resistant CEM-C1-15 ALL cells[53]. In intrinsically GC-resistant primary CLL cells, elevated phosphorylation of inhibitory GR Ser226 residues were observed compared to GR Ser211 sites[189]. Yet, Ibrutinib, a bruton's tyrosine kinase inhibitor, sensitized these circulating CLL cells to Dex-induced apoptosis, increased GILZ expression and GR Ser211 phosphorylation and inhibited GR Ser226 phosphorylation. Nevertheless, besides Ibrutinib, additional JAK inhibition was necessary to obtain the aforementioned effects when studied in presence of the microenvironment[189].

3.2.4. Altered expression of GR isoforms

Alternative splicing of GR precursor mRNA generates 5 transcriptional isoforms: GRα, GRβ, GRγ, GR-A and GR-P (Fig. 3), which differ in their transcriptional activity [132], hence, altered expression levels of GR isoforms may play a role in GC resistance. A study from 2018 with over 70 B-cell precursor ALL cell lines established from patients examined the contribution of the 5 GR splicing variants to GC-induced apoptosis and pinpointed GRα as the most crucial GR isoform [154]. Nevertheless, elevated levels of the dominant-negative GRβ isoform were reported in several lymphoid malignancies [19,132,190]. Low GRβ/GRα were even shown to correlate with prednisolone-induced apoptosis in patient-derived ALL cells [191]. However, controversy remains regarding the functional consequences of elevated GRβ levels [19,132], as several other studies could not find a correlation between GRβ levels and GC resistance in primary ALL samples [190,192]. In contrast, elevated GRγ levels did correlate with GC resistance in ALL samples [190,193]. In the myeloma context, of all transcriptional GR isoform levels determined in GC-sensitive, early and late GC-resistant MM cells GRβ was the least expressed isoform throughout and GRγ was only detectable in the sensitive and early resistant cells [194]. GR-P was found to be the predominant isoform in the late resistant MM cells and GR-A was only detectable in the early resistant MM cells [194]. In contrast, GR-P expression did not correlate with GC resistance in primary ALL cells [192]. In 2015, two studies tried to correlate the levels of the GR transcriptional isoforms with the ALL disease stage. Sun and coworkers showed that initially GRα/GRγ and GRα/GR-P levels were higher than upon relapse and complete remission, whereas GRγ/GR-P levels were higher in complete remission than initially and upon relapse [195], yet, no relapse-specific GR isoform was designated by these authors. Bedewy *et al.*

further reported in ALL patient samples that GRα expression was associated with complete remission, while GC-resistant patients and non-responders showed higher GRγ expression [151].

Alternative translation initiation from GRα mRNA gives rise to additional translational isoforms of which the N-terminal domains differ in length (Fig. 3). These include GRα-A, GRα-B, GRα-C1/C2/C3 and GRα-D1/D2/D3 [196], which were shown to have divergent abilities to mediate GC-induced apoptosis in different cell line models [197,198]. For instance, Wu and co-workers found that Dex could not induce apoptosis in Jurkat ALL cells that exclusively expressed the GRα-D isoforms [198]. In contrast to the other translational isoforms, GRα-D was also unable to repress the anti-apoptotic Bcl-XL, cIAP1 and survivin, and could not inhibit NF-κB activity, exemplifying that GRα-D can contribute to the resistance of cells towards GC-induced apoptosis [199]. Further studies in primary cells seem needed to resolve the role of the translational isoforms in GC responsiveness.

3.2.5. Altered GR transcriptional activity and coregulator levels

Although GR inhibits transcription driven by TFs such as NF-κB and AP-1, the latter TFs can in turn repress GR-mediated gene expression [200]. Therefore, enhanced NF-κB and AP-1 expression may play a role in GC resistance by promoting the transcription of cytokines, survival genes and adhesion molecules [107,163,164]. For instance, it was demonstrated that NF-κB protected MM cells against Dex-mediated cell death by expression of IL-6 [201]. Concerning AP-1, logic programming, based on regulatory networks and the gene expression profiles of 602 MM patients and 9 healthy controls, revealed low activity of the AP-1 heterodimer Jun/Fos in almost all MM patients compared to controls and identified low FOXM1 activity in a subgroup of MM patients, which was associated with a trend of longer OS [202]. The group of Demonacos even identified Ets related gene (Erg) and AP-1 as markers for GC responsiveness in ALL cell lines, as GC treatment decreased activated c-Jun (phospho-c-Jun) in GC-sensitive cells and elevated Erg levels in GC-resistant cells [203]. In the same study, combined Dex and Erg inhibition also stimulated apoptosis in GC-sensitive and GC-resistant ALL cells, while Dex and JNK inhibition only enhanced apoptosis in GC-sensitive ALL cells [203]. In addition, Fan *et al.* showed that JunB, another AP-1 family member, was rapidly induced when MM cells were co-cultured with BM stromal cells. Knockdown of JunB not only inhibited MM cell proliferation and survival, but also reestablished Dex sensitivity in Dex-resistant MM cells [204].

Small molecule inhibitors that target eukaryotic initiation factor 4 (eIF4) halted cell survival and Dex resistance in MM cell lines and primary MM cells by decreasing c-myc and Mcl-1 pro-survival factors[205]. In 2020, an integrated bioinformatics analysis revealed c-myc as *the* core gene in the protein-protein interaction network that was resolved to characterize GC resistance in ALL [206], making c-myc inhibitors potential therapeutic strategies to combat ALL[207].

Concerning coregulators, the corepressor NCOR1 was mentioned before to be part of a transcriptional repression complex that blocks GR gene expression, as an indirect contributory mechanism to GC resistance upon prolonged GC treatment[150]. Complementary herewith, in an ALL cell line, knockdown of a protein involved in the stabilization of nuclear hormone repressor complexes, TBL1XR1, resulted in decreased GR chromatin recruitment by increased levels of NCOR1 and HDAC3[208]. Comparison of the endogenous GR coregulator profiles of GC-sensitive to -resistant ALL cell lines using coregulator peptide arrays showed that GC resistance in the CEM-C1-15 cells is partially mediated by quantitative differences in the GR coregulator profile rather than qualitative differences[209].

3.2.6. Disturbed balance and interaction between pro- and anti-apoptotic proteins

As GC-induced apoptosis is largely driven by stimulation of pro-apoptotic and inhibition of anti-apoptotic Bcl-2 family proteins (Table 1), a deregulation of these Bcl-2 family rheostats can lead to GC resistance[19,40,164,165,210]. A systematic analysis of the GC regulation of the Bcl-2 family members in ALL patient samples, revealed that triggering pro-apoptotic Bim and to a lesser extent Bcl-2-modifying factor (Bmf) was sufficient for GC-induced apoptosis, while the anti-apoptotic proteins were not consistently downregulated by GCs, although their overexpression did delay GC-induced cell death[211]. By using GC-resistant ALL xenografts, GC resistance was further linked to a decreased ability to induce Bim expression, although GR was still transcriptionally active, as evidenced by induction of GILZ[139]. Moreover, Jing *et al.* showed that opposite regulation of Bcl-2 and Bim in ALL determined the extent of GC-induced apoptosis. Indeed, persistent MYB expression in GC-resistant ALL PDXs resulted in sustained Bcl-2 expression and blockade of apoptosis, while absence of GR binding to an intronic Bim GR binding site resulted in Bim silencing and GC resistance[29]. In a follow-up study, a high-throughput screening for GC sensitizing agents identified the small molecule GCS-3 to specifically synergize with GCs to induce cell killing in GC-sensitive and -resistant xenografts resembling B-ALL and T-ALL[212]. The combination of GCs and GCS-3 decreased c-myc expression and markedly elevated Bim expression[212].

Lynch and coworkers further showed that stimulation or inhibition of apoptosis in GC-sensitive CEM-C7-14 and GC-resistant CEM-C1-15 cells, respectively, was determined by the equilibrium between pro-apoptotic Noxa and anti-apoptotic Mcl-1 gene expression, which was shown to be influenced by the GR phosphorylation status[53]. In GC-resistant mixed lineage leukemia (MLL)-rearranged ALL cells, the Mcl-1 inhibitors gossypol and AT-101 sensitized these cells to GCs, yet, not by decreasing Mcl-1 levels, but by upregulation of pro-apoptotic Bim and Bid[213]. In CLL cells, siBim treatment reduced GC-mediated upregulation of Bim and induced resistance to GC-triggered apoptosis in GC-sensitive cells, resulting from a failure of Bim/Bcl-2 complexes to activate Bax and Bak[32].

Together, this shows that the balance between the levels of pro- and anti-apoptotic proteins as well as the interactions between the Bcl-2 family members[40,210]co-dictate whether a cell undergoes GC-induced apoptosis or becomes GC resistant, with Bim as a crucial determinant[29,212].

3.2.7. Signaling pathway interactions

GR-mediated apoptosis also involves the crosstalk with other signaling pathways (Fig. 4), which can in turn influence GC responsiveness[2,19]. Concerning MAPKs, the balance between anti-apoptotic JNK and ERK signaling and pro-apoptotic p38 signaling was shown to determine the responsiveness of ALL cell lines to GC-induced apoptosis[214]. This is exemplified by GC-resistant CEM-C1-15 cells which harbored high constitutive JNK activity and Dex-induced ERK activity, and displayed low Dex-induced p38 activity[214]. In line herewith, inhibition of ERK and JNK or activation of PKA reestablished GC sensitivity in 7/8 GC-resistant, GR-containing cell lines that represent several lymphoid cell lines (e.g. MM, lymphoma, ALL), which concurred with increased Bim, GR and phospho-Ser211 GR levels[26]. In contrast to the above-mentioned role of JNK in GC resistance, low-dose anisomycin, a protein synthesis inhibitor and an agonist of p38-MAPK and JNK, combined with Dex sensitized GC-resistant CEM-C1 cells to Dex by inducing caspase 3 cleavage, upregulation of Bim, p21 and p27 and by decreasing Mcl-1, Bcl-2, c-myc and cyclin D1 levels[215]. Combined anisomycin and Dex treatment increased GR, p38-MAPK and JNK activity, which was halted by the GR antagonist RU486[215].

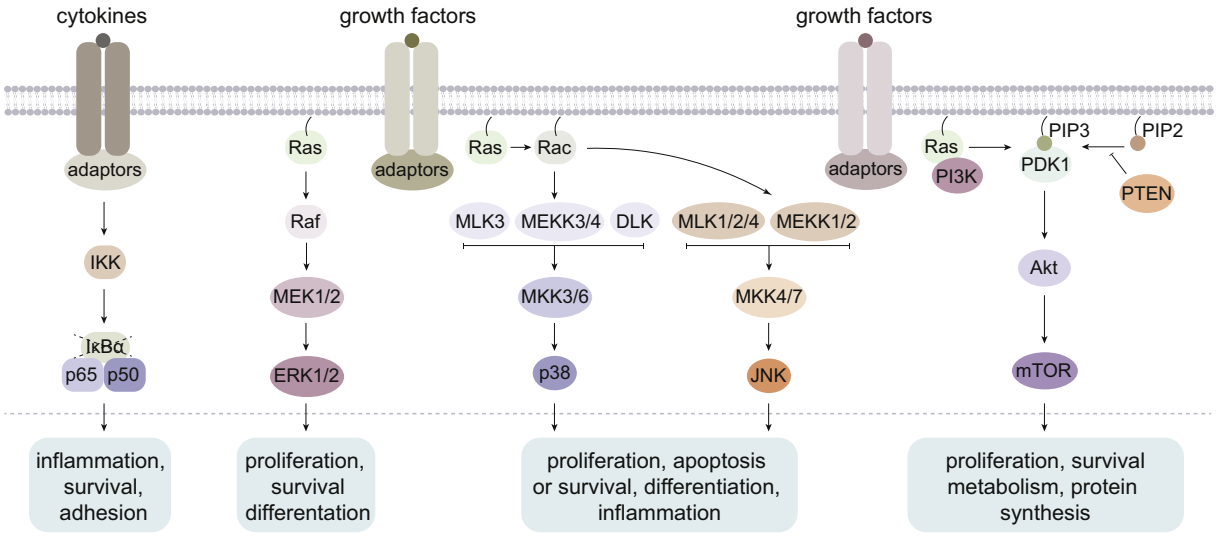

Fig. 4. Simplified overview of signaling pathways. (Left) Cytokines can trigger the activation of the NF-κB signaling pathway. The activation of the IKK complex leads to phosphorylation and subsequent proteasomal degradation of IKBα, releasing NF-κB (p65, p50) to translocate into the nucleus and promote gene transcription. (Center) Growth factors typically activate receptor tyrosine kinases (RTKs), which can trigger mitogen-activated protein kinase (MAPK) signaling pathways. Three main families of MAPKs exist, including the extracellular-signal-regulated kinases (ERKs), Jun amino-terminal kinases (JNKs) and (stress-activated protein kinases) p38 MAPKs. Each cascade starts with the activation of the MAPK kinase kinase (MAPKKK, e.g. Raf), which in turn fuels the successive activation of the MAPK kinase (MAPKK, e.g. MEK1/2) and MAPK (e.g. ERK1/2). Each MAPK has specific (sometimes overlapping) cytoplasmic and nuclear targets, resulting in the described biological effects. (Right) Growth factors can also trigger the activation of phosphatidylinositol-3-kinase (PI3K) and overcome PTEN's blockade on the conversion of phosphotidylinositol 4,5-bisphosphate (PIP2) to phosphotidylinositol 3,4,5-triphosphate (PIP3), hereby stimulating the activation of PDK1, in turn eliciting successive activation of protein kinase B (Akt) and mammalian target of rapamycin (mTOR), giving rise to diverse biological functions.

Also, ERK-mediated phosphorylation of Bim lead to Bim inactivation in ALL cells, while combination of Dex and a MEK/ERK inhibitor resulted in Bim accumulation, Bax and Bak activation and cytochrome C release[41]. In line herewith, the MEK inhibitor trametinib in combination with Dex showed synergistic cell killing in KRAS mutant myeloma cell lines, which was accompanied by increased Bim and decreased Mcl-1 expression[216]. Jones *et al.* also identified the MAPK pathway to evoke prednisone resistance in pediatric ALL, while knockdown of the MAPK pathway member MEK4 sensitized GC-resistant ALL cells to prednisone by increasing GR levels[217]. Matched diagnosis and relapse samples also showed increased ERK activity and an enhanced response to MEK inhibition upon relapse[217].

Piovan *et al.* identified Akt as a driver of GC resistance in T-ALL, as Akt blocked GR gene expression and induced Ser134 phosphorylation which blocks GR nuclear translocation[218]. Inhibition of Akt with MK2206, however, reversed GC resistance *in vitro* and *in vivo* and sensitized T-ALL cells to GCs[218]. Different PI3K/Akt inhibitors could also increase GILZ expression in MM cell lines and clinical samples, while combination of Dex with PI3K/Akt inhibitors strongly elevated GILZ expression and enhanced apoptosis[46]. Yet, exogenous IL-6 and IGF-1, activators of the PI3K/Akt pathway, could inhibit GC-induced and PI3K/Akt inhibitor-mediated GILZ upregulation[46]. In 2016, Oppermann *et al.* also found that PI3K inhibitors increased Dex-induced apoptosis in CLL cells[219]. Patient-derived T-ALL cells treated with GCs in combination with a MEK, Akt, mTOR or dual PI3K/mTOR inhibitor strongly enhanced GC-induced apoptosis[158]. A pan PI3K p110 inhibitor and an isoform-selective dual γ/δ PI3K p110 inhibitor were further shown to restore GC sensitivity in B-ALL cells by reinstating GR nuclear translation and alleviating microenvironment-induced GC resistance [220]. In a shRNA screen that was designed to identify genes that characterize the GC cell killing response in B-ALL, GCs remarkably repressed key factors both in early B-cell development and B-cell receptor signaling genes, highlighting that B-cell development and GC efficacy are closely intertwined [58]. This seminal study also showed that inhibition of lymphoid-specific PI3Kδ, which is at the crossroads between IL-7R and pre-B-cell receptor signaling pathways, promoted GC-mediated transcription to synergistic cell killing of both sensitive and resistant B-ALL cell lines and patient cells [58]. In line herewith, a study from 2020 agrees that in the presence of IL-7, GCs paradoxically induced GC resistance in one-third of primary ALL cells and normal thymocytes by upregulation of the IL-7R, which gave rise to STAT5 signaling and upregulation of Bcl-2 [221].

In support of the advantage of combination strategies, the mTOR inhibitor rapamycin induced growth arrest but not apoptosis in GC resistant CEM-C1 cells, while combination of Dex and rapamycin upregulated GR and pro-apoptotic Bim levels, evoked apoptosis and enhanced cell cycle arrest in CEM-C1 cells[222]. Yet, rapamycin alone could induce apoptosis in primary MM cells and sensitized MM cell lines and primary cells to GC-mediated apoptosis, which was accompanied by reduced cyclin D2 and survivin levels[223]. Interestingly, the rapamycin and Dex combination could also suppress the anti-apoptotic effects of exogenously added IL-6 and IGF-1[223]. Gu *et al.* further showed that lymphoma cells that are resistant to GCs and rapamycin alone, were sensitized to the combination treatment with rapamycin and Dex, which lead to apoptosis and cell cycle arrest[224]. These effects were mediated by blocking mTOR/p70S6K signaling, in turn leading to the halted glycolysis and autophagy induction[224]. In 2016, Hall and coworkers demonstrated that a dual PI3K/mTOR inhibitor enhanced Dex-induced apoptosis in both ALL cell lines and primary cells, and in an *in vivo* T-ALL PDX model by increasing Bim expression and downregulation of Mcl-1[225].

High expression levels of CDK4 and CDK6 were also identified in a cohort of pediatric B-ALL patients[226]. Use of the CDK4/CDK6 inhibitor ribociclib in combination with Dex strongly reduced proliferation and enhanced cell killing of two Dex-resistant B-ALL cell lines and primary B-ALL cells[226].

Lymphocyte cell-specific protein tyrosine kinase (LCK) was further found to be hyperactivated in prednisone poor responder T-ALL patients, giving rise to IL-4 overexpression, which in turn triggered resistance to Dex[227]. LCK inhibitors in combination with Dex, however, reverted the GC resistant phenotype in GC-resistant cell lines and *ex vivo* patient cells[227].

Intrinsic GC resistance in pediatric T-ALL was shown to be present in both early thymic precursor (ETP) T-ALLs and non-ETP T-ALLs at diagnosis[228]. The latter subgroup displayed high JAK/STAT signaling activity upon IL-7 administration, while inhibition of JAK/STAT or removal of IL-7 sensitized these T-ALLs to GCs, in part by lowering Bcl-2 activity[228].

Together, these studies highlight both the complexity of signaling pathway regulation and the potential of targeting the kinome in lymphoid malignancies. Specifically, the connection between GC resistance and Akt/mTOR axis deregulation appears to be a common theme across lymphoid malignancies.

3.2.8. Deregulated metabolism

Several studies support that GCs can alter the metabolism of lymphoid malignant cells, for instance, by inhibiting glycolysis, which positively contributed to GC-induced apoptosis[69,71]. This also suggests that GC resistance can emerge from a deregulated metabolism[70,138]. Beesley and colleagues could correlate GC resistance in T-ALL cells with enhanced metabolism at multiple levels, e.g. upregulation of glycolysis, oxidative phosphorylation, glutamine metabolism and cholesterol synthesis[138]. In a follow-up study, the oxidative phosphorylation inhibitor oligomycin was shown to synergize with GCs to sensitize previously GC-resistant cells to cell death[229]. A similar synergism was observed with GCs and the cholesterol metabolism inhibitor simvastatin[229].

Furthermore, GC-resistant ALL cells were reported to have a higher glucose demand than GC-sensitive cells[99]. Interestingly, combining GCs with 2-deoxy-D-glucose, a glycolysis inhibitor in solid tumors, synergistically decreased the viability of GC-resistant ALL cells[99]. Yet, the action mechanism of 2-deoxy-D-glucose in ALL cells was to inhibit N-linked glycosylation, which lead to abnormal protein folding and promoted ER stress and the induction of the unfolded protein response[99,230]. In 2018, elevated levels of the glycolytic enzyme enolase 2 (ENO2) were also demonstrated in relapsed ALL patients[231]. In line herewith, overexpression of ENO2 in ALL cells promoted cell proliferation and glycolysis, the latter evidenced by increased mRNA levels of GLUT1, LDHA and pyruvate kinase M2 (PKM2) and lead to GC resistance[231]. Besides that, a CRISPR/Cas9-based screen was used to search for transcriptional targets of the B-lymphoid transcription factors IKZF1 and PAX5. The results showed that GR, the glucose feedback sensor TXNIP and the cannabinoid receptor were central effectors of the energy deprivation that was enforced by IKZF1 and PAX5 in B-ALL[232]. A strong synergistic cell killing was observed when glucocorticoids were combined with TXNIP or cannabinoid receptor agonists or with AMPK inhibitors, suggesting that the latter may function as therapeutic (co-)targets[232].

In primary CLL cells, GCs were shown to induce PPARα expression and fatty acid (FA) oxidation and adipocyte-derived lipids and lipoproteins inhibited GC-induced cell death, suggesting that FA oxidation may contribute to GC resistance [70]. In line herewith, inhibitors of PPARα or FA oxidation blockers augmented Dex-induced cell killing in patient-derived CLL xenografts [70]. In contrast, another study showed that polyunsaturated fatty acids increased the GC sensitivity of MM cells by induction of p53 and miR-34a, of which the latter was connected to suppression of anti-apoptotic Bcl-2 [233].

Besides blocking glycolysis and stimulating FA oxidation, GC treatment elevated the expression of glutamine-ammonia ligase (GLUL), an ammonium scavenger that promotes the production of glutamine, in GC-sensitive but not in GC-resistant ALL cells[72]. In GC-treated GC-sensitive ALL cells, removing glutamine or adding dimethyl α-ketoglutarate, which is converted in cells into α-ketoglutarate, increased glutamate production, diminished glutamine uptake and reduced the Dex-induced LC-II accumulation (autophagic flux) as well as caspase 3 cleavage [72]. Together, this indicates that glutamine metabolism influences autophagy and possibly the onset of GC-induced cell killing.

3.2.9. Epigenetic changes

DNA methylation and histone modifying enzymes, such as histone methyltransferases (HMTs) and histone deacetylases (HDACs), have emerged as crucial determinants of GC responsiveness[234–236]. Treatment of GC-resistant CEM-C1-15, Molt-4 (both ALL) and RPMI-8226 (MM) cell lines with a DNA demethylating agent restored GC-induced apoptosis in these cell lines[237]. This altered epigenetic state also induced p38 activation in all 3 cell lines, changed the expression of GR coregulators in RPMI-8226 cells, and increased GR function, GR protein levels and GR phosphorylation in CEM cells[237]. Sequencing of matched diagnosis and relapse samples from ALL patients identified mutations in the transcriptional coactivator and HAT CREB-binding protein (CREBBP or CBP) in approximately 18% of relapse cases, which functionally impaired histone acetylation as well as GR-mediated transcription of target genes, suggesting that these mutations may steer therapy responsiveness[238]. An analysis of the GC sensitivity of 444 newly diagnosed ALL patients further revealed a high expression of caspase 1 and its activator NLRP3, a component of the inflammasome, in GC-resistant ALL cells[234]. This was caused by lower methylation of the corresponding promoters of these inflammasome components, which resulted in GR cleavage, decreased GR transcriptional activity and increased GC resistance[234].

Lymphocyte-specific open chromatin domains were identified in 2018 to be crucial for GC-induced apoptosis of ALL cells[235]. At these open chromatin domains, GR collaborated with CTCF, a chromatin architectural protein, to trigger DNA looping. The latter was halted in GC-resistant ALL and non-lymphoid cells because of increased DNA methylation[235]. In AML cells, ASH2L, a core subunit of a H3K4-specific MLL/SET HMT complex, was shown to interact with the unliganded GR through chromatin looping and resulted in a remarkable Bcl-XL upregulation[239]. Dex treatment, however, nullified this interaction, which lead to reduced Bcl-XL expression and ultimately the induction of cell death[239]. In 2019, the group of Pufall applied a functional genomics approach to resolve GC resistance in B-ALL and found that the transcriptional coactivators EHMT2, EHMT1 and CBX3 are crucial for effective GC-mediated apoptosis[236]. In relapsed B-ALL, however, EHMT1 and EHMT2 were phosphorylated by Aurora kinase B, preventing CBX3 recruitment and hereby suppressing GR-mediated gene activation of pro-apoptotic genes[236].

The pan-HDAC inhibitor (HDACi) SAHA, which did not synergize with Dex, induced apoptosis in GC-sensitive and GC-resistant cells to a similar extent, yet, through different death pathways[240]. In CEM-C7 cells, SAHA activated the extrinsic pathway, while in CEM-C1 cells SAHA achieved cell death by a combination of the intrinsic mitochondrial pathway and caspase-independent apoptosis[240]. Furthermore, high levels of HDAC4 were linked to poor response to prednisone in ALL patients[241]. In primary MM cells, HDAC1-3, HDAC4, HDAC6 and HDAC11 transcript levels were elevated compared to normal plasma cells and were correlated with a shorter PFS in patients[242]. In addition, Vogl *et al.* studied in a phase I/II trial the combination of the HDAC6i ricolinostat with bortezomib and Dex in relapsed and refractory myeloma[243]. This combination was found to be safe, well-tolerated and active, showing the potential of HDAC6i in MM therapy[243].

miRNAs can lower GR levels and hereby influence GC

responsiveness. For instance, miR-130b overexpression in MM1.S cells resulted in decreased GR levels, diminished GC-induced GILZ induction and inhibition of GC-mediated apoptosis[244]. miR-142-3p was also shown to be upregulated in T-ALL cell lines and primary T-ALL cells from patients and decreased GR protein levels and cAMP/PKA activity, while a miR-142-3p inhibitor could effectively revert GC resistance due to elevated GR levels and cAMP/PKA activity[245]. Liang and coworkers further found miR-124 was upregulated in ALL patients which responded poorly to prednisone [246]. miR-124 evoked GC resistance by stimulating proliferation, inhibiting apoptosis and decreasing the expression of GR[246]. In contrast, several miRNAs, such as miR-185-5p, were reported to sensitize GC-resistant cells to GCs, by increasing apoptosis and cell cycle arrest, and by augmenting GR expression[247].

miRNAs also influence GC-induced apoptosis and resistance by targeting pro- and/or anti-apoptotic proteins. For instance, overexpression of the miR-17~92 cluster was shown to reduce Bim induction and inhibited GC-induced apoptosis, while GC treatment decreased miR-17~92 expression in a murine T-cell lymphoma cell line[248]. miR-150-5p was further identified as a GC-inducible miRNA in GC-sensitive MM1.S but not in GC-resistant MM1.R cells, although overexpression of miR-150-5p did not trigger cell death in MM1.S or MM1.R cells in absence of GCs[249]. Nevertheless, low dose GC combined with miR-150-5p overexpression in MM1.S cells resulted in sensitization to GC therapy[249]. Another example is miR-221-222, which targeted the pro-apoptotic p53-upregulator modulator of apoptosis (PUMA) and induced Dex resistance in MM1.S cells, while anti-miR-221-222 partially restored Dex sensitivity of MM1.R cells[250]. Increased levels of miR-221-222 were even detected in MM cells derived from patients upon relapse compared untreated controls, suggesting an even broader role for miR-221-222 in MM drug resistance[250]. In line herewith, GC sensitivity was inversely correlated with miR-221-222 levels in MM cell lines[251]. miR-221-222 inhibited the autophagy-related gene 12 (ATG-12)/p27-mTOR autophagy pathway and hereby conferred GC resistance in MM cells[251].

3.2.10. BM environment-induced drug resistance

Both soluble factor-mediated drug resistance (SFM-DR) and cell adhesion-mediated drug resistance (CAM-DR)[252,253]contribute to bone marrow microenvironment-induced drug resistance. Concerning SFM-DR, autocrine IL-6 production and/or IFNα induced resistance to dexamethasone-induced apoptosis in MM cells [254,255]. Liu and coworkers further showed that 90 days after withdrawal of Dex, an IL-6-dependent Dex-resistant mouse B cell hybridoma (7TD1-Dex) became sensitive again to the growth inhibiting and apoptotic effects of Dex, hereby showing that sensitization to Dex therapy is possible [256].

CAM-DR in MM results from adhesive interactions between MM cells and BM stromal cells and/or extracellular matrix components [252,253]. Therefore, several adhesion molecules are involved in this process: integrins (VLA-4, VLA-5, β1 integrins, β7 integrins), syndecan-1 (CD138), CD44, LFA-1, VCAM-1, ICAM-1 and MUC-1 [253]. For example, VLA-4 induces resistance to vincristine, a cell cycle-dependent chemotherapeutic, and dexamethasone, which could be overcome by bortezomib-induced VLA-4 downregulation [257]. Adhesion of MM cells to stromal cells further resulted in IL-6-induced PD-L1 expression on MM cells. This not only increased myeloma cell proliferation, but also induced resistance to dexamethasone and melphalan, and blunted the anti-tumor T cell response [258]. Moreover, Wang *et al.* found that miR-21 expression in myeloma cells was upregulated upon adhesion to BM stromal cells, which resulted in significantly reduced Dex-induced apoptosis [259]. Furthermore, anti-adhesion treatments, such as Natalizumab, which binds α4 integrins and inhibits MM cells from interacting with BMSCs and the ECM, not only inhibited MM cell proliferation and angiogenesis, but also enhanced the MM cell killing activity of dexamethasone [260].

4. Conclusions and future perspectives

Given the extensive number of factors that can contribute to GC resistance, GC resistance is clearly not governed by one single mechanism, but by several mechanisms acting consecutively or alternating to achieve full-blown resistance. Interpatient variability in the underlying mechanisms is also to be expected, as both the GC dose and the duration of GC therapy is often different between patients, in turn affecting the moment of onset and the degree of GC resistance (Fig. 2). Frontline technologies such as single cell RNA-sequencing will further help dissecting the gradual emergence and inherent heterogeneity of GC resistance. Indeed, this technology has characterized the inter-patient and intra-patient heterogeneity in multiple myeloma and was able to pick up rare circulating tumor plasma cells, hereby opening perspectives for accurate liquid biopsies in myeloma[261].

Concerning the mechanisms underpinning GC-induced cell killing and GC resistance, the exact pinpointing of mechanisms that are common or specific to each malignancy remains to be established. Multicentric large-scale gene expression studies with primary cells from different types of lymphoid malignancies at diagnosis seem to be instrumental in resolving these long-standing questions. GC-responsive genes identified at a treatment-naïve stage should be further compared in longitudinal patient samples to establish the evolution of (potential target-specific) GC responsiveness across disease stages (relapse/refractory setting) and disease types, hereby taking into account the complexity that GCs are always combined with other treatments. Noteworthy, intrinsic disease heterogeneity as well as intra-patient heterogeneity complicate these analyses. Disease-intrinsic differences may also underlie why GCs are more effective in certain lymphoid malignancies and why GC resistance mechanisms exhibit a cell type-specific component. Therefore, multicentric, disease-spanning approaches as proposed above may be a good first step to resolve some of these conundrums.

Nevertheless, we may conclude that having sufficient levels of transcriptionally active GR remains an essential characteristic to achieve and maintain GC-induced cell death. Yet, the markers to identify GR transcriptional activity in hematological disorders are scarce and seem to be often limited to GILZ, which, as our literature overview reveals, does not always correlate well with GC cell killing capacities. Besides that, seminal studies from the last five years have added DNA methylation and altered HMT levels and/or activity to the list of crucial contributors to GC responsiveness [235,236]. A growing number of studies have also put miRNAs forward as biomarkers for GC treatment response and, more generally for diagnosis and disease classification, yet, the lack of standardization in miRNA detection still limits their widespread use [262]. Although there are currently limited strategies to therapeutically target miRNAs, it seems worth exploring more deeply whether miRNAs can be pinpointed as critical regulators of GC sensitivity. Signaling pathway molecules that are implicated in GC resistance (e.g. PI3K/Akt/mTOR axis deregulation) may particularly be of clinical relevance, especially since the therapeutic targeting of some molecules within this protein class has been demonstrated before as a viable means to overcome GC resistance.

Pioneering studies in ALL that compare different disease stages, i.e. from diagnosis to (multiple) relapse(s)[263–265], have identified genetic changes, deregulated pathways and gene expression profiles that are specific for disease stages. Yet, in the context of combination treatments, specific GC resistance signatures have so far not been unambiguously distinguished from overall therapy resistance signatures. Therefore, despite a plethora

of relevant and insightful studies and intense efforts to resolve GC resistance, there is still no clinical test that specifically identifies GC resistance in patients. Even so, all patients receiving long-term GC treatment will eventually transition towards full-blown GC resistance and suffer too long from the GC-related side effects, arguing for tissue-specific GC resistance. Hence, early and reliable identification of GC resistance in patients remains an important challenge that needs to be tackled[266], as this would allow a faster reorientation of a patient's treatment protocol. *Ex vivo* GC and drug testing may provide a viable means to optimize the treatment schedule, especially in the relapsed or refractory setting[267]. Of note, once GC treatment ceases, e.g. when a patient is cured or when GCs are omitted from a certain treatment cocktail, it remains to be determined whether spontaneous sensitization to GC treatment after long-term GC withdrawal can be achieved. Finally, establishing relevant GC resistance models[268]and finding alternative strategies to strengthen the pro-apoptotic action of GCs by partially rewiring GR action using novel therapeutic concepts[269] or drug repurposing approaches represents another important challenge, especially given the continued widespread use of GCs in lymphoid malignancies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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