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Review

Glucocorticoids and natural killer cells: A suppressive relationship

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ABSTRACT

Glucocorticoids exert their pharmacological actions by mimicking and amplifying the function of the endogenous glucocorticoid system's canonical physiological stress response. They affect the immune system at the levels of inflammation and adaptive and innate immunity. These effects are the basis for therapeutic use of glucocorticoids. Innate immunity is the body's first line of defense against disease conditions. It is relatively nonspecific and, among its mediators, natural killer (NK) cells link innate and acquired immunity. NK cell numbers are altered in patients with auto immune diseases, and research suggests that interactions between glucocorticoids and natural killer cells are critical for successful glucocorticoid therapy. The aim of this review is to summarize these interactions while highlighting the latest and most important developments in this field. Production and release in the blood of endogenous glucocorticoids are strictly regulated by the hypothalamus–pituitary adrenal axis. A self-regulatory mechanism prevents excessive plasma levels of these hormones. However, exogenous stimuli such as stress, inflammation, infections, cancer, and autoimmune disease can trigger the hypothalamus-pituitary-adrenal axis response and lead to excessive systemic release of glucocorticoids. Thus, stress stimuli, such as sleep deprivation, intense exercise, depression, viral infections, and cancer, can result in release of glucocorticoids and associated immunosuppressant effects. Among these effects are decreases in the numbers and activities of NK cells in inflammatory and autoimmune diseases (e.g., giant cell arteritis, polymyalgia rheumatica, and familial hypogammaglobulinemia).

1. Introduction

Glucocorticoids (GCs) exert their pharmacological actions as they mimic and amplify functions of the endogenous GC system's canonical physiological stress response [1]. Endogenous GCs are hormones produced in the cortex of the adrenal gland, a pair organ located at the upper poles of the kidney tissue around the renal medulla where the other stress hormone, adrenaline, is produced. Corticosteroids and male and female sex hormones are produced in the adrenal cortex. These hormones complete maturation in the sex organs. All three biosynthetic pathways of the adrenal cortex (i.e., GCs, mineralcorticoids, and sex hormones) originate from cholesterol. Therefore, all cortical hormones are very liposoluble [1].

Production and release of GCs into the blood is subject to regulation by the hypothalamus–pituitary-adrenal (HPA) axis. The hypothalamus produces corticotropin-releasing hormone (CRH) and releases it into the portal circulation that connects the hypothalamus directly to the adenopituitary gland. In this organ, CRH stimulates the production and secretion of adrenocorticotropic hormone (ACTH) into the blood, which in turn stimulates release of cortisol by the adrenal cortex. The cycle is completed when circulating cortisol binds to its receptor (GC Receptor [GR]) in the hypothalamus and pituitary gland to inhibit further release

Abbreviations: NK, Natural killer; PD-1, programmed cell death 1; GCs, glucocorticoids; HPA, hypothalamic–pituitaryadrenal; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropichormone; GR, glucocorticoid receptor; hsp, heat shock protein; GRE, glucocorticoid-responsiveelement; Th, T-helper; Treg, T regulatory; GILZ, glucocorticoid-induced leucine zipper; TCR, T cell receptor; NKR, NK receptor; TLR, toll-like receptor; TIGIT, T cell immunoreceptor with-immunoglobulin and ITIM domains; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITSM, immunoreceptor tyrosine-based motif; PD-L, PD-1 ligand.

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of CRH and ACTH, respectively. As a result of this negative feedback, cortisol released into the blood self-limits its production and release, thus avoiding excessive blood concentrations of the hormone [2]. Because of this regulatory mechanism, plasma GC concentrations are associated with circadian fluctuations with higher peaks in the morning upon awakening, a second lower peak in the afternoon, and low nighttime levels [1–3]. An excess of these hormones is also released during the response to stress as a consequence of the overactivation of the HPA axis [4]. Endogenous GCs and drugs mostly act by binding to a specific intracellular receptor via a genomic action; non-genomic mechanisms are also used. GRα and GRβ are the two types of GR receptors. GRα is the classic receptor present in cytosol and consists of three domains (i.e., the domain binding to GCs, the domain binding to DNA, and the domain binding to regulatory molecules). In the cytoplasm, the receptor is in an inactive form as it links to various chaperones (e.g., heat shock proteins, hsp90, and hsp56) and increases GR affinity for GCs. When it links with a GC, the chaperone detaches and a GC/GR complex is formed that moves into the nucleus where it homodimerizes with another GC/GR complex. The homodimer binds to specific DNA sequences (i.e., GC-responsive elements [GREs]) present in target genes [1,3]. Homodimer linkage with a GRE result in an increase in gene transcription. GC/GR monomers can also bind to specific negative GREs (nGREs), resulting in inhibition of target gene transcription [5]. Because it does not bind to GCs, GRβ likely does not have a role in this process. In addition to a gene transcription modulation action, the GC/GR complex can bind to other transcription factors (e.g., NF-κB, NFAT) and prevent their actions as transcription modulators [6] (Fig. 1). Because GRs are ubiquitously expressed in the body, GCs can affect many functions and metabolic processes in organisms. For example, symptoms associated with Cushing's disease are due to an excess of GCs; Addison's disease symptoms are associated with GC deficiency. These relationships are the basis for therapeutic use of GCs for autoimmune diseases. Examples of diseases treated using GCs include primary hemophagocytic lymphohistiocytosis in children [7], acute graft-versus-host disease [8], severe ANCA-associated vasculitis [9], systemic lupus erythematosus [10], and asthma [11]. Unfortunately, this wide distribution of functions results in large numbers of side effects as well as pharmacological effects when GCs are used. They thus have limited long-term therapeutic use.

2. Effects of glucocorticoids on the immune system

The immune system is strictly regulated by the release of GCs during both circadian release and the stress response [4]. The circadian rhythm results in diurnal fluctuations of immune cells, promoting their functions in defending against infection. However, during the stress response, the excessive secretion of GCs shifts the balance toward an immunosuppressive function, allowing for the development of viral infections and cancer. GCs play roles in inflammation, both cellular and humoral adaptive immunity, and innate immunity [4].

2.1. Glucocorticoids in inflammation

Inflammation is characterized by three sequential phases: the alarm, mobilization, and resolution phases. In the alarm phase, which occurs from minutes to hours after exposure to inflammatory stimuli, molecules released by invading pathogens (pathogen-associated molecular patterns) or due to tissue damage (damage-associated molecular patterns) bind to transmembrane and cytoplasmic receptors, known as pattern recognition receptors (PRRs). PRRs stimulate inflammatory cells, including fibroblasts, macrophages, and mast cells. Stimulated inflammatory cells release soluble inflammatory mediators, such as histamine from mast cells and prostaglandins (such as prostaglandin E2), leukotrienes (such as leukotriene B4), and inflammatory cytokines (such as interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF]-α) from macrophages and fibroblasts. GCs regulate the alarm phase by controlling the PRR signaling cascade by inducing the transcription of inhibitory genes, including interleukin-1 receptor associated kinase 3 (IRAK3) [12], dual-specificity protein phosphatase 1 (DUSP1), inhibitor of nuclear factor-κB (IκB) [13], and glucocorticoid-induced leucine zipper (GILZ) [14]. Additionally, they limit the activity of pro-inflammatory cytokines at several levels, including inhibiting the transcription of *IL1B*, *IL6,* and *TSLP* [5], decreasing cytokine receptor signaling [15], and shortening the half-life of mRNAs such as *TNF* [16]. GCs also inhibit the production of prostaglandins [17,18] and leukotrienes and the release of histamine by mast cells [19]. Additionally, GCs directly bind to and repress the activity of pro inflammatory transcription factors, such as activator protein 1 (AP-1), nuclear factor-κB (NF-κB), and interferon-regulatory factor 3 (IRF3). In the mobilization phase, which lasts from hours to days, inflammatory mediators released by inflammatory cells induce the expression of E-selectin, which promotes the tethering of leukocytes (neutrophils and monocytes) to blood vessel endothelial cells. The binding of chemokines with receptors promotes rolling on the endothelium, and the binding of integrins promotes the strong adhesion of leukocytes to the endothelium, which is required leukocytes to pass through the blood vessel wall and migrate to the inflammatory site [20]. In the mobilization phase, GCs inhibit the transcription of chemokines, such as IL-8, IL-16, CC-chemokine ligand 2 (CCL2), CCL3, CCL5, CCL11, CCL24, and CCL26. GCs also promote the decay of *CCL2* and *CCL7* mRNA [21]. GCs inhibit the transcription or reduce the expression level of E-selectin; the integrin ligands, vascular cell adhesion protein 1 and intracellular adhesion molecule 1 [22]; and the adhesion molecules CD44, lymphocyte function associated antigen 1, and very late antigen 4 [23]. Finally, in the resolution phase, which lasts for days, the absence of inflammatory stimuli stops the inflammation process. Complete recovery is promoted by neutrophils and macrophages that phagocytose apoptotic debris, along with M2c macrophages that secrete anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β (TGF-β) [1]. GCs promote the phagocytosis of apoptotic debris by monocytes and macrophages [1,24–26].

2.2. Glucocorticoids in adaptive immunity

Naïve Th cells (Th0) differentiate into different cell subtypes depending upon cytokine stimuli. Th1 cells are stimulated by IL-12 and interferon-γ (IFN-γ), Th2 cells by IL-4, Th17 by IL-6 and TGF-β, and T regulatory (Treg) cells by TGF-β [27]. GCs depress the production, migration, and activity of T cells. In the thymus, likely due to mediation by GC-induced protein GILZ, GC levels affect apoptosis of CD4/CD8 double-positive thymocytes, which depresses production of CD4 and CD8 T cells and their export to the periphery [28,29]. In the periphery, the activation and proliferation of T cells is indirectly inhibited by GCs, which act on dendritic cells (DCs) to inhibit the transcription of CD80, CD86, major histocompatibility complex (MHC) class II molecules, CD1a, IL-12, and TNF-α, and promote the transcription of IL-10 [30], dampening the antigen-presenting function of DCs. Additionally, GCs act directly on T cells by inhibiting transcription factors, such as NF-κB, AP-1 and nuclear factor of activated T cells (NFAT) [31], and kinases, including lymphocyte-specific tyrosine kinase and Fyn [32,33]. GILZ alters the ratios of CD4/CD8 T cells [34]. Moreover, GCs polarize T cells toward Th2 [35], Treg [36], and Th9 cells and inhibit differentiation into Th1 and Th17 cells [37,38]. GCs are an effective treatment for autoimmune diseases mediated by autoantibodies (e.g., rheumatoid arthritis [RA]) and appear to inhibit the activity of B cells, resulting in antibody production [1].

2.3. Glucocorticoids in innate immunity

Innate immunity is the body's first line of defense and is relatively nonspecific. Genome-wide expression studies have highlighted that GCs enhance genes expression that promotes innate immunity, including PRRs, cytokine receptors, and complement system components. Meanwhile, GCs also inhibit pro-inflammatory genes, including pro-

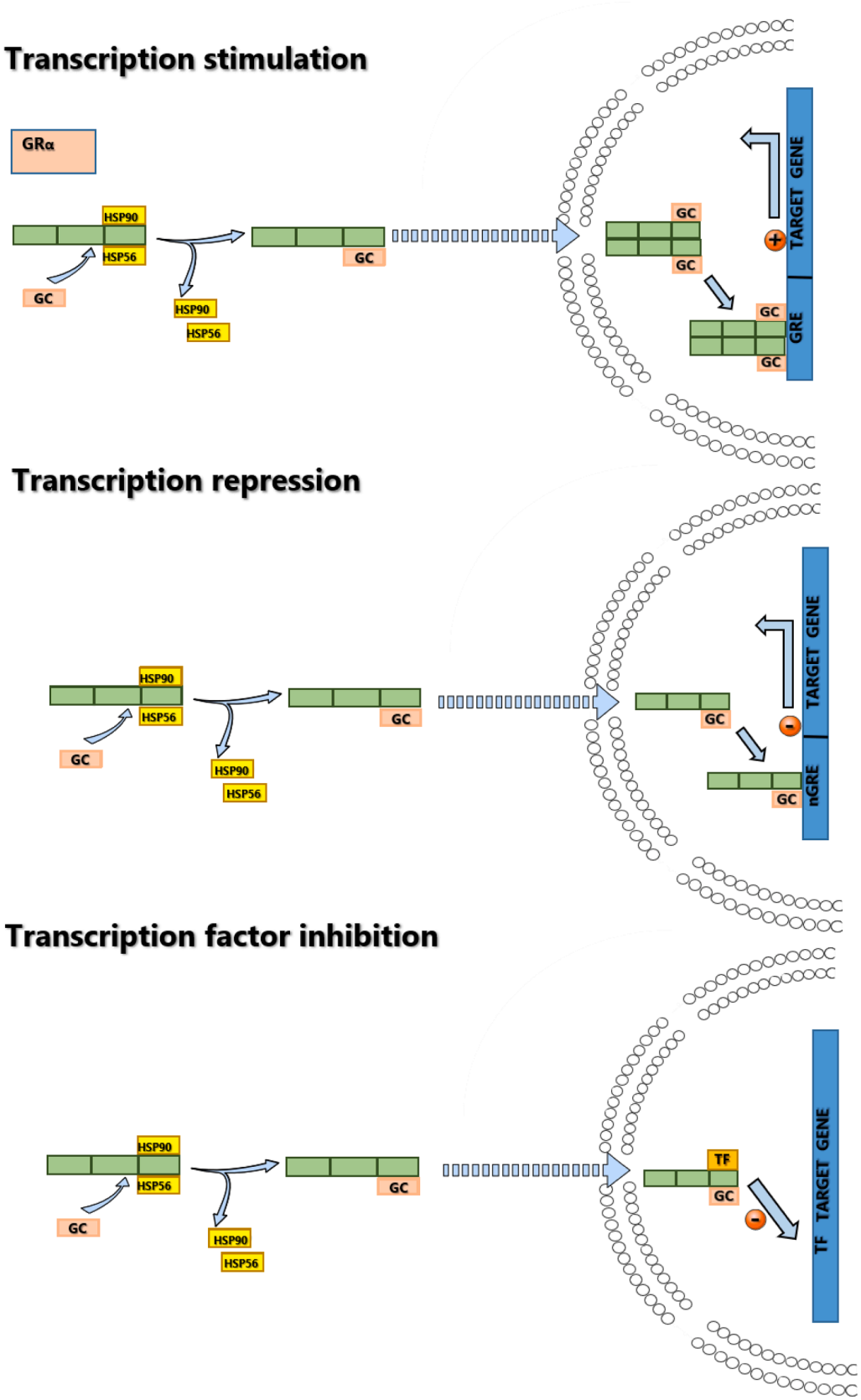

Fig. 1. Mechanism of action of glucocorticoids through glucocorticoid receptor α. GCs mostly act by binding to a specific intracellular receptor (GRα) via a genomic action. GRα consists of three domains (i.e., the domain binding to GCs, the domain binding to DNA, and the domain binding to regulatory molecules). In the cytoplasm, the receptor is in an inactive form as it links to various chaperones (e.g., heat shock proteins, hsp90, and hsp56). When it links with a GC, the chaperone detaches and a GC/GR complex is formed that moves into the nucleus where it homodimerizes with another GC/GR complex. The homodimer binds to specific DNA sequences (GRE) present in target genes. Homodimer linkage with a GRE result in an increase in gene transcription. GC/GR monomers can also bind to specific negative GREs (nGREs), resulting in inhibition of target gene transcription. In addition to a gene transcription modulation action, the GC/GR complex can bind to other transcription factors (TF) and prevent their actions as transcription modulators.

inflammatory cytokines and chemokines. Cain and Cidlowski hypothesize that this generates a biphasic immune response to GCs: low GC promotes the innate immune response, whereas high GC, induced by stress or pharmacological doses, suppress immune response through the inhibition of immune receptors [1]. However, the enhancement of the innate immune response does not appear to apply to the GC effect on NK cells, which plays a key role among the mediators of innate immunity. They also serve as a link between innate and acquired immunity [38].

3. The role of glucocorticoids in natural killer cells

3.1. Natural killer cell overview

Natural killer cell differentiation. Natural killer (NK) cells differentiate in the bone marrow (BM) [39] from hematopoietic stem cells that colonize the BM from the fetal liver just before birth. In mice, NK progenitors are defined as $CD44^{dim}$T-cell receptor $(TCR)^{neg}$ cells [40] or as lineage negative (Lin^-) $NK1.1^-CD49b^-CD122^+$ cells able to give rise to NK cells *in vitro* or to NK and T cells *in vivo* [41,42]. Notably, NK cells can also be ectopically generated in the adult liver from $Lin^-Sca\text{-}1^+Mac\text{-}1^+$ progenitors in case of BM failure, although this population preferentially gives rise to $CD49a^+CD49b^-$ ILC1 cells, a different innate immune cell type [42]. NK cell differentiation is partly due to cytokines (e.g., IL-2), factors derived from marrow stromal cells, and adhesion molecules, such as CD44 [43]. *Mature NK cell function.* After differentiation, they migrate to the periphery to perform defense-related functions. There are two mature NK cell subpopulations. In humans, mature NK cells are defined as $CD56^+CD3^-$ cells. The more immature $CD56^{bright}$ cells produce cytokines, including IFN-γ, whereas mature $CD56^{dim}$ cells fully exercise cytotoxic roles against virus-infected and cancer cells and, as it has been recently shown, against neuroinflammation [44,45]. NK cells express activator and inhibitor receptors (NKRs) on their surfaces (Fig. 2). The balance between these receptors results in the ability to attack infected or transformed cells (via NKR activators) or to develop tolerance toward self (via NKR inhibitors) [44]. Specifically, tolerance develops when inhibitory receptors prevail, such as killer inhibitory receptors (KIRs) and NKG2A, and bind to their respective ligands. KIRs bind to human leukocyte antigen (HLA) class I (HLA-A, HLA-B, HLA-C, HLA-E, and HLA-G), and NKG2As bind to HLA-E on target cells. KIRs expressed on developing NK cells that interact with self-MHC molecules determine the acquisition of complete NK cell function, a process called "licensing" [46]. However, when the balance is shifted toward activator receptor expression, two types of NK cell cytotoxicity are possible: 1) the induced self and 2) the missing self. In the induced self, more activator receptors, such as NKG2D, bind to MHC class I polypeptide–related sequence A (MICA), MICB, or ULBP/RAET1 family ligands than KIRs, leading to the release of granzyme B and cytokines, such as IFN-γ and TNF-α, causing the consequent cytotoxicity of target cells. In the missing self, the activation of NK cells occurs due to the downregulation of KIR or NKG2D ligands, such as HLA-I or HLA-E, in target cells [47] (Fig. 2).

An additional killing mechanism is antibody-dependent cell cytotoxicity, which occurs when CD16 expressed on the surface of NK cells binds to the constant region of immunoglobulins on the surface of target cells [46] (Fig. 2). Importantly, in addition to the defensive role of NK cells against viral infection, a wealth of published data highlights an equally important role for NKs in the defense against cancer. For example, the level of NK cell infiltration in the tumor microenvironment is correlated with better remission prognosis. The infiltration of tumors by NKs depends on the establishment of a gradient of chemokine/chemokine receptors on NK cells, such as CXCR3-CXCR4, CX_3CR1, and CCR3-CCR5 [47].

The importance of NK cell activation in fighting against tumors is highlighted by the strategies of immune evasion operated by cancer cells. In normal cells, NK cell activation is inhibited by the expression of HLA-I and HLA-E, which bind to inhibitory KIRi and NKG2A, respectively, expressed on the surface of NK cells. The downregulation of HLA-I in cancer cells activates NK cells via the missing self. However, cancer cells can escape NK cell activation through 1) HLA-E upregulation in cancer cells, dendritic cells, and macrophages; 2) the reduction of MICA and MICB, which block the NKG2D receptor on NK cells; and 3) increasing the expression of various immune checkpoint ligands that bind to immune checkpoint receptors, inhibiting NK cell activation. Examples of these immune checkpoint ligands include programmed cell death protein 1 (PD-1), T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT), CD112/PVRIG, and CD96/TACTILE [48]. Similarly, tumor cells can decrease NK cell activity via 1) the production of TGF-β, which affects multiple aspects of NK activity, including cytokine secretion, degranulation, metabolism, and mammalian target of

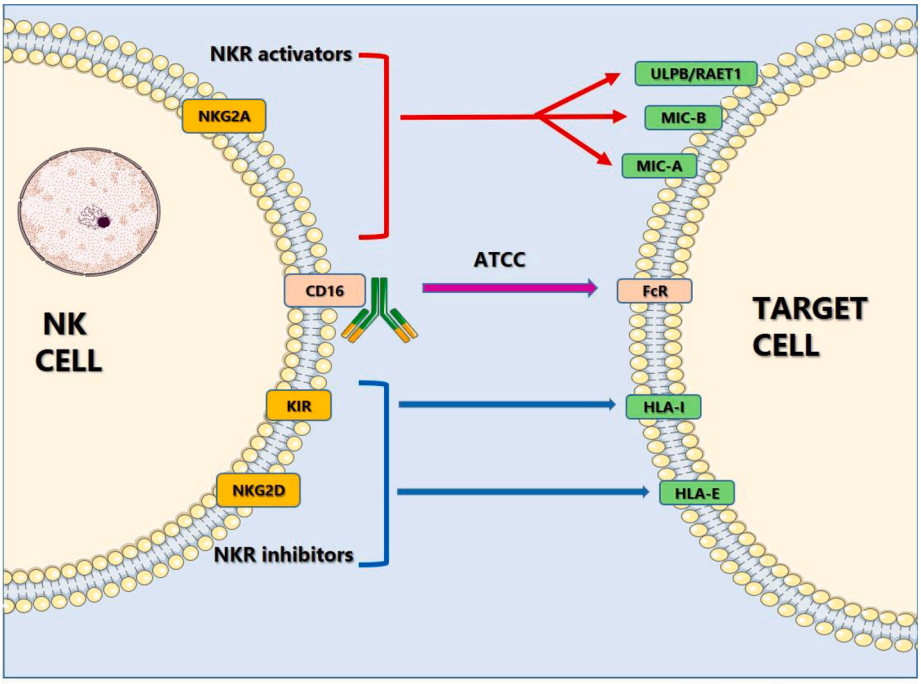

Fig. 2. Interaction between natural killer cell and its target cell. NK cells receptors (NKR) can be activators (NKR activators) such as NKG2A, inhibitors (NKR inhibitors) such as KIR and NKG2D and CD16. The balance between these receptors results in the ability to attack infected or transformed cells (via NKR activators) or to develop tolerance toward self (via NKR inhibitors). Specifically, tolerance develops when inhibitory receptors such as KIRs and NKG2A, prevail and bind to their respective ligands. KIRs bind to human leukocyte antigen class I (HLA-I), and NKG2As bind to HLA-E on target cells. However, when the balance is shifted toward activator receptor expression, two types of NK cell cytotoxicity are possible: 1) the induced self and 2) the missing self. In the induced self, more activator receptors, such as NKG2D, bind to MHC class I polypeptide–related sequence A (MICA), MICB, or ULBP/RAET1 family ligands than KIRs, causing the consequent cytotoxicity of target cells. In the missing self, the activation of NK cells occurs due to the downregulation of KIR or NKG2D ligands, such as HLA-I or HLA-E, in target cells. An additional killing mechanism is antibody-dependent cell cytotoxicity, which occurs when CD16 expressed on the surface of NK cells binds to the constant region of immunoglobulins on the surface of target cells.

rapamycin signaling; 2) hypoxia in tumor microenvironment, which abrogates NK cell activity; 3) shedding of MICA and MICB as soluble ligands for NKG2D expressed by NK cells, preventing binding with MICA and MICB expressed on tumor cell membranes; 4) IL-37, produced by Treg cells present in the tumor microenvironment, which negatively regulates NK cell activity; and 5) SH2-containing protein (CIS), a negative regulator of IL-15, which serves as a crucial homeostatic cytokine for NK cells [47]. Another important mechanism adopted by tumor cells to block the antitumor activity of NK cells is to promote NK cell exhaustion by chronic activation. Augmented numbers of activated NK cells are associated with increased severity and poor clinical outcomes in patients with B- and T-cell acute lymphoblastic leukemia [49]. Notably, NK cells also represent a bridge between the gut microbiome and inflammation in the central nervous system. The gut microbiome stimulates the expression of meningeal NK cell IFN-γ, which stimulates the expression of TNF-related apoptosis-inducing ligand (TRAIL) in lysosome-associated membrane protein 1 $(LAMP1)^{+}TRAIL^{+}$ astrocytes to limit neuroinflammation by promoting T cell apoptosis [45]. IFN-γ produced by NK cells also maintains the dormancy of breast cancer cells to fight against their metastasis. In fact, an increase in the NK cell number in the dormant microenvironment and the infusion of IL-15–stimulated NK cells both support dormancy of cancer cells, preventing hepatic metastasis and prolonging the survival of mice. Furthermore, the number of NK cells decreases when cancer cells exit dormancy. Activated hepatic stellate cells, which are particularly abundant in hepatic metastases, oppose the protective effects of NK cells by secreting the chemokine CXCL12, which binds to the CXCR4 receptor on NK cells to maintain quiescence [50].

NK cell regulation. Activating and inhibitory molecules cannot activate NK cells without the assistance of stimulating cytokines. Some of the most-studied stimulating cytokines are IL-2 and IL-15. However, IL 12 [51], IL-21, and FMS-related tyrosine kinase 3 ligand (FLT3L) can also increase cytotoxicity and IFN-γ production in competent NK cells [52,53]. Another important stimulator of NK cell function, IL-18, can increase NK cell activity via IL-2 and IL-15 [54]. Lastly, IFN-β produced by myeloid and B cells triggers NK cells to become cytotoxic [55]. *NK cell–based therapies.* Therapies targeting NK cells used for cancer treatment are based either on adoptive NK cell therapy or on the stimulation of NK cell activity *in vivo*. For adoptive NK cell therapy, many sources of NK cells have been identified, including autologous or allogeneic NK cells; umbilical cord blood NK cells; NK cell lines, such as NK-92 cells; stem cell-derived NK cells; and chimeric antigen receptor (CAR) NK cells. CAR NK therapy is based on the infusion of genetically modified NK cells to increase their anti-cancer activity. For example, Liu et al., generated umbilical cord blood NK cells retrovirally transduced to express an anti-CD19 CAR, IL-15, and an inducible caspase-9 apoptotic gene able to eliminate engineered NK cells *in vivo* [56]. In phase I and II clinical trials, CAR NK cells derived from cord blood were administered to 11 patients with relapsed or refractory $CD19^{+}$ cancers. Most patients responded to treatment with no toxic effects [57]. To increase the efficiency of the therapy and to reduce costs, NK cells were expanded *in vitro* before infusion by co-culturing NK cells with a K562 leukemia feeder cell line expressing membrane-bound IL-21 and 4-1BBL, which generated a 47967-fold expansion of NK cells [58]. One can use the *in vivo* stimulation of NK cells with activating cytokines, such as IL-2 and IL-5, as a therapeutic strategy to boost their anti-cancer activity. Similarly, one can also produce NK cell–directed immune cell engagers to increase the NK cell response against tumors while also avoiding mechanisms of immune evasion by cancer cells. NK cell–directed immune cell engagers are molecules that bring NK cells into contact with cancer cells. Upon contact, bi-specific or tri-specific engager proteins stimulate NK cells and simultaneously bind specific tumor-associated antigens. For example, a tri-specific NK engager currently being evaluated in a phase I trial is a cocktail using anti-CD16, IL-15 (able to stimulate NK cell activity) and anti-CD33, which targets CD33 on acute myeloid leukemia cells [59]. Finally, immune checkpoint inhibition is a very promising NK cell–mediated antitumor strategy. Engagement of checkpoint molecules expressed on NK cells may be able to inhibit the NK cell–cancer cell interaction, a possibility that is currently being studied. Targeted checkpoints and inhibitory molecules include NKG2A inhibited by anti-NKG2A mAb, KIR antagonists, anti-TIGIT, CD96 inhibitors, anti–PD-1 and antiprotein death-ligand 1 (PD-L1) mAbs, T cell immunoglobulin mucin receptor 3 (TIM-3) inhibitors, and lymphocyte activation gene 3 protein (LAG-3). Preliminary data show that the use of these immune checkpoint inhibitors is a promising therapy [47]. Many studies have shown a strong influence of stress and the nervous system on NK cell activity. This influence may be the reason why chronic stress leads to a higher incidence of infections and cancers [4]. Furthermore, stress also induces the release of GCs through the HPA axis. Thus, the question remains: do correlations exist between these phenomena?

3.2. Stress, HPA axis, glucocorticoids, and NK cells

That stress conflicts with immune system activation has been found using animal models in which a stressogenic stimulus (20-h wet cage exposure) and an immune stimulus (CpG-C, a toll-like receptor (TLR)-9 stimulator) are applied at the same time. Prolonged stress nullifies or limits the immuno-stimulating capacity of CpG-C, but this capacity improves when GR and adrenergic receptors are blocked. Both the CpG-C-mediated enhancement of NK activity and the acquisition of resistance to the metastatic spread of MADB106, experimental metastases sensitive to NK cells, are depressed. However, the latter effect is not blocked by anti-GR antagonists [60]. The animal sleep deprivation model of stress leads to increased levels of GCs and adrenaline. Prolonged sleep deprivation (72 h) in mice results in decreases in NK cell numbers and cytotoxicity. Blocking these receptors abolishes the effects. This result indicates that they are caused by increased expression of adrenergic receptors on NK cells. On the other hand, as found *in vitro* using the synthetic GC, dexamethasone, the increased expression of 'adrenergic' receptors in NK cells is the consequence of GC stimulation [61]. NK cell reduction dependent on prolonged sleep deprivation is associated with the promotion of tumor lung metastasis [62]. This notion has been confirmed since sleep deprivation, with its associated HPA axis stimulation and increased GC production, can have negative effects on the immune response. In mice, experimentally induced lung metastases develop earlier and have increased growth rates compared with the control group. Reductions in the numbers of NK cells and other immune parameters are also evident under these conditions. TIGIT is an important molecule that is upregulated in NK cells as a result of stress. In mice undergoing prolonged psychological stress due to seclusion, TIGIT expression increases on NK cells and other lymphocytes; blocking GRs reverses this response. TIGIT, therefore, is another target to support immunity during conditions of prolonged physiological stress [63]. The direct effects of stress in humans have been studied in adolescents with histories of ill-treatment in childhood but no development of psychopathology. Increases in cortisol levels with associated decreases in percentages of NK cells [64] have been found. Finally, the effects of exercise on GC production and immune function depend on intensity and duration. Prolonged periods of intense exercise can cause immunosuppression; moderate intensity and regularly performed exercise increases immune defenses. These effects are partly due to redistribution of lymphocytes mediated by release of GCs following activation of the HPA axis. In this context, a single extended exercise session alters NK function [65]. Forced swimming, together with surgery, altered NK cell activity and promoted tumor progression and metastases with elevated mortality in rats [66]. This process can be antagonized by inhibiting GCs [67]. However, the results of some studies should be considered with caution since this effect could be amplified during *in vitro* and *ex vivo* study procedures, compared with *in vivo* conditions [68].

GCs have an inhibitory role in NK cell function. This activity is due to transcriptional gene modulation by GCs in NK cells. GCs reduce expression of adhesion molecules (e.g., LFA-1) or cytotoxic molecules (e.

g., granzyme B and granzyme A) in NK cells. GCs also decrease expression of IFN-γ [4]. Cytoskeletal dependent lytic granule trafficking in NK cells with formation of an immune synapse is a mechanism used to trigger and maintain cytotoxic activity of NK cells. Therefore, LIM kinase activity is necessary for NK cell cytotoxicity. Dexamethasone, a synthetic GC, downregulates expression of LIM kinase and thus inhibits lytic granule function and NK cytotoxicity [60].

3.3. Glucocorticoid therapy and NK cells in disease

GC therapy is the first-line treatment for several different types of disease, including immunological diseases, endocrinology disorders, cancers, infections, inflammatory and allergic diseases. A critical problem with GC therapies is the development of resistance. For example, GCs are the first-choice treatment for patients with severe alcoholic hepatitis (SAH), but 40% of patients are unresponsive to this therapy. To identify genes differentially expressed between unresponsive and responsive SAH patients, RNA-seq analysis has been performed on peripheral blood mononuclear cells isolated from 32 SAH patients. RNA-seq identified 346 blood transcription modules. Among the top 100 genes expressed in the unresponsive patients, several modules were identified related to lymphoid lineage, with the blood transcription module of enriched NK cells and the KIR cluster showing the highest difference between the unresponsive and responsive groups. The higher expression of this cluster was due to an increased number of NK cells. Thus, unresponsive patients had a greater expression of the NK cluster, which may be related to an increased cell number, highlighting the importance of NK cells as markers and, possibly, as effectors of resistance to GC therapy [69].

3.3.1. Infections

The influence of GCs on immune functions is double. Under normal conditions, the circadian rhythm of GC secretions determines the correct distribution and response of T cells, supporting the activation of the immune system and protecting against infections. However, under stressful conditions, the excess release of GCs or the administration of exogenous GCs in pharmacological doses inhibits the immune response, predisposing patients to infections [62]. Viral infections are particularly influenced by the effects of GCs on NK cells, as mice with GR deficient DC cells display excess IL-12, enhancing the production of IFN-γ by NK cells. NK cells specifically deficient in GR show increased production of IFN-γ upon stimulation with IL-12 and IL-18 [70]. IFN-γ released by NK cells is an important antiviral mechanism [71]; however, the role of IFN-γ *in vivo* is difficult to define. Infection with cytomegalovirus in mice leads to HPA axis activation, causing the production of GCs that stimulate the expression of the checkpoint PD-1 in NK cells. This, in turn, decreases the expression of IFN-γ, which limits the lethality of infection but does not enhance the clearance of viruses [72]. Thus, a decrease in endogenous GC-dependent IFN-γ production by NK cells is compatible with a better antiviral response, although in mice under restraint stress infected with herpes simplex virus (HSV), NK cells show decreased cytotoxic activity against the virus [73,74]. Therefore, GCs may be a novel therapy for coronavirus disease 2019 (COVID-19), as patients with severe COVID-19–related pneumonia show significant decreases in the number of NK cells ($CD16^{+}CD56^{+}$) and of T cell subtypes [75] (Fig. 3).

3.3.2. Inflammatory diseases

Classical NK cells and NK-T cells, which are a bridge between innate and adaptive immunity, have important functions in some chronic inflammatory diseases such as chronic obstructive pulmonary disease and bronchiolitis obliterans syndrome. In these diseases, affected cells are resistant to GCs because some GC-dependent mechanisms are altered in NK cells. As a result of this resistance, these drugs do not have their typical anti-inflammatory therapeutic effects [76].

3.3.3. Cancer

GCs are commonly used as an adjuvant therapy for certain types of cancer to reduce side effects caused by chemotherapy (e.g., vomiting and allergy). However, because GCs are immuno-depressants their use can weaken the immunological response of these patients. However, one study of the effects of GCs on the numbers and functions of leukocytes (including NK cells) that infiltrate tumor tissue found that GCs have little to no effect on highly effective chemotherapy protocols. The effect of GCs on the overall efficacy of chemotherapy treatments is likely only modestly negative [77], even though some experimental results indicated GCs have an inhibitory effect on NK cells and other leukocytes, and

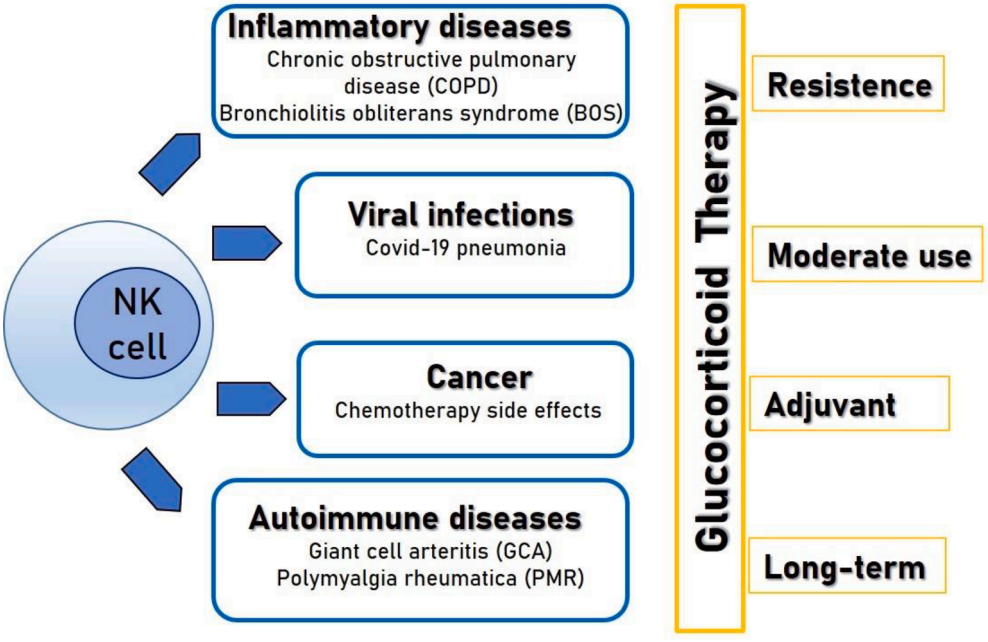

Fig. 3. Glucocorticoid therapy. Effects of glucocorticoids of different glucocorticoid therapies on functions of NK cells involved in viral infections, cancer, and autoimmune disease.

mathematical models indicate that GC treatment suppresses the immune antitumor response [78]. An interesting model for dissecting the role of GCs and their relationship with NK cells is adrenocortical carcinoma, which produces an excess of GC in approximately 50% of cells. In GC^{+} adrenocortical carcinoma cells, many pathways related to NK cells are downregulated compared with GC^{-} adrenocortical carcinoma cells, and, *in vitro*, cortisol suppressed NK cell activation, proliferation, and NK tumor cell killing. All of these NK functions are restored with the GC receptor antagonist relacorilant [79]. Dexamethasone administered for anti-emetic prophylaxis did not change different immunological markers (e.g., LAP, CCR4, CCR7, CTL-4, CD95, and TNFR2) on NK cells, possibly because only a single dose was administered to healthy volunteers [80]. GC can also affect the function of NK cells in a rare form of hyperaggressive NK neoplasm. Treatment of hyperaggressive NK neoplasms with drug cocktails containing the clinically approved Janus kinase (JAK) inhibitor ruxolitinib led to the development of resistance in hyperaggressive NK neoplasms. However, when ruxolitinib was combined with dexamethasone, hyperaggressive NK neoplasms did not develop resistance [81], which may be due to the fact that GCs promote tumor progression by reducing the number of NK cells [82].

3.3.4. Autoimmune disease

The innate immune system acts together with the adaptive immune system to avoid the loss of immune self-tolerance and the development of autoimmune diseases [83]. NK cell numbers are altered in patients with autoimmune diseases, such as type 1 diabetes (T1D), RAs, systemic-onset juvenile RA, systemic lupus erythematosus (SLE), primary biliary cholangitis, systemic sclerosis, Sjogren's syndrome, inflammatory bowel disease, and Bechet's disease [84]. For example, in pediatric patients with T1D, total NK cell numbers and NK cell subsets are reduced. The reduction of CD16 in total NK and NK_{eff} (NK effector, a subset of $CD56^{dim}CD16^{+}$ cells) after one year from diagnosis indicates exhaustion of NK cells and a loss of NK activity control [85]. In SLE, mononucleosome autoantigens induce the expression of MICA in monocytes, which causes a chronic activation and subsequent repression of NK cell function [86]. The involvement of NK cells in the development of autoimmune diseases may have important implications in the development of novel therapeutic strategies. For example, molecules expressed by NK cells may be novel drug targets because they exert an important role in the pathogenesis of autoimmune diseases [84]. Examples of such targets include soluble CD83 (the B isoform of chemokine-receptor 3 [CXCR3]) and the checkpoint inhibitor TIGIT.

Examples of effects of GCs on NK cells in autoimmune diseases have been examined in studies of giant cell arteritis and polymyalgia rheumatica. These diseases are treated using long-term GC therapy. During these diseases, the leukocyte component in the peripheral blood shifts toward the myeloid component, with a reduction in the NK cell count. This change persists during GC treatment [87]. In the NF-KB2 gene mutation-associated familial hypogammaglobulinemia, deficient NK cell function is associated with an absence of GC deficiency [88]. In RA, dendritic cell immunoreceptor (DCIR) is overexpressed by NKs and other immune cells, which may contribute to chronic inflammation in autoimmune diseases. Treatment with GCs downregulates DCIR overexpression [89]. It has been hypothesized that anti-arthritic effects of other drugs, including cyclosporine and perhaps GCs, are partially attributable to the inhibition of P-glycoprotein (P-gp) function, blocking TNF-α release by macrophages and subsequent TNF-α activation of NK cells and NK cell secretion of cytotoxins in the rheumatoid joint [90]. In multiple sclerosis, GC treatment induces apoptosis of peripheral blood leukocytes; however, NK cells showed a relative increase after GC therapy, without a change in the rate of apoptotic cells [91].

4. Glucocorticoids and NK cell function

GR suppresses NK cell cytotoxicity and activity [62], which may be an indirect effect of GCs on the production of IL-12 by DCs [71]. IL-12 is critical for the cytotoxic activity of NK cells through stimulation of NK cell IFN-γ production. One of the most significant discoveries in recent years is the ability of GCs to modulate expression of the PD-1 molecule in NK cells. PD-1 (i.e., CD279) is, together with CTLA4, a negative co-stimulatory receptor expressed on the surface of T cells. This glycoprotein is characterized by a variable Ig type domain (V-type) at the extracellular n-terminal end, a transmembrane domain, and a cytoplasmic domain. The cytoplasmic domain contains an ITIM and an immune receptor tyrosine- based motif (ITSM). ITSM has a critical role in PD-1 activity because activity correlates with engagement of SHP-1 and SHP-2 (Src homology 2-containing protein tyrosine phosphatase 1 and 2). PD-1 binds to PD-L1 (B7-H1; CD274) and PD-L2 (B7-dendritic cell; CD273) with different affinities. PD-L2 is three times more powerful than PD-L1 in PD-1 binding [92].

As a result of T cell stimulation, PD-1 inhibits Akt phosphorylation by interfering with CD28-mediated PI3K activation. This change reduces cytokine synthesis and blocks T cell proliferation and survival. Expression of PD-L1 in cancer cells and its consequent link with PD-1 expressed by T lymphocytes infiltrating the tumor result in blockage of T cell antitumor activity. The tumor can then evade T lymphocyte antitumor mechanisms. The importance of this mechanism of evasion by cancer cells is indicated by the therapeutic efficacy of PD-1/PD-L1 binding inhibitors that prevent the tumor evasion resulting from the PD-1/PD-L1 interaction [93].

The relationship between GCs, NK cell activity, and PD-1 is particularly important in viral infections (Fig. 4). Infection with mouse cytomegalovirus is an experimental model for cytomegalovirus infection in humans. Infection of mice results in increases in production of endogenous GCs (corticosterone in mice) when the HPA axis is activated. This response leads to increased PD-1 checkpoint expression on NK cells which, in turn, limits production of IFN-γ and the immunopathology responsible for the lethality of infection. These relationships were found using mice in which the GC receptors on NK cells were genetically ablated. When these mice were infected with mouse cytomegalovirus, absence of GRs on the surfaces of spleen NK cells resulted in reduced PD-1 expression, increased IFN-γ production, and a consequent increased lethality. However, no impairment of the NK cell viral clearance function was found [72,94,95]. Capellino et al. hypothesized that the discrepancy between the two NK cell functions (production of IFN-γ and viral clearance) is due to the different time frames or concentrations required for GCs to interfere with the two NK functions [4] In the same $GR^{-/-}$ NK cell system, another GC-dependent protein (i.e., GILZ) besides PD-1 is downregulated without impairment of proliferation [14,96,97] and apoptosis [98,99]. These functions are usually ascribed to GILZ activity. In cooperation with cytokines such as IL-12, IL-15, and IL-18, GCs induce increased PD-1 expression in NK cells that infiltrate the tumor. This GC-associated immune suppression mechanism [100,101] and GCs together with IL-2 and IL-12 increase instead of block proliferation of human NK cells [102]. The importance of the HPA axis on PD-1 expression in NK cells has also been demonstrated in patients with depression and in an animal chronic mild unpredictable stress model of depression. The animal model revealed that the rate of progression of liver cancer is significantly accelerated. The progression is associated with increased GC production that results in increased PD-1 expression on the surface of NK cells that infiltrate liver cancer; expression does not increase in NK cells in the blood or spleen. *In vitro* GC-dependent upregulation of PD-1 is accompanied with strong decreases in NK cell cytotoxicity. Thus, GC-induced exhaustion of NK cells promotes tumor progression, which supports the hypothesized significant association between mental conditions and organic disease [103]. Study results indicate that PD-1 has a role in autoimmune disease. The suppressive functions of Treg cells on autoimmunity are modulated by PD-1, as demonstrated by inhibition of the development of colitis by Tregs expressing PD-1. The role of PD-1 has been studied for autoimmune diseases such as type I diabetes, RA, systemic lupus erythematous, myocarditis, autoimmune encephalopathy, and autoimmune

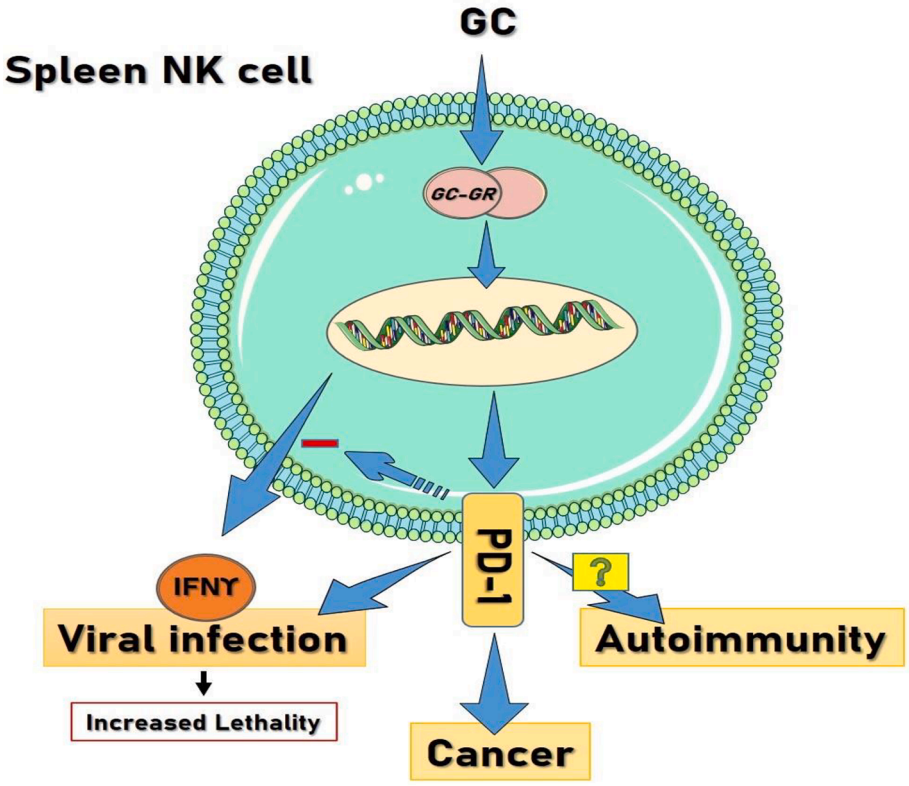

Fig. 4. Natural killer (NK) cells and programmed cell death-1 (PD-1). In spleen NK cells, GCs receptor binding leads to increased PD-1 expression, which has an inhibitory effect on the IFN-γ production. IFN-γ decrease is responsible for the worsening of viral infection with a consequent increased lethality. PD-1 is also involved in cancer and possibly in autoimmunity.

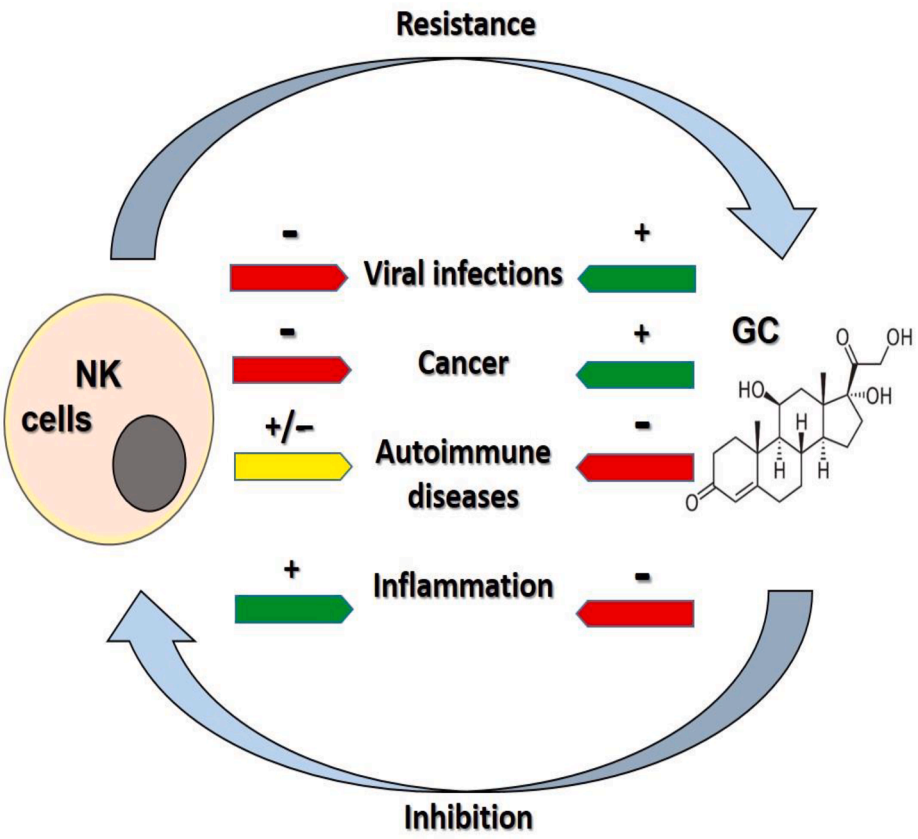

Fig. 5. Effects of NK cells and GCs on immunological diseases. NK cells and GCs exert essentially the opposite effect (red arrows represent a negative effect whereas green arrows a permissive effect. The yellow arrow indicates an ambivalent effect) on diseases in which the immune system is involved such as viral infections, cancer and inflammation, while in autoimmune diseases the role of NK cells can be ambivalent. These opposite effects are due, at least in part, to a direct action of inhibition of NK cells by GCs (lower arrow). On the other hand, NK cells can, in turn, exert a negative effect on GC therapies by inducing resistance to them (upper arrow).

enteropathy [92]. Expression of PD-1 by T cells regulates its activation, has a protective role during development of autoimmunity, and allows a balanced immune response [93,104]. Given these findings, we hypothesize that NK cell-expressed PD-1 has a significant role in autoimmune disease.

5. Conclusions

This review summarizes work from mostly the last 5 years that links the effects of endogenous and exogenous GCs with NK cell functions in normal and pathological contexts (e.g., stress, infections, cancer, and autoimmune disease). NK cells and GCs exert essentially the opposite effect on diseases in which the immune system is involved such as viral infections, cancer and inflammation, while in autoimmune diseases the role of NK cells can be ambivalent. These opposite effects are due, at least in part, to a direct action of inhibition of NK cells by GCs. On the other hand, NK cells can, in turn, exert a negative effect on GC therapies by inducing resistance to them (Fig. 5). The ability of GCs to increase PD-1 checkpoint expression on NK cells is becoming increasingly important, especially for pathological conditions such as viral infections and cancer. Given that study findings indicate the importance of NK cells and the PD-1 molecule for autoimmune processes, we hypothesize that PD-1 modulation by GCs in NK cells are an important source of protection against development of autoimmune disease. Given the scarcity of studies and knowledge gaps, this topic represents fertile ground for discovery of new pharmacological targets and new therapeutic strategies in the field of autoimmune disease therapy.

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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