Cross-talk between HPA-axis-increased glucocorticoids and mitochondrial stress determines immune responses and clinical manifestations of patients with sepsis

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Various stressors activate the hypothalamo-pituitary-adrenal axis (HPA-axis) that stimulates adrenal secretion of glucocorticoids, thereby playing critical roles in the modulation of immune responses. Transcriptional regulation of nuclear genes has been well documented to underlie the mechanism of glucocorticoid-dependent modulation of cytokine production and immune reactions. Glucocorticoids also regulate inflammatory responses via non-genomic pathways in cytoplasm and mitochondria. Recent studies have revealed that glucocorticoids modulate mitochondrial calcium homeostasis and generation of reactive oxygen species (ROS). Although redox status and ROS generation in inflammatory cells have been well documented to play important roles in defense against pathogens, the roles of glucocorticoids and mitochondria in the modulation of immunological responses remain obscure. This review describes the role of stress-induced activation of the HPA-axis and glucocorticoid secretion by the adrenal gland in mitochondria-dependent signaling pathways that modulate endotoxin-induced inflammatory reactions and innate immunity.

Introduction

Stress is defined as a response to various stressors that include hazardous chemicals, pathogens, and psychological events. Various stressors activate the hypothalamo-pituitary-adrenal axis (HPA-axis) to maintain a wide variety of homeostatic processes including immune responses. When exposed to stressors, HPA-axis-stimulated adrenal secretion of glucocorticoid modulates immunological reactions by regulating the transcription of nuclear genes encoding various cytokines and inflammation-related proteins. It has been well documented that strong stress suppresses innate immune reactions against a variety of pathogens, though its precise mechanism remains obscure. Hyper-activation of the HPA-axis and dysregulation of the neuro-endocrine network have been reported to underlie the pathogenesis of stress-induced emotional disorders, such as anxiety, anorexia nervosa and depression, and down-regulation of the host defense system against bacterial infection.[1–4]

Mitochondria are multi-functional organelles that synthesize ATP and regulate cell proliferation, differentiation, and oxidative signaling pathways leading to cell death. Thus, oxidative stress in and around mitochondria and their dysfunction have been postulated to underlie the pathogenesis of various diseases including mental disorders with abnormal immune reactions.[5–7] Recent studies have revealed that glucocorticoids also modulate mitochondrial functions[8,9] to regulate reactive oxygen species (ROS) generation and immune responses.[10,11]

The present article describes the role of mitochondria and HPA-axis-stimulated glucocorticoid release in the modulation of endotoxin-induced immunological reactions and the mechanism of immunosuppression.

Inflammatory response in sepsis

Sepsis is a syndrome induced by severe infection that causes uncontrolled acute systemic inflammation and organ dysfunction, and is a major cause of death in many countries.[12,13] The acute phase reaction against bacterial and/or viral infection is first initiated locally, followed by systemic reactions including

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fever, leukocytosis, tachycardia, tachypnea, and other symptoms of inflammation.[14] The current understanding of the immune response to sepsis is still controversial. Classically, the acute inflammatory response that elicits sepsis has been characterized by an over-reaction of innate immunity followed by perturbation of systemic immune reactions. Recent studies with patients and animal models have revealed that immunosuppression plays critical roles in the pathogenesis of sepsis.[14–16] Both pro-inflammatory and anti-inflammatory responses occur in an early phase of sepsis that causes immunosuppression. Hotchkiss *et al.*[17] suggested that immunosuppression associated with T-cell exhaustion is the major abnormality in sepsis. Thus, the balance between pro-inflammatory and anti-inflammatory responses and subsequent modulation of antigen-specific adaptive immune responses might determine the fate of patients with sepsis.

In an early phase of sepsis, ROS generation by damaged mitochondria, diminished cellular ATP level, and dysfunction of antioxidant systems might contribute to induction of multiple organ failure and

systemic inflammatory response syndrome (SIRS).[18,19] An uncontrolled innate immune reaction activates signaling pathways to generate pro-inflammatory cytokines that enhance ROS production and oxidative stress (Fig. 1). Interferon-γ, a pro-inflammatory cytokine, plays critical roles in the formation of ROS in macrophages to protect hosts against a wide variety of pathogens.[20] Furthermore, pro-inflammatory cytokines activate inflammation-related enzymes, such as GTP cyclohydrolase-I, indoleamine 2,3-dioxygenase, and inducible nitric oxide synthase.[20] Activation of these enzymes alters cellular redox balance to modulate the activity of NF-κB, a redox-sensitive transcription factor (TF), and immune responses.[21,22] Plasma levels of the products of these enzymes have been shown to be useful markers of the inflammatory response in patients with sepsis.[20,23,24]

Macrophages play pivotal roles in innate immune responses in patients with sepsis by producing ROS, nitric oxide, and cytokines. Stimulation of macrophages by pathogens is crucial for triggering the subsequent innate immune reactions.[25] The perception and
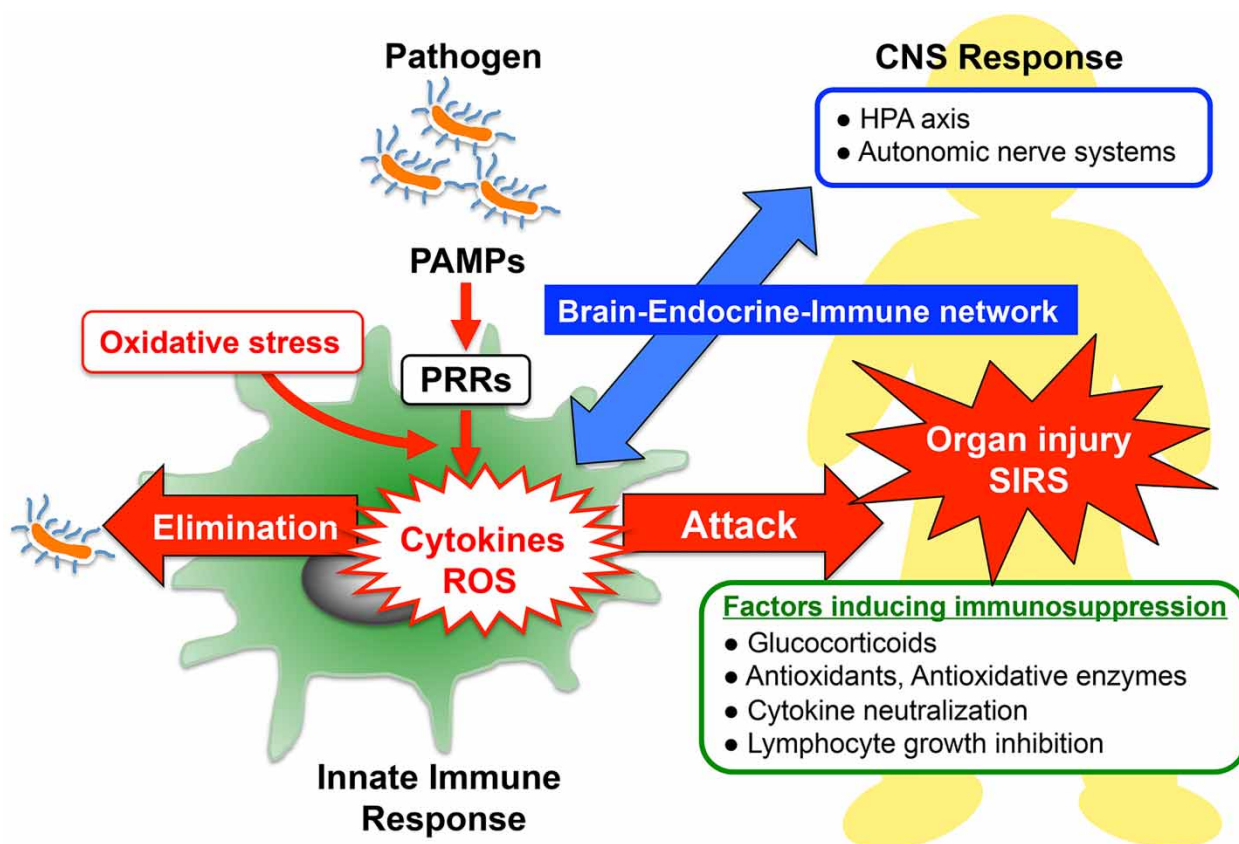
Figure 1 Innate immune response and host defense systems: The recognition of pathogen-associated molecular patterns (PAMPs) by pattern-recognition receptors (PRRs) located on the surface of host immune cells is a primitive part of the innate immune systems for protecting the host against invading pathogen. In the early phase of sepsis, an uncontrolled innate immune system enhances release of cytokines and generation of reactive oxygen species (ROS), which contribute to induce multiple organ failure and systemic inflammatory response syndrome (SIRS). Enhanced protective activity of the antioxidant network, cytokine neutralization or inhibition of lymphocyte growth might be of therapeutic potential in SIRS. In addition, optimal glucocorticoid secretion via HPA-axis stimulation in response to immune stress shows anti-inflammatory effects and enhances resistance against septic shock. Thus, the brain–endocrine–immune network might be important for the modulation of immunological balance during sepsis.

recognition of pathogen-associated molecular patterns (PAMPs) by pattern-recognition receptors (PRRs) localized on the surface of host immune cells is a primitive reaction of the innate immune system (see Fig. 1). Discovery of toll-like receptors (TLRs) and transmembranous PRR as primary sensors for microbial infection led to significant advances in understanding the pathogenesis of sepsis.[26] TLRs are expressed in various types of cells including neutrophils, T-cells, macrophages, and dendritic cells. Lipopolysaccharide (LPS) of gram-negative bacteria activates the TLR4 signaling pathway that stimulates ROS generation and cytokine production in immune cells.[27,28]

Besides stimulation by invading pathogens, extracellular and/or intracellular oxidative stress also enhances immune responses to LPS via a TLR4-dependent signaling pathway.[27,29–31] Oxidative stress enhances the recruitment of TLR4 to lipid rafts in plasma membranes of macrophages, thereby stimulating their response to LPS.[31] Oxidative stress-enhanced innate immune reactions might induce priming of inflammatory cells. Thus, modulation of the TLR4 signaling pathway and suppression of oxidative stress and/or oxidant-induced TLR4 recruitment to membranous lipid rafts of macrophages might be of therapeutic potential for the prevention of LPS-induced inflammation leading to septic shock.

Danger signals, including PAMPs and host-derived molecules, such as uric acid crystals, DNA and RNA, enhance the generation of inflammatory cytokines and elicit sepsis through the activation of inflammasomes. Recent studies have revealed the presence of the signaling pathway for innate immune responses involving mitochondria-dependent activation of inflammasomes.[32] Inflammasomes are molecular platforms for inflammatory signaling pathways that control the activity of caspase-1 to catalyze the maturation of pro-inflammatory cytokines, such as IL-1β and IL-18. Accumulating evidence suggests that modulation of mitochondrial functions, such as ROS generation, membrane potential, and mitochondrial DNA release into cytosol, is associated with inflammasome-dependent innate immune reactions. Enhanced activation of inflammasomes by inhibiting autophagy causes mitochondrial dysfunction and increases the susceptibility of macrophages to release mature forms of IL-1β and IL-18 after challenge with LPS and ATP.[32,33] Furthermore, mice lacking autophagy-related proteins in hematopoietic cells showed enhancement of ROS generation in macrophages and the inflammatory immune response to LPS.[34] These reports suggest that mitochondrial dysfunction and/or ROS generation in immune cells enhance the LPS-induced inflammatory response through the activation of inflammasome.

Factors that modulate inflammatory response

The redox buffer capacity plays a pivotal role in regulating immune responses. The roles of endogenous antioxidants and systemic redox balance have been investigated in patients and animals with sepsis.[35,36] Endogenous antioxidants, such as vitamin E, reduced glutathione (GSH), and ascorbic acid, play important roles in the metabolism of ROS. As ascorbic acid and GSH are water-soluble major antioxidants, various types of cells possess these antioxidants in high concentrations.[37,38] Perturbation of GSH metabolism by infection enhances cellular susceptibility to oxidative stress, thereby causing apoptosis and tissue injury in animals during sepsis. Since oxidative stress underlies the pathogenesis of endotoxin-induced septic shock,[21,35,39] the effects of various antioxidants and related enzymes have been evaluated.[19,40–42] Administration of the glutathione precursor N-acetyl-cysteine (NAC) decreased bacterial colonies, and improved survival in a mouse with polymicrobial sepsis induced by cecal ligation and puncture.[40] Wang *et al.*[43] reported that repeated administration of NAC during the early stage of severe sepsis effectively inhibited the activation of lung dendritic cells and their apoptosis, thereby preserving cellular functions in animals with zymosan-induced, generalized inflammation. Selenium-dependent antioxidant enzymes including glutathione peroxidase and thioredoxin reductase also play important roles in the regulation of cellular redox balance. The activity of these enzymes is affected by the availability of selenium. Patients with septic shock exhibited low levels of selenium and glutathione peroxidases in plasma and these showed negative correlations with the severity of manifestation of patients with sepsis.[44] Angstwurm *et al.*[45] reported that administration of a high dose of sodium selenite reduced the mortality of patients with severe sepsis and septic shock. Nrf2 is a major sensor of oxidative stress and a master regulator of antioxidant defense mechanisms.[46] Oxidative stress induces the dissociation of Nrf2 from Keap1, a negative regulator, and its translocation into the nucleus where it binds to the antioxidant response element in the promoter region of several antioxidant genes.[47] Since Nrf2 plays essential roles in the regulation of NADPH oxidase-dependent ROS generation, its disruption significantly increases the mortality of animals with polymicrobial sepsis and endotoxin shock.[29] As mentioned above, oxidative damage of mitochondria is also involved in the development of organ dysfunction associated with sepsis.[18,19] Treatment of septic animals with mitochondria-targeted antioxidants inhibited mitochondrial damage and inflammatory responses, thereby ameliorating organ failure.[41,42] Thus, increases in the protective

activity of the antioxidant network and mitochondrial integrity might be of therapeutic potential in septic patients with elevated oxidative stress.

Various stresses modulate signaling pathways leading to cytokine production, thereby altering immune responses.[48–50] Stress can either enhance or reduce immune responses.[51,52] Strong exercise stress exacerbated skin inflammation while mild exercise stress suppressed inflammatory responses in atopic dermatitis.[53] The mechanism for the strength-dependent pivotal modulation of immune responses by stress remains unknown. Dhabhar and McEwen[54] have reported that mild and short-acting stress enhances delayed-type hypersensitivity (DTH) reactions by adrenal stress hormones glucocorticoid and epinephrine, whereas high-dose corticosterone, chronic corticosterone administration significantly suppressed skin DTH. Yin *et al.*[55] have reported that strong and chronic stress induces immunosuppression by decreasing immune cells through a mechanism involving Fas-mediated apoptosis dependent on endogenous opioids. Inhibition of lymphocyte growth and changes in the balance of Th1/Th2 cytokines also affect inflammatory responses during sepsis. Chronic restraint stress increased Th2-related cytokines but decreased Th1-type cytokines by a TLR4-dependent mechanism,[55,56] and stress-induced up-regulation of TLR4 expression in lymphocytes and activation of the TLR4-PI3 K/AKT pathway play critical roles in lymphocyte apoptosis and immune suppression.[56] These results showed the role of stress-related hormones in immune response, and the divergent effects of stress on immune function.

When challenged with endotoxin, the HPA-axis stimulates adrenal secretion of glucocorticoids that have potent immunomodulatory and anti-inflammatory activities. Stress-induced glucocorticoids have been shown to induce enhanced resistance against septic shock.[57] Beneficial effects of glucocorticoids in sepsis-associated organ injury have been reported in animal experiments.[58,59] Thus, glucocorticoids have been used for treating patients with septic shock.[60–62] However, the effectiveness of glucocorticoids for improving the mortality of patients with sepsis is still under debate. Although a high dose of corticosteroid showed no beneficial effect on the prognosis of septic patients, physiologically low doses provided promising results.[60,62] Thus, optimal levels and duration of HPA-axis-stimulated glucocorticoid secretion might be important for the modulation of immunological balance in patients with sepsis.

Role of the HPA-axis in the modulation of immune reactions

Responses to stressors play critical roles in the maintenance of homeostasis in animals, aiding their survival by adapting to their environments. Stimulation of the HPA-axis and sympathetic adrenal–medullary axis through neuronal networks enhances the secretion of glucocorticoids and catecholamine, an adrenergic neurotransmitter. The neuro-endocrine system plays important roles in the regulation of stress-induced biological reactions including digestion of food, energy metabolism, immune systems, and control of emotion. Neuro-endocrinological regulation of immune responses is essential for the survival of a host suffering from infection and inflammatory diseases and glucocorticoids released by HPA-axis-dependent mechanisms plays critical roles in the regulation of immune systems.[63] In response to various stressors, corticotropin-releasing factor (CRF) is released from the hypothalamus into the hypophysial portal vein to stimulate the anterior pituitary gland, thereby releasing adrenocorticotropic hormone (ACTH) into the systemic circulation (Fig. 2). ACTH in the circulation binds to the type-2 melanocortin receptor (MC2R) in the adrenal cortex, where it stimulates the synthesis and release of glucocorticoids into the circulation.[64] Glucocorticoids secreted into the circulation inhibit further activation of the HPA-axis through the glucocorticoid receptor (GR)-mediated feedback mechanism in the brain, to regulate homeostasis of stress-related hormones.

Dysregulation of the HPA-axis also exacerbates the manifestation of sepsis syndrome and SIRS. Lipinska-Gediga *et al.*[65] reported that the median level of pro-atrial natriuretic peptide (pro-ANP), an ACTH-inhibiting factor, was significantly higher in non-survivors than in survivors with septic shock. They suggested that the plasma level of pro-ANP in these patients could be a valuable prognostic marker. Chida *et al.*[64] have established mice having an inactive MC2R gene in order to study its roles *in vivo*. MC2R-deficient mice lack the ability to produce glucocorticoids. In response to LPS, they showed increased release of inflammatory cytokines to exacerbate endotoxin-induced septic shock suggesting the important role of adrenal glucocorticoid release for immunosuppression.[66]

In contrast, the central nervous system (CNS) is also modulated by excessive release of pro-inflammatory cytokines, reactive oxygen and nitrogen species in the circulation and hypotension, associated with inflammation.[67,68] Macrophages at the site of infection are important for the initiation of the acute phase reaction of the innate immune system[69] that activates the HPA-axis in patients with sepsis. Circulating pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, stimulate the secretion of CRF and/or arginine vasopressin to release glucocorticoids. Thus, the release of glucocorticoids in response to peripheral inflammatory stress
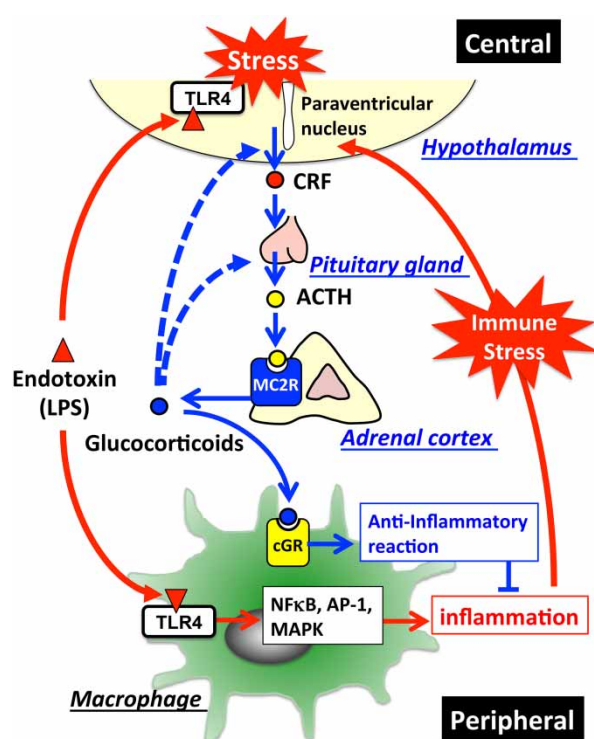
Figure 2 HPA-axis in response to LPS and cross-talk between the brain and immune system: The major part of the HPA-axis system is constituted by the hypothalamus, the pituitary gland, and the adrenal glands. When exposed to stressors, secretion of corticotropin-releasing factor (CRF) into hypophysial portal vessels stimulates the anterior pituitary gland thereby releasing adrenocorticotropic hormone (ACTH) into the circulation. Circulating ACTH binds to the type-2 melanocortin receptor (MC2R) in the adrenal cortex, where it stimulates glucocorticoid release. Elevated glucocorticoids in the circulation inhibit further activation of the HPA-axis through glucocorticoid receptor-mediated mechanisms in the brain so as to maintain homeostasis. Invading pathogens enhance glucocorticoid release that modulates the systemic immune response. TLR4-stimulated immune cells in response to LPS release excessive amounts of cytokines into the circulation, thereby stimulating the HPA-axis. In addition, LPS directly affects activation of the HPA-axis via the TLR4 signaling pathway exhibited in both the resident immune cells and neurons in the brain. Blue lines represent the HPA-axis to maintain homeostasis; blue dotted lines represent suppression of glucocorticoid release by negative feedback loops; red lines represent stimulation of the HPA-axis in response to LPS.

might be attributed to the ability of immune cells to produce various cytokines. The cross-talk between the peripheral immune system and the CNS via cytokines has important implications for modulation of host defense systems in stress condition.[49,70]

Direct effects of pathogens on the immunological activity of the brain also have been investigated. It has been reported that blood–brain barrier breakdown presents an early key step of pathogenesis in sepsis-associated encephalopathy.[71] TLR4, widely expressed in mouse brain, functions independently from the circulating cytokines to modulate brain-specific

inflammatory reactions and HPA-axis-induced adrenal secretion of corticosterone during endotoxemia.[72] Restraint stress significantly increased TLR4 transcripts in the hypothalamus compared to those in control mice, suggesting that preconditioning with restraint stress primes responsiveness of the hypothalamus to LPS through TLR4 signaling.[66] Neurons also function as key sensors for the modulation of inflammation through the TLR4 signaling pathway in the brain.[73] Thus, LPS-mediated direct activation of CNS may result in enhanced activation of the HPA-axis, leading to elevated levels of ACTH and glucocorticoids, which in turn suppress the release of pro-inflammatory cytokines from peripheral tissues. It appears that LPS may exert the bimodal effects in case of septic inflammation; that is, LPS may initiate and accelerate the inflammatory responses in the systemic organs, and, at the same time, LPS may activate the HPA-axis directly for suppressing the systemic inflammatory responses (Fig. 2).

Role of adrenal glucocorticoids in inflammatory response and immunological signaling pathways

Although therapeutic effects of corticosteroids in patients with septic shock remain controversial, it is certain that HPA-axis-stimulated adrenal secretion of glucocorticoids shows various beneficial effects against infectious diseases and disruption of the immune systems in patients with sepsis. Recent studies showed that stimulation of the HPA-axis followed by glucocorticoid release, increased expression of GRs, and up-regulation of glucocorticoid-induced leucine zipper (GILZ) contribute to enhanced resistance to endotoxin-induced septic shock.[57,74,75] Furthermore, antagonism of GR by RU486 enhanced the generation of LPS-induced pro-inflammatory cytokines and decreased the survival rate of septic mice[75] without altering the stimulation of HPA-axis-induced glucocorticoid secretion.[66] These findings suggest that receptor-dependent glucocorticoid signaling plays critical roles in the modulation of the LPS-induced immune response.

Glucocorticoids regulate various cellular events, such as energy metabolism, mitochondrial activity, apoptosis, and immune responses.[76] Among various functions of glucocorticoids, anti-inflammatory and immunosuppressive effects have been well documented.[77] The cellular response to glucocorticoids is initiated by binding to an inactive form of GRs in the cytosol (Fig. 3). Then, the GR complex exhibits transrepression to inhibit the transcriptional promoting activity in cytosol by interacting with TFs and transactivation in nucleus by binding to its responsive elements on DNA. Transcriptional activation by homodimeric GRs increases the synthesis of anti-
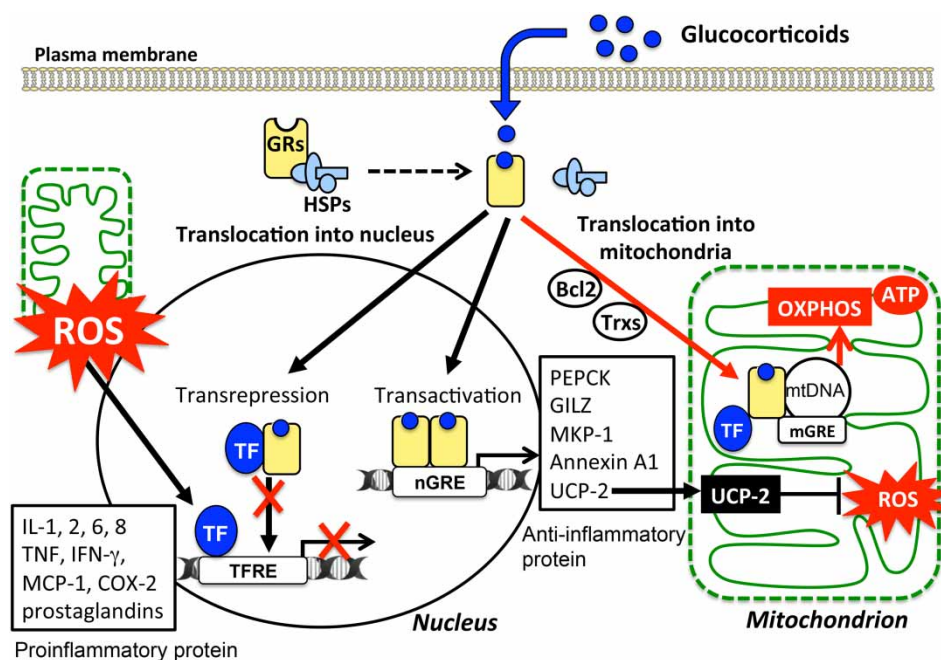
Figure 3 Variety of cellular responses to glucocorticoids and modulation of mitochondrial functions: Cellular responses to glucocorticoids are initiated by its binding to the cytosolic glucocorticoid receptors (GRs) in their inactive form. Homodimers of the GR complex bind to nuclear glucocorticoid response elements (nGREs) and activate the gene transcriptions driving the expression of anti-inflammatory genes including those encoding annexin A1, glucocorticoid-induced leucine zipper protein (GILZ), and mitogen-activated protein kinase phosphatase-1 (MKP-1) (transactivation). In addition, GR complex up-regulate the expression of uncoupling protein-2 (UCP2) thereby suppressing mitochondrial ROS generation. On the other hand, GRs may complex with transcription factors (TFs) such as NFκB and AP-1 thereby preventing them from binding to their target genes, including pro-inflammatory genes such as *IL-1B*, *TNFA,* and chemokines (transrepression). Mitochondrial generation of ROS enhances the activity of these TFs. Activated GRs also modulate mitochondrial functions in various cells including neurons, hepatocytes, and immune cells. The mitochondrial genomes of human and rat contain sequences similar to that of the nGREs. GREs in the mitochondrial genome (mGRE) modulate the biosynthesis of the proteins involved in oxidative phosphorylation (OXPHOS) by regulating mitochondrial gene expression. Furthermore, interactions of GRs with B-cell lymphoma-2 (Bcl-2), and mitochondrial thioredoxin (Trx2) regulate mitochondrial function including oxidation, energy production, and cellular survival.

inflammatory proteins including annexin A1, GILZ, and mitogen-activated protein kinase phosphatase-1. On the other hand, glucocorticoids bound to monomeric receptors form a complex with TFs, such as NFκB and AP-1, to inhibit their binding to the pro-inflammatory target genes (TFRE) including pro-inflammatory genes such as *IL-1B*, *TNFA*, and chemokines (transrepression).

Besides transrepression of pro-inflammatory cytokines and transactivation of anti-inflammatory proteins, a non-genomic glucocorticoid signaling pathway has been reported recently. Several lines of evidence suggest the presence of a novel pathway of glucocorticoid action that modulates mitochondrial respiration, calcium homeostasis, and apoptosis.[8–10,78,79] The nucleus and mitochondria coordinately regulate cellular expression of various genes encoding gluconeogenesis-related enzyme (PEPCK), fatty acid synthase (FASN), and mitochondrial respiratory proteins in order to maintain cellular homeostasis. Recent studies demonstrated the presence of activated GRs in mitochondria.[78] Furthermore, the genomes of human and rat mitochondria contain sequences similar to those of the glucocorticoid

responsive elements (GREs) in the nucleus.[80,81] Glucocorticoids modulate the biosynthesis of proteins involved in oxidative phosphorylation (OXPHOS) by regulating mitochondrial gene expression.[78,82] Besides a direct action of the GR complex on mitochondrial gene expression, GRs in mitochondria interact with TFs and proteins to modulate mitochondrial functions. GRs have been shown to interact with thioredoxin (Trx2) and regulate gene expression in mitochondria.[83] In response to corticosterone, the glucocorticoid–GR complex also interacts with Bcl-2 and translocates into mitochondria to regulate mitochondrial oxidation, membrane potential, and calcium homeostasis, thereby affecting neuronal death and plasticity.[8] Thus, exposure to glucocorticoids might directly modulate mitochondrial function through the GR signaling pathway.

The activities of the glucocorticoid–GR complex often exhibit conflicting and biphasic effects on cell survival and immune responses. Elucidation of non-genomic mechanisms of glucocorticoids that modulate mitochondrial functions and immune responses might contribute to evaluating the efficacy of glucocorticoid therapy in patients with sepsis.

Role of mitochondrial ROS and glucocorticoids in the mechanism of immunomodulation

Mammalian tissues have a high concentration of ATP generated by OXPHOS. In a human being, fairly large amounts of oxygen ($\sim$500 l/day) are required to regenerate this amount of ATP. Most molecular oxygen used in mitochondria is converted to H_2O by a four-electron reduction mechanism. However, under physiological conditions, significant fractions (about $\sim$2%) of the inspired oxygen are converted to the superoxide radical and related ROS using electrons released from the electron transport system. Therefore, mitochondria play critical roles in intracellular generation of ROS. Most but not all ROS rapidly react with a variety of molecules, thereby modulating cell functions. Because of the high reactivity of ROS, they should be effectively metabolized at or near the site of generation by enzymatic and/or non-enzymatic mechanisms.

Mitochondria in macrophages play critical roles in the regulation of innate immunity.[84] We previously reported that mitochondrial density and their respiratory state contribute to LPS-induced immune responses of macrophages via an ROS-dependent mitogen-activated protein kinase (MAPK) pathway, without activating NFκB.[85] Uncoupling protein-2 (UCP2) regulates the extent of uncoupling of the electrochemical gradient of mitochondria and reduces ROS generation in mitochondria. Suppression of mitochondrial ROS generation by UCP2 in macrophages has been shown to modulate the innate immune response.[86] Several reports have suggested the physiological importance of UCP2 for suppressing the generation of ROS in cells and tissues.[87–89] Expression of UCP2 is fairly high in the spleen, lung, and macrophages,[90] suggesting its role in innate immunity and/or inflammatory reactions. *UCP2$^{-/-}$* mice are more resistant to infection with *Toxoplasma gondii* and *Listeria monocytogenes* by generating a higher level of ROS than wild-type mice.[90] They showed high levels of cytokines that mediate macrophage-dependent innate immunity. In contrast, transgenic mice overexpressing UCP2 showed reduced oxidative damage and inflammatory response in ischemic brain injury.[91] These reports suggested that regulation of mitochondrial ROS by UCP2 plays critical roles in the signaling pathways that control immune responses.

Recent studies have suggested the involvement of glucocorticoids in the anti-inflammation and immunosuppression through inhibition of mitochondrial ROS generation.[66,92,93] Recent studies in this laboratory using restraint stress mice suggested that glucocorticoid-induced up-regulation of UCP2 in macrophages reduced mitochondrial ROS generation and production of pro-inflammatory cytokines in LPS-induced sepsis.[66] The promoter region of UCP2 gene contains GC-rich domains and the regulatory elements for Sp1, AP-2, AP-1, CREB, and the GREs.[94] These reports suggest
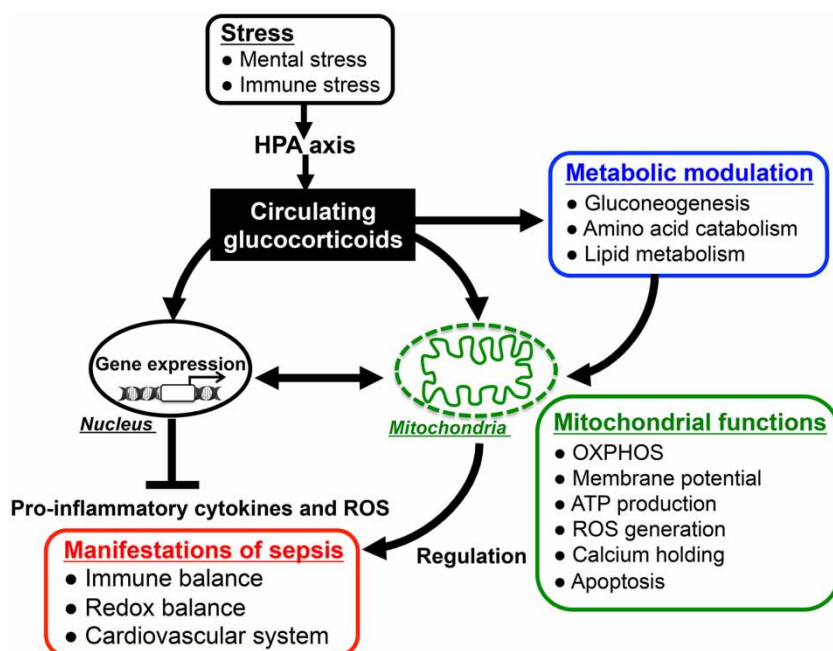
Figure 4 Glucocorticoid actions for immunomodulation via nucleus- and mitochondria-dependent signaling pathways: Glucocorticoids have pleiotropic effects on energy metabolism (gluconeogenesis, amino acid catabolism, fatty acid metabolism), mitochondrial activity, and immune responses. The alteration of mitochondrial functions such as oxidative activity, ATP production, and apoptotic signaling in response to glucocorticoids plays important roles in modulating host immune responses and redox systems. Thus, appropriately stimulated HPA-axis followed by glucocorticoid release in response to endotoxin-induced immune stress might reduce the parameters of inflammatory response and improve the mortality in sepsis through both nucleus- and mitochondria-dependent signaling pathways.

the possible novel glucocorticoid action for suppressing immune response through UCP2 up-regulation. In immune cells, LPS-stimulated signals itself suppress UCP2 expression and up-regulate mitochondrial ROS generation, thereby increase production of pro-inflammatory mediators in macrophages.[87,95] In contrast, it has been reported that oxidative stress induce UCP2 expression thereby down-regulating ROS generation in immune cells.[87,96] Although expression of UCP2 in immune cells is down-regulated in mice during the early stage of the LPS response, it increased at a later stage and protected cells from oxidative stress.[87,95,97]

The glucocorticoid-dependent immunosuppression might be caused, in part, by alteration of mitochondrial functions and ROS generation. Thus, stress-induced glucocorticoid release by the HPA-axis might contribute to the suppression of inflammatory immune response of patients with sepsis through both nuclear and mitochondrial signaling pathways (Fig. 4).

Conclusion

The neuro-endocrine-immune network driven by the cross-talk of the HPA-axis, glucocorticoids, and mitochondria plays critical roles in the modulation of host defense systems against invasive pathogens that cause septic shock. Modulation of this cross-talk might have therapeutic potential for treating patients with severe infection and septic shock.

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Disclaimer statements

Contributors Kasahara conducted this work. Inoue contributed to this study with his critical discussion and suggestion. Kasahara and Inoue interpreted this study and wrote the paper.

Conflicts of interest None.

Ethics approval This work was approved by the ethical committee of Osaka City University, Graduate School of Medicine.

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