WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 5, 185-212. Review Article ISSN 2277– 7105

THE IMPACT OF STRESS ON IMMUNITY, MECHANISM AND PATHWAYS INVOLVED

Muhammad Sohail, Xinghua Gao, Yan Cheng, Qiuhua Cao, Stephanie Stella Mica Avouloumeyo, Yang Yong*

State Key Laboratory of Natural Medicines, Jiangsu KeyLaboratory of Drug Discovery for Metabolic Disease, Center for New Drug Safety Evaluation and Research, China Pharmaceutical University, Nanjing 211198, China.

Article Received on
12 March. 2017,

Revised on 02 April 2017,
Accepted on 22 April 2017

DOI: 10.20959/wjpr20175-8262

***Corresponding Author**
Prof. Yang Yong
State Key Laboratory of Natural Medicines, Jiangsu KeyLaboratory of Drug Discovery for Metabolic Disease, Center for New Drug Safety Evaluation and Research, China Pharmaceutical University, Nanjing 211198, China.
yy@cpu.edu.cn

ABSTRACT

This is established fact that stress is harmful for human body. There is a need to identify the adaptive and curative measure to manage physiological stress reaction at the time of fight and flight. Usually treatment of chronic stress has the potential to suppress and deregulates the adaptive and innate immune responses while the short term stress has shielding effects to organize an individual to deal with challenges. Chronic and acute stress can encourage the pronounced modifications in inborn and adaptive immune response and these modifications are largely mediated through mediators of neuroendocrine from sympathetic–adrenal axis and hypothalamic–pituitary–adrenal axis. In depression, the immune system response is impaired with chronic stress by continuous stimulation of the HPA. Activation of SAM and HPA in response to chronic stress causes excessive production of catecholamine and glucocorticoid hormones. The key mechanistic evidence about the physiological changes and stressor is provided by psychoneuroimmunology (PNI). Immune cells (binds with the cartisol) having highly expressed glucocorticoid receptors interfere with the function of NF-κB which is responsible for the regulation of cytokine-producing immune cell's activity. Epinephrine and norepinephrine bind and stimulate the response of cAMP, resulting in transcription of the genes encoding various cytokines. The variations in gene expression that deregulate immune function are mediated by glucocorticoid hormones and catecholamine. This review study

summarizes the positive and negative impact of short term as well as chronic stress on the immune system.

KEYWORDS: Stress, Immunity, Hypothalamic-pituataryaxis, Sympathetic nervous system, cytokines.

INTRODUCTION

The two dominant flexible component systems of the body are immunity and brain, the correlation between these two systems results homeostasis.[1] The biomedicine researches from the last few decades proved a strong reciprocal connection between stress, immunity and inflammation.[1 2] The associations among immunity, stress, inflammation and health are broadly reported[1] and mainly focus upon anti-inflammation.[3] In the field of psycho-neuroimmunology(PNI) researchers are focused[4 5] on the interaction of immune system with the central nervous system, different physiological reactions and endocrine system.[6 7] It mainly focuses the interactions among immunity, central nervous system (CNS) and endocrine system and their impact on health. The inflection of immune feedback by the central nervous system is resolved by a complicated system of signals that perform dual directional link between immunity, nervous and endocrine system.[8] The immune functions which are associated with the stress can be altered by many pathways, for example; SAM pathway and HPA Axis pathway.[1 2 9] The catecholamine and cortisol[10] are the products of SAM and HPA pathways which are produced by the receptors exhibited by granulocytes, lymphocytes, macrophages as well as monocytes.[6,8,10,11] The hormones which link with the HPA and SAM Axis, for that immune cells have more than one or one receptors and that are called stressor hormones and these hormones either bind directly or indirectly to the surface of cell and effect the cytokine production, such as IL1,IL2,IL6,INFγ, TNF,[12,13] and immune response might[14] be affected by the stressors through many pathways.[12,15,16]

Immunosenescence,[17,18] and prolonged stress can cause the abnormalities in endocrine and immune system[19] that is associated with different kinds of pathological conditions such as asthma, development of HIV and AIDS[20,21] diabetes, cancer, osteoporosis, infectious disease, auto-immune responses and Alzheimer's disease.[18,22,23] Moreover prolonged inflammation and irregularity in immune system can develop various kinds of life threatening diseases[24 25] like metabolic syndrome, cancer [26 27] and cardiovascular disease(CVD).[28]

The elucidation of biological and psychological processes through which the health is weakened by these chronic stressors is imperative in order to develop the pharmacological and behavioral treatments to eradicate the harmful impacts of the chronic stress. The activation of different systems takes place in response to short term stress, such as neuromuscular system, cardiovascular system, neuroendocrine system are activated for ‘’fight or flight’’ response and thus short term stress is also associated with the preparation of the immune system to deal with the infection or wound caused by the stressors. There are several studies that have discussed the role of short term stress in the activation of the immune system and also in the enhancement of the reaction.[6,29,30]

The primary and secondary adaptive immune responses can be enhanced by the short term stress and the activation of these types of responses is dependent on the characteristics of the activating agents and the conditions.[30,31] When the duration of the stressors continues for a prolonged time, the immune response decreases gradually (Figure 1).

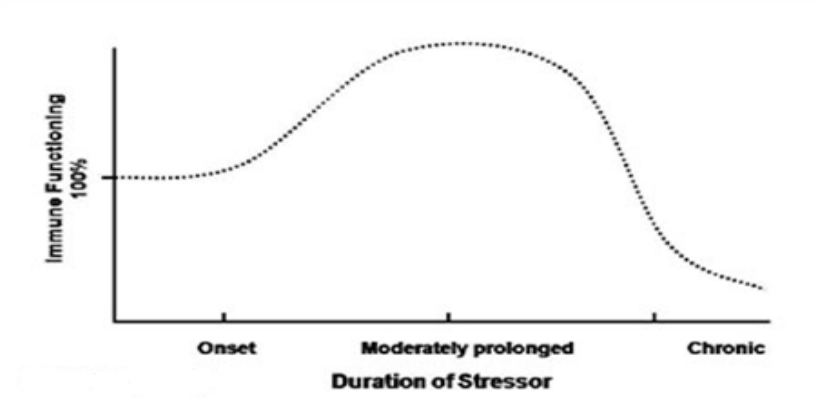

Fig 1: Relationship between duration of stressor and immune functions.

There are different types of immune response produced by different range of the stress. This review describes about the stress and immunity in a comprehensive manner as well as it is also associated with the description of the impact of the continuous stress in decreasing the immunity with the aid of description of the possible mechanisms that are associated with the stress and immunity. This review study is also based on the description of the correlation between the stress pathway and immunological pathways.

STRESS IMPACT ON IMMUNITY

In medical context, the term stress is used to represent the emotional, mental or the physical element which may cause the mental tension or body tension. The stresses are of two

different types, internal and external. The example of internal stress is illness while the examples of external stresses are any type of social or psychological conditions.[32] In 1930 Hans Selye suggested that chronic stress can be the cause of shortening life period by weakening the body.[33] Stress has both negative and positive aspects for the brain and the positive aspect of stress is essential for survival.[34] Where as the negative side is associated with the chronic stress, because stress hormones vary the functions of brain.[34 35]

Impact of Short term and chronic stress on immunity

Acute stress condition alerts the species to cope up with the condition, but that response is for the short time. When the stress is continuous, it causes the activation of sympathetic nervous system and cortisol level that decrease immunity and can cause inflammation easily in the patient.[36] High level of glucocorticoids produced in a chronic stress condition that can decrease the body response to insulin and increase the level of fat and glucose in the blood stream so the individual is at high risk to develop the Type 2 diabetes and heart disease. Furthermore it also interacts with the hypothalamus to decrease infertility by inhibiting the hormones which are responsible for reproduction such as LH and FSH.[37,38] Acute stress has some advantages, like it cause the activation of sympathetic nervous system that increase the heart rate and blood flow and alter the blood flow from kidneys and stomach to the muscles and brain but, continuation of this condition for long time cause coronary disease or atherosclerosis.[39,40] Different kinds of gastrointestinal tract infections, mood disorder, dermatologic and respiratory infections are related to HPA dysfunction and chronic stress.[9] (Fıg 2).

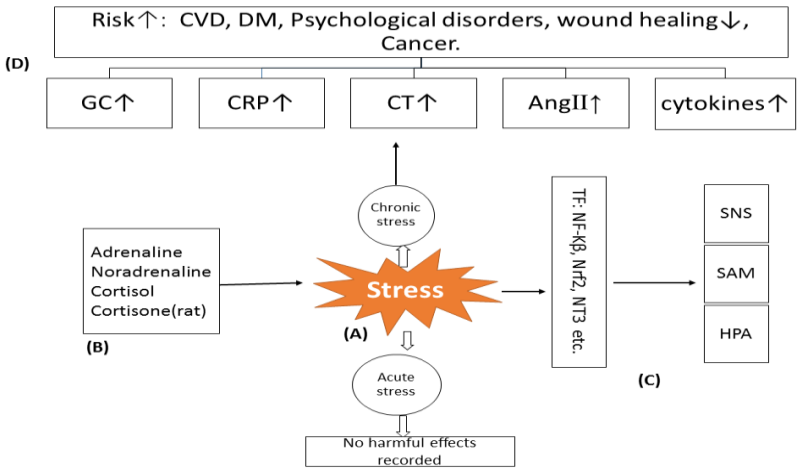

Fig: 2. Stress may be acute (short term) or chronic (long term). While with short term stress no significant diseases recorded. B: stress hormones C: transcription factors and pathway Hypothelamic pituatory adrenal HPA axis, Sympathetic adrenal medullary

axis etc. D: chronic stress increases the level of glucocorticiod, endothelin, angiotensin 2, various cytokines thus the chances of disease increase.

The link of the stress and the stress proteins on the immune system in the infections, depression, cancer etc. has revealed the impact of stress on the immune pathways of the body. The inflammation is an immune response to the infection or pathogen exposure and the stress has a close link with inflammation as both can activate or inhibit each other. The activation or inhibition is dependent on the cell type of the immune system and the nature of the stress inducing signals which can be any physical agent, any chemical or pathogen.[40 41] Many studies in animal and human provide strong evidence that stress episodes alter various immunologic mechanisms that are essential for health. To know about the relationship among the psychosocial stressors and expansion of infection, the researchers have given various kinds of vaccines to the subjects.[42-45] The individual who gave, delayed response to vaccines were considered to be at high risk for infectious diseases because of the slow immune response.[46] The stress is beneficial in many ways as it leads to the activation of the immune system thus defending the body; however, the long term psychological stress leads to the activation of the defense mechanisms which are not beneficial and causes the acceleration of the disease.[38]

OVERVIEW OF IMMUNITY

According to medical context, the immunity is the term that representing a balanced state when person have adequate defense system to fight against any type of the biological invasion, diseases and infection. Moreover, it is the state of the body in which body has the tolerance to fight against autoimmune diseases and allergy.[47] When a pathogen attacks on the body first mucosal membrane and skin block that pathogens, but if it is failed, then neutrophil, macrophage and monocyte detect the pathogens and engulf them. Furthermore, it causes the activation of transcription factors such as NF-κB and interferon (IFN) and these factors manifest the pro-inflammatory immune response genes(IL-1,TNF-α).Then these genes create cytokines which are responsible for inflammation.[48,49]

TNF-α, IL-6, IL-1 (pro-inflammatory cytokines) boost while IL-10 (anti-inflammatory cytokine) reduces the inflammation. Natural killer cells have also role in the innate immunity. Natural killer cells produce some harmful materials on the cell surface that break them into pieces. The response of innate immune is nonspecific. When the innate immune response is unable to control the pathogen, acquired immune response is activated which is specific in

action. Lymphocytes T(TH,Tc) &B are the basic cells TH helps in the recognitions of antigen B cells help in the production of antibodies while cytotoxic T cells causes breakdown. The action of acquired immune response is slow.[50] Two kinds of responses are associated with acquired immunity, cellular immune response with the help of Th1 works against the pathogen which are inside the cell (virus etc.) and produces various cytokines(IL-2,TNFb,IFNγ)that promotes inflammation and stimulate cytotoxic T cells and macrophage and causes the breakdown of sick cells. While the humoral response with the help of Th2 (sub class of helper T cells) work against the extracellular (parasites) and causes the production of IL-4 which motivate the eosinophil and mast cells. It suppresses the macrophage stimulation, T cells propagation and creation of pro-inflammatory cytokines.[51] Normally, the reaction of immune system depends upon the balance between Treg and Tcells which are responsible for many kinds of fragments regulations like cytotoxic T lymphocytes antigen 4,IL-10, CD25etc.[52 53] Immune response in mammals can also be varied on the basis of gender differences. Innate immunity reaction in mammals shows variation according to gender difference. It may be because of encoding of the germ line. May be because of inactivation from the X chromosome. The appearance stage of Toll Like receptor TLR7 is more in females than males.[54] IFNα is highly produced in females as compared to males because the peripheral mononuclear cells are exposed to TLR7.[55] Research on humans shows that the Treg cell count is more in men than women.[56] disregarding of age the immunoglobulin, B cells concentration and the response of antibody is more in women as compared to men.[57-59] Worldwide study on the gene expression of B cells tells that most of the genes variably express among the genders and meaningfully managed in women than men.[60]

Stress as a trigger for activating the immune system

Pre-clinically different kinds of stress paradigms are used to study the development of depressive-like behavior.[61] It is thought that clinical condition may be more reflected by the chronic mild stress. Exposure to mild stressors for a long time encourage the anhedonic behaviors in rodents, and their preference for sucrose solutions is reduced.[62] Stress in the early life has also a very vital impact on the improvement of neurological systems concerned in mood and stress responses, thus increasing the susceptibility to stress and so the risk of developing depression later in life, specifically in response to secondary stress.[63-68] Preclinical studies shows that gut permeability can be increased by the psychological stress, therefore enabling gut flora to reach the systemic system.[69] Another study reported that in

the plasma of depressed patients the presence of antibodies against endotoxin, form a various commensal bacteria. Accordingly it is possible that on the outer cell wall of gram negative bacteria, the presence of potent innate immune stimulus and bacterial endotoxin, lipopolysaccharide (LPS) could activate the systemic low grade inflammatory response in the stressed patients, but that mechanism is not fully cleared.[70] Similarly a study suggest that the isolated T and B cell from mice ,when it exposed to the chronic stress its increase the expression of muscarinic receptors.[71] The mechanistic propulsive force underpinning stress-induced immune stimulation involves synergistic properties of the SAM, PVN and HPA axis.[72] Thus it is clear that stress acts as a trigger to activate the immune system.

PATHWAYS OF STRESS AND IMMUNE FUNCTION

Stress can affect the immunity by many pathways among these pathways sympathetic nervous system SNS and hypothalamic pituitary adrenal HPA axis are important.

Sympathetic nervous system

Autonomic nervous system ANS is activated in many stress condition e.g. entering the examination hall, situations at the time of first kiss etc. ANS have two classes sympathetic nervous system SNS and parasympathetic nervous system PNS. Stimulation of SNS activates the body to deal with harmful stimuli and also increase the flow of blood to the main parts of the body (kidney, heart, lungs, brain, muscles).[73] It also causes the reduction of blood flow to skin and GI tract.

SNS is also known as for fight or flight from adrenal medulla it releases the catecholamine (epinephrine, norepiephrine) and interacts with the α and beta adrenergic receptors and promote IL-1,TNFα, IL-6 productivity.[74,75] Norepinephrine stimulates the NFkB which further proliferates the expression of genes of various proinflammatory cytokines(IL-6,IL-8) and this condition increases the inflammation.

The activity of norepinephrine is potentiated by neuropeptide Y (NPY). It is also imagined to be the type of stress hormone that facilitates coronary belonging of stress e.g. (BP control etc.).[76] NPY in combination with epinephrine and nor epinephrine increase the platelets clumps, adhesion of leukocytes and stimulation of macrophage.[74] Chronic activation of SAM causes the disregulation of immune system. The connection between the sympathetic nervous system and immune system can be suggested that the sympathetic nerve fibers which are noradrenergic move from CNS to the other lymphoid tissues.[77]

Hypothalamic pituitary adrenal axis

Locus ceruleus-norepinephrine (LC-NE) and corticotropin-releasing hormone (CRH) are the main parts of the CNS that control the action of SNS and HPA.[78,79] Arginine vasopressin (AVP) also contributes but CRH plays the key role in the activation of HPA. The CRH moves through pituitary gland and activates the releasing of adrenocorticotropic hormone (ACTH).[11,80] AVP acts as a strong synergistic influence with CRH activation and release. Additionally, in the hypothalamus, AVP and CRH mutually interact with the neuropeptide secretions. ACTH starts to circulate in the blood and activate the adrenal medulla (outer part) and secretes glucocorticoids.[11] (see fig 3). The action of cortisol (human) in muscles motivates the lysis of amino acids to glucose for energy purpose and also stimulates the insulin resistance and allows the glucose in blood flow. To deal with the stress condition, it also increases the cardiac output and BP.[11,81] In healthy situations, cortisol suppresses the immune system, decreasing the count and action of inflammatory cells which circulates (monocytes, lymphocytes, neutrophils, macrophages, mast cells, eosinophil) preventing the formation of proinflammatory cytokines, also preventing macrophage antigen performance. Cortisol acts on cytoplasmic receptor, inhibition of stimulated receptors, interaction between proteins and NF-κB (transcription factor).

The negative role of cortisol on HPA Axis is that, in Hippocampus it attaches to the receptor of glucocorticoids and decreases the ACTH and CRH production that automatically power off the stimulated coordination. In brain the neurotransmitters and neuropeptides (γ-aminobutyricacid-benzodiazepines GABA-BDZ) and ACTH negatively control the CRH. These mechanisms assure that the inflammatory response is not beyond the limits that are harmful for the organisms.[11]

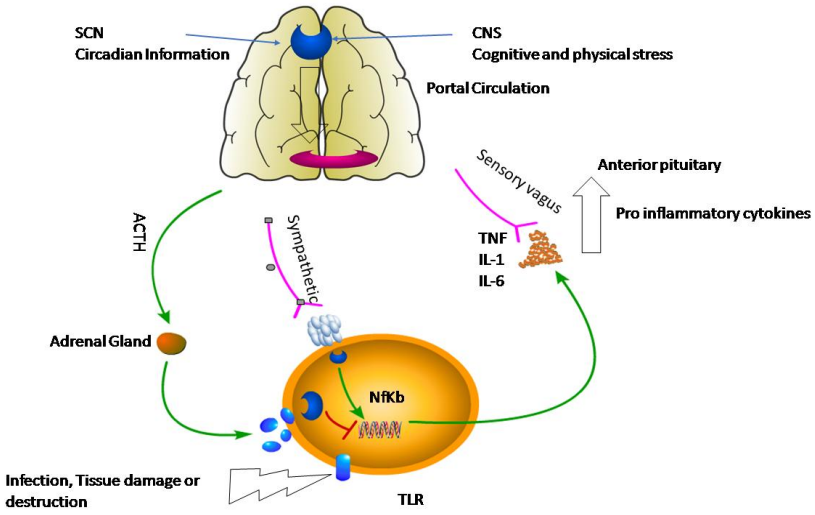

Fig. 3: TLR activate NF-be which further stimulate the pro-inflammatory cytokines, with the help of sensory nerves to sensory nerve it deliver the information to brain in PVN it release the CRH which further cause the release of ACTH, and adrenal gland cause the release of glucocoticoid. While in sympathetic nervous system the released neuro-transmitters bind with α and beta receptors.

Alteration in SNS and HPA axis and Immune system

The lymphoid tissues (elementary& up elementary) are furnished by sympathetic noradrenergic nerve fibers.[82] Interaction between hormone and its receptor on cell surfaces directly related with immune regulation. Stress hormones that are responsible for the stimulation of HPA axis and sympathetic (adrenergic) activity, for those nearly all immune cells have receptors.[6,12,83] Particularly, receptors present on B cells, T cells macrophage and monocyte for the Substance P, glucocorticoids, neuropeptide, growth hormones, catecholamine's, serotonin and prolactin. For corticotrophin-releasing hormone T cells also have receptors. Finally, complex of stress hormones and its receptor on the cell surface can affect the initial reaction within the cells that resulting alteration in the cell function.

Immune responses are also regulated by the stress hormones indirectly, deviating the production of cytokines (TNF,IL-1, IL-2, IL-6).[6] The mentioned cytokines have many roles in targeting different cells and differentiations on functions of these cytokines can occur late downstream effects. Immune cells produce cytokines and these cytokines perform dual actions and can regulate and feedback the brain (counting HPA axis and SNS).[21 72 84]

Interaction of HPA axis with immune system

HPA axis can be activated by different mechanisms of some cytokines. Their primary role on PVN is stimulating CRH release[85,86] but they also have direct effects on the the level of the pituitary and adrenal.[87]

Concurrently, glucocorticoids have impacts on viability and functions of many immune cell types, including T cells, B cells, monocytes, macrophages, and granulocytes.[88 89] Synthesis and release of cytokines are suppressed by glucocorticoids, therefore it is directly related on protecting the host organism from the detrimental consequences of a long-term hyperactivity of the immune system.[90] Immunosuppressive actions of glucocorticoids are demonstrated by Hench, Kendall, and Reichstein almost 70 years ago.

In recent studies, it is thought that glucocorticoids can also have permissive effects on immunity system, for instance while acute stress enhances, chronic stress suppresses the peripheral immune response but the mechanism of this dual role is not well elucidated yet.[91-93]

Moreover, in several studies it is reported that glucocorticoids induce expression of innate immune-related genes, including members of the toll-like receptor (TLR) family, such as TLR2 and TLR4 and also rapidly induce a central component of the inflammasome,[94-96] NLRP3, in macrophages, which stimulates secretion of pro-inflammatory cytokines.[97]

CORRELATION BETWEEN STRESS PATHWAY AND IMMUNOLOGICAL PATHWAY

Nuclear factor (Nrf2) is a transcription factor that is associated with the regulation of the expression of genes with the help of a promoter sequence in several types of cytoprotective phase II detoxification and antioxidant enzymes. The promoter sequence is termed as responsive element (ARE) which is found in wide variety of the cytoprotective genes. The pivotal role is played by Nrf2 in the ARE-driven cellular defense system leading to protection of the body against different types of environmental stresses. Different agents that make the ARE/Nrf2 pathway are tested for wide variety of diseases with the help of the Nrf2-activating drug. The in vivo and in vitro experiments are performed by several scientists and the results of clinical trials have proved that Nrf2-activating strategies such as some types of drugs, foods, supplements and some exercises can lead to the prevention of diseases, prevention of the re-occurrence of disease, slowing down the disease progression a very early stage.

Therefore Nrf2-activation which is a stress pathway is very promising in order to tackle the pathophysiology of cancer.[98] The Nrf2 pathway activation has now become widely accepted as chemoprevention beneficial, but it may be harmful or even un-harmful in established cancers. For instance, Nrf2 activation may result in the interference with the chemotherapies or radiotherapies or may cause additional growth to the tumor cells[99] ARE/Nrf2 pathway thus has a great importance both by activation and by inhibition, as a possible target for the pharmacological control of immunological and degenerative diseases, and the regulation of this pathway is a promising biological target for developing advanced therapies.

MECHANISM INVOLVED IN STRESS AND IMMUNITY

A wide range of research carried out in the last decade, has revealed that the receptors related to the recognition of innate immunity and the intracellular pathways related to signaling terminate the inflammatory processes. In addition to the role of cell stress in cytoprotection, it has now become evident that cell stress is also significant in the defense process against pathogens and inflammation. There are several mechanisms that link the stress with immunity. One mechanism involved is that in case of any disease or adverse condition; the stressors are released that activate the cortisol to inhibit the expression of the TNF-α and IL-1,IFN-γ from the immune cells. Moreover, the stressors also increase cytokines that has a control on the activity of helper T-cells. This stress mechanism is related to immunity as it is effective mechanism to protect the immune system from over activation that can be weakened by the process of inflammation.[100,101] The other mechanism related to stress and inflammation is that to any stressor response, different physiological changes occur to assist the person to overcome stress. The chronic stress has a bad impact on the immune system and the mechanism is that the chronic activation of the stressors, at the SAM axis and the HPA axis lead to the formation of the catecholamine's and glucocorticoid hormones. The glucocorticoid receptors that are expressed on several types of immune cells that then make the binding with the cortisol. These bindings result in the interference with the functions of the NF-kB leading to the regulation of the function of the cytokine-producing immune cells. The binding of the adrenergic receptors to the epinephrine and norepinephrine causes the activation of the cAMP response element binding protein that causes the induction of the transcription of genes that encodes several cytokines. The immune function can be dysregulated by the catecholamines and glucocorticoid hormones mediated gene expression.[13,102]

The immuno-enhancement mechanism of the stress leads to the alteration in the dendritic cell, macrophage, neutrophil, and trafficking and maturation of lymphocyte and other immune enhancement mechanism of immune system is cytokine production. However, the immune-suppressive mechanism by which continuous stress leads to dysregulation and suppression of innate and adaptive immune system include the alteration in the balance of cytokines type 1 and type 2, that suppress the function of immune protective cells and induction of low-grade chronic inflammation. Moreover, chronic stress follows the mechanism of suppression of the protective T cells and Type 1 cytokines and increasing the function of the suppressor T cell, that can lead to the cancer.[13]

ROLE OF STRESSORS IN IMMUNITY

A series of examination are carried out in mice and other non-human primates to evaluate the role of stressors in the induction of immunity after the exposure to antigen. The results of such experiments revealed enhancements in the induction and immunization phase and different stressors produced at the time of exposure to antigen are responsible for such induction and sensitization. Furthermore, the review of other studies has revealed that a notable elevation in the contact hypersensitivity (CHS) response of cells and receptors is due to the activation of stressors in short term stress. Moreover, the link between the short term stress and the immune system has been elucidated by some studies that concluded that short term stress acts as the cellular and molecular mediators of the enhanced effects of immunity. Up-regulated macrophage chemoattractant protein-1 (MCP-1), TNF, IFN-c, IL-1a, IL-1b, IL-6, macrophage inflammatory protein-3a (MIP-3a) gene expression after the antigen exposure is also associated with the short term stress.[16,17,74]

The review of the studies has also demonstrated that the proteins in the different cellular responses, for example, endoplasmic reticulum (ER) stress, the response to heat shock and DNA damage show the interaction and results in the regulation of the signaling intermediates that are associated with the activation of adaptive and innate responses of the immune system. Such regulation which is caused by the cell stress protein shows the inflammatory profile of the response shown by the immune system at the time of disease and infection. The review of the related literature has demonstrated that different type of stress response proteins are involved in the cell stress that regulates innate immune response. The immune disorders may worsen the condition, thus, it is imperative to understand the interrelation between stress, immune responses and immunity disorders.[17]

The survival mechanism that are also termed as cellular stress responses are activated as a result of any stressful stimuli. Depending on the type of stress, the stress can be heat shock response, the response to oxidative stress, DDR, etc. The key proteins that are involved in the stress pathways are involved in the cellular protection, but the role of these stress proteins in the regulation of defense system is not clear. A better understanding of the novel targets in the treatment of the immune manipulations can be understood by taking into consideration the function of stress proteins in immune responses. The injured, stressed and dying cells release the molecules Damage-associated molecular patterns (DAMPs) which have the functional ability to act as the danger or the adjuvant signal for immune system. The relation between the stress, immune system and cancer is understandable from the fact that secreted ATP, surface-exposed calreticulin (CRT), and high mobility group protein B1 (HMGB1) are the essential components for the immunogenic cell death (ICD) of cancerous cells.[103-105]

The capability of different therapeutic treatments to induce ICD is dependent on their potential to induce the production of reactive oxygen species (ROS) and the ER stress and both of these are vital components in the instigation of intracellular danger signaling pathways that leads to ICD. The endoplasmic reticulum (ER) is an organelle of a eukaryotic cell which is associated with signaling, sensing and biosynthetic functioning and is also associated with the synthesis and post-translational modifications of many proteins. ER homeostasis is disturbed in ER Ca2+ depletion, hypoglycemia infections and injury etc. that leads to the production of reactive oxygen species (ROS) production, thus creating an imbalance in the protein folding load and capacity and this situation is termed as ER stress. The ER produces the response against this stress by causing the activation of the complex signaling pathway which is called as unfolded protein response (UPR).[106,107] The receptor level overview shows that it is comprised of three prime signaling branches that originate from ER-sessile proteins, PERK, IRE1α and activating transcription factor. The prime objective of these signaling pathways is the maintenance of ER homeostasis and to promote the survival. In the case of severe ER stress UPR turns into a pro-death pathway causing apoptosis. The immunogenicity that is associated with ICD can be effective if the ROS based ER stress is focused. This is induced by the hypericin-based photodynamic therapy (PDT) which is type II ICD induced in comparison to the collateral ER stress effects (as mitoxantrone and oxaliplatin in the case of type I ICD inducers). Oncogene-mediated transformation and some type of infection results in the activation of various pathways in cells, such as stress pathways, that affects cellular physiology in the complex ways. Some

alteration may lead to intrinsic cell-death that can suppress the infection and tumorigenesis and/or limit infections. The exposure of the ligands in the infected or cancerous cells results from various pathways associated with stress pathways. The activating receptor NKG2D and the ligands of this receptor represent a specific system that leads to the recognition and elimination of the infected, cancerous and unhealthy cells.[107]

MICA and MICB promoters are activated by heat shock stress with the aid of HSF1 transcription factor. NF-kB bind and trans activate genes and thus results in the encoding of some human NKG2D ligands, and thus it can be estimated that expression of Toll-like receptor (TLR)-induced NKG2D ligand is linked with the activation of NF-kB. The DNA damage response induces NKG2D ligands expression. The ligands induction depends on the kinases that have potential to sense the damage in DNA, CHK1 and ATR. The heat shock or radiation induced cellular stress, the stability of ligand MULTI is affected leading to expression of MULTI, thus providing a clue to the infection or other pathological condition.

ONCOGENIC STRESS AND DNA DAMAGE

Oncogenic stress is mediated by the activation of the p53/p21 and pl6/Rb tumor suppressor pathways, which then lead to senescence by trans-activating genes, cause the arrest of cell progression. A pool of premalignant cells is generated by the activation of the oncogene and proliferative signals. Premalignant cells cause the activation of pl9 which are subjected to DNA replication stress and lead to DNA damage and activation of DNA damage response. It is evident from the literature based studies that regulation of NKG2D ligand expression is regulated by NKG2D biogenesis, and this provides the evidence that stress pathways and signals are required for optimal ligand expression. Multiple regulatory steps are involved which demonstrates the complexity of the system.[108]

ROS is the secondary messengers in the process of signal transduction and has a significant role in the activation of the inflammatory pathways as it activates stress kinases of NF-κB and MAPK family. However in the case of excess stress, ROS inflict damage and by different processes lead to the inflammatory processes causing cell death. However, in most of the cases, it is demonstrated that this association is related to the stress-induced deregulation of the HPA axis.[6,103,104,107] Some studies have worked on the role of psychological stress on the condition of the patients. The impacts of the prolonged stress on the HPA axis in some human subjects have determined that stress-induced changes in HPA axis have an imperative role in the risks of the disease.[106-108] It has now become less likely to say that the chronic

stress acts by the effects of the increased level of circulating cortisol. The stress regulated mediators of the immune system and the molecular mechanism between stress and immune response has been used in the recent research to develop new targets for treatment intervention[106,107,109]

CHRONIC STRESS AND CANCER

Various studies have explored the relationship of chronic stress with cancer. [110-112] Many studies showed that chronic period of stress can lead to inflammation and spread of various diseases including cancer.[113-116] Clinical studies shows that prolonged period of stressful events lead to poor cancer survival[111,117] Many studies found that chronic stress motivate the inflammatory cells to tumors and increase the blood vessels formation[113,116], that may contribute a path for the tumor cell dissemination. Furthermore dissemination via blood vessels, through lymphatic vasculature cancer cells also departs from tumors.[118-120] Chronic stress activates the signaling from the SNS that leads to cancer growth the tumor cell dissemination pathways are still not cleared.[121] With the reference of immunosuppressive effects of chronic stress, and given the significance of cell mediated immunity in eradication of immune responsive tumor such as squamous cell carcinoma SCC[122], studies have also significantly showed the chronic stress effects on cancer emergence[123] and cancer progression.[113,123-125] Chronic stress increased the development of SCC. The chronically stressed mice had lower CCL27, IFN- c, CD4+ and CD8+, gene expression of CD3, and T cells moving around and within the tumors as compared to the controlled group mice. The growth of tumor in the chronically stressed mice was more as compare to controlled group. These studies indicated that chronic stress enhanced the vulnerability to UV induced SCC by decreasing skin immunity, protective T cells, and Type 1 cytokines,[123] High-anxious behavioral phenotype, that is related with the increased vulnerability to chronic stress, and this decrease the antitumor immunity and increase the growth of SCC. [126]

CONCLUSION

This review study established the relationship between stress and the immune system and it also explain that how some components of the immune system are affected by the stress. We also focused in this review that short term stresses motivate the individual to deal with the harmful stimuli while the chronic stress is responsible for the activation of many pro inflammatory cytokines that damage the body by various ways. The social stress has a prime role in the up-regulation of the inflammatory activity and the genetic factors whereas neural

factors have to be determined to mediate the impact. Stress-related elevation in the inflammatory process to mediate the depression has been discussed by various studies. The overview of the evidences suggests the contributing role of oxidative stresses and inflammation in the depressive disorder. In the case of depressive disorder, the increase in the oxidative stress biomarkers and inflammation is related to the neuro progression which affects neurogenesis and causes cell death. Moreover, it has also been emphasized the Reactive Oxygen Species (ROS) and antioxidants imbalance lead to oxidative stress which causes the loss of the signaling pathways related to the control of the intracellular redox-related signaling pathways.

Although we have studied the mechanism in this review but a lot of work need to be done to clarify the mechanism to understand the stress phenomenon in detail. The review of the literature related to stress mechanism will be valuable because in life stress is the most critical part. Chronic stresses play a vital role in the causes of various diseases that results heavy expenses and loss of lives in over populated and poor people around the globe. On the other hand, the recent studies favors that acute stress (stort term) is one of the nature fundamental process that can help in the immunoprotection. It is expected that the present study will help to classify the reasons and aim/targets that may be therapeutically manipulated to improve the response of immune protection, or to eradicate /improve the stress related proinflammatory/autoimmune diseases, and to encourage situations that maximally improve healing and health.

FUNDING

This work was supported by the National Science Foundation of China (Nos.91529304, 81473230, 81403020, 81603132).

REFERENCES

1. Tausk FA, Elenkov I, Paus R, et al. Stress and Immunity. In: Gaspari AA, Tyring SK, eds. Clinical and Basic Immunodermatology. London: Springer London, 2008; 45-65.
2. Lupien SJ, Ouellet-Morin I, Herba CM, et al. From Vulnerability to Neurotoxicity: A Developmental Approach to the Effects of Stress on the Brain and Behavior. In: Spengler D, Binder E, eds. Epigenetics and Neuroendocrinology: Clinical Focus on Psychiatry, 1. Cham: Springer International Publishing, 2016; 3-48.
3. Christian LM, Glaser R. The Impact of Everyday Stressors on the Immune System and Health. In: Chouker A, ed. Stress Challenges and Immunity in Space: From Mechanisms

to Monitoring and Preventive Strategies. Berlin, Heidelberg: Springer Berlin Heidelberg, 2012; 31-43.

4. Capuron L, Ravaud A, Miller AH, et al. Baseline mood and psychosocial characteristics of patients developing depressive symptoms during interleukin-2 and/or interferon-alpha cancer therapy. Brain, Behavior, and Immunity, 2004; 18(3): 205-13. doi: http://dx.doi.org/10.1016/j.bbi.2003.11.004[published Online First: Epub Date]|.
5. Maier SF. Bi-directional immune–brain communication: Implications for understanding stress, pain, and cognition. Brain, Behavior, and Immunity, 2003; **17**(2): 69-85. doi: http://dx.doi.org/10.1016/S0889-1591(03)00032-1[published Online First: Epub Date]|.
6. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol, 2005; **5**(3): 243-51
7. Ader R, Felten DL, Cohen N. *Psychoneuroimmunology*. San Diego: Academic Press, 2001.
8. Perez-Tejada J, Arregi A, Gomez-Lazaro E, et al. Coping with chronic social stress in mice: hypothalamic-pituitary-adrenal/ sympathetic-adrenal-medullary axis activity, behavioral changes and effects of antalarmin treatment: implications for the study of stress-related psychopathologies. Neuroendocrinology, 2013; **98**(1): 73-88. doi: 10.1159/000353620[published Online First: Epub Date]|.
9. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its behavioral and metabolic correlates: from HPA axis to glucocorticoid receptor dysfunction. Annals of the New York Academy of Sciences, 2012; **1261**: 55-63. doi: 10.1111/j.1749-6632.2012.06633.x[published Online First: Epub Date]|.
10. Madden KS, Livnat S. Catecholamine Action and Immunologic Reactivity A2 - ADER, ROBERT. In: Felten DL, Cohen N, eds. Psychoneuroimmunology (Second Edition): Academic Press, 1991; 283-310.
11. Reed RG, Raison CL. Stress and the Immune System. In: Esser C, ed. Environmental Influences on the Immune System. Vienna: Springer Vienna, 2016; 97-126.
12. Webster JI, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. Annual review of immunology, 2002; **20**: 125-63. doi: 10.1146/annurev.immunol.20.082401.104914[published Online First: Epub Date]|.
13. Padgett DA, Glaser R. How stress influences the immune response. Trends in immunology, 2003; **24**(8): 444-8.
14. Rabin BS. *Stress, immune function, and health : the connection*. New York: Wiley-Liss, 1999.

15. Black PH. The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. Brain, Behavior, and Immunity, 2003; **17**(5): 350-64. doi: http://dx.doi.org/10.1016/S0889-1591(03)00048-5[published Online First: Epub Date]|.
16. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychological bulletin, 2004; **130**(4): 601-30 doi: 10.1037/0033-2909.130.4.601[published Online First: Epub Date]|.
17. Bauer ME, Fuente Mde L. The role of oxidative and inflammatory stress and persistent viral infections in immunosenescence. Mechanisms of ageing and development, 2016; **158**: 27-37. doi: 10.1016/j.mad.2016.01.001[published Online First: Epub Date]|.
18. Aspinall R, Del Giudice G, Effros RB, et al. Challenges for vaccination in the elderly. Immunity & ageing : I & A, 2007; **4**: 9 doi: 10.1186/1742-4933-4-9[published Online First: Epub Date]|.
19. Antoni MH, Lutgendorf SK, Cole SW, et al. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. Nature reviews Cancer, 2006; **6**(3): 240-8. doi: 10.1038/nrc1820[published Online First: Epub Date]|.
20. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. Jama, 2007; **298**(14): 1685-7. doi: 10.1001/jama.298.14.1685[published Online First: Epub Date]|.
21. Dantzer R, O'Connor JC, Freund GG, et al. From inflammation to sickness and depression: when the immune system subjugates the brain. Nature reviews Neuroscience, 2008; **9**(1): 46-56. doi: 10.1038/nrn2297[published Online First: Epub Date]|.
22. Han D, Chen W, Gu X, et al. Cytoprotective effect of chlorogenic acid against hydrogen peroxide-induced oxidative stress in MC3T3-E1 cells through PI3K/Akt-mediated Nrf2/HO-1 signaling pathway. Oncotarget, 2017. doi: 10.18632/oncotarget.14747[published Online First: Epub Date]|.
23. Pera A, Campos C, Lopez N, et al. Immunosenescence: Implications for response to infection and vaccination in older people. Maturitas, 2015; **82**(1): 50-5. doi: 10.1016/j.maturitas.2015.05.004[published Online First: Epub Date]|.
24. Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annual review of medicine, 2000; **51**: 245-70. doi: 10.1146/annurev.med.51.1.245[published Online First: Epub Date]|.
25. Hotamisligil GS. Inflammation and metabolic disorders. Nature, 2006; **444**(7121): 86 0-7. doi: 10.1038/nature05485[published Online First: Epub Date]|.

26. Nabipour I, Vahdat K, Jafari SM, et al. The association of metabolic syndrome and Chlamydia pneumoniae, Helicobacter pylori, cytomegalovirus, and herpes simplex virus type 1: the Persian Gulf Healthy Heart Study. Cardiovascular diabetology, 2006; **5**: 25. doi: 10.1186/1475-2840-5-25[published Online First: Epub Date]|.
27. Parkin DM. The global health burden of infection-associated cancers in the year 2002. International journal of cancer, 2006; **118**(12): 3030-44. doi: 10.1002/ijc.21731[published Online First: Epub Date]|.
28. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. The New England journal of medicine, 2005; **352**(16): 1685-95. doi: 10.1056/NEJMra043430[published Online First: Epub Date]|.
29. Godbout JP, Glaser R. Stress-induced immune dysregulation: implications for wound healing, infectious disease and cancer. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology, 2006; **1**(4): 421-7. doi: 10.1007/s11481-006-9036-0[published Online First: Epub Date]|.
30. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. Immunologic research, 2014; **58**(2-3): 193-210. doi: 10.1007/s12026-014-8517-0[published Online First: Epub Date]|.
31. Joels M, Karst H, Krugers HJ, et al. Chronic stress: implications for neuronal morphology, function and neurogenesis. Frontiers in neuroendocrinology, 2007; **28**(2-3): 72-96. doi: 10.1016/j.yfrne.2007.04.001[published Online First: Epub Date]|.
32. Fink G. Stress: Concepts, Definition and History☆. Reference Module in Neuroscience and Biobehavioral Psychology: Elsevier, 2017.
33. Conrad CD. Chronic stress-induced hippocampal vulnerability: the glucocorticoid vulnerability hypothesis. Reviews in the neurosciences, 2008; **19**(6): 395-411.
34. Lupien SJ, McEwen BS, Gunnar MR, et al. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nature reviews Neuroscience, 2009; **10**(6): 434-45 doi: 10.1038/nrn2639[published Online First: Epub Date]|.
35. Tsolaki M, Kounti F, Karamavrou S. Severe psychological stress in elderly individuals: a proposed model of neurodegeneration and its implications. American journal of Alzheimer's disease and other dementias, 2009; **24**(2): 85-94. doi: 10.1177/1533317508329813[published Online First: Epub Date]|.
36. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. Ann N Y

Acad Sci., 2012; **1261**: 55-63. doi: 10.1111/j.1749-6632.2012.06633.x[published Online First: Epub Date]|.

37. Gore AC, Attardi B, DeFranco DB. Glucocorticoid repression of the reproductive axis: effects on GnRH and gonadotropin subunit mRNA levels. Molecular and cellular endocrinology, 2006; **256**(1-2): 40-8. doi: 10.1016/j.mce.2006.06.002[published Online First: Epub Date]|.
38. Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. Neuroscience and biobehavioral reviews, 2012; **36**(2): 764-85. doi: 10.1016/j.neubiorev.2011.12.005[published Online First: Epub Date]|.
39. Lazzarino AI, Hamer M, Gaze D, et al. The Association Between Cortisol Response to Mental Stress and High-Sensitivity Cardiac Troponin T Plasma Concentration in Healthy Adults. Journal of the American College of Cardiology, 2013; **62**(18): 1694-701. doi: 10.1016/j.jacc.2013.05.070[published Online First: Epub Date]|.
40. Glaser R, Kiecolt-Glaser JK. *Handbook of human stress and immunity*. San Diego: Academic Press, 1994.
41. Voorhees JL, Tarr AJ, Wohleb ES, et al. Prolonged restraint stress increases IL-6, reduces IL-10, and causes persistent depressive-like behavior that is reversed by recombinant IL-10. PloS one, 2013; **8**(3): e58488. doi: 10.1371/journal.pone.0058488[published Online First: Epub Date]|.
42. Kiecolt-Glaser JK, Glaser R, Gravenstein S, et al. Chronic stress alters the immune response to influenza virus vaccine in older adults. Proceedings of the National Academy of Sciences of the United States of America, 1996; **93**(7): 3043-7.
43. Glaser R, Sheridan J, Malarkey WB, et al. Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. Psychosomatic medicine, 2000; **62**(6): 804-7.
44. Vedhara K, Cox NK, Wilcock GK, et al. Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. Lancet (London, England), 1999; **353**(9153): 627-31. doi: 10.1016/s0140-6736(98)06098-x[published Online First: Epub Date]|.
45. Morag M, Morag A, Reichenberg A, et al. Psychological variables as predictors of rubella antibody titers and fatigue--a prospective, double blind study. Journal of psychiatric research, 1999; **33**(5): 389-95.

46. Patriarca PA. A randomized controlled trial of influenza vaccine in the elderly. Scientific scrutiny and ethical responsibility. Jama, 1994; **272**(21): 1700-1.
47. Koonin EV. 94 Origin and evolution of adaptive immunity systems. Journal of biomolecular structure & dynamics 2015; **33 Suppl 1**: 61 doi: 10.1080/07391102.2015.1032711[published Online First: Epub Date]|.
48. Medzhitov R. Recognition of microorganisms and activation of the immune response. Nature, 2007; **449**(7164): 819-26. doi: 10.1038/nature06246[published Online First: Epub Date]|.
49. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends in immunology, 2006; **27**(1): 24-31. doi: 10.1016/j.it.2005.11.006[published Online First: Epub Date]|.
50. Barton GM. A calculated response: control of inflammation by the innate immune system. The Journal of clinical investigation, 2008; **118**(2): 413-20. doi: 10.1172/jci34431[published Online First: Epub Date]|.
51. Elenkov IJ. Neurohormonal-cytokine interactions: implications for inflammation, common human diseases and well-being. Neurochemistry international, 2008; **52**(1-2): 40-51. doi: 10.1016/j.neuint.2007.06.037[published Online First: Epub Date]|.
52. Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: mechanisms of differentiation and function. Annual review of immunology, 2012; **30**: 531-64. doi: 10.1146/annurev.immunol.25.022106.141623[published Online First: Epub Date]|.
53. Lochner M, Peduto L, Cherrier M, et al. In vivo equilibrium of proinflammatory IL-17+ and regulatory IL-10+ Foxp3+ RORgamma t+ T cells. The Journal of experimental medicine, 2008; **205**(6): 1381-93. doi: 10.1084/jem.20080034[published Online First: Epub Date]|.
54. Pisitkun P, Deane JA, Difilippantonio MJ, et al. Autoreactive B cell responses to RNA-related antigens due to TLR7 gene duplication. Science (New York, NY), 2006; **312**(5780): 1669-72. doi: 10.1126/science.1124978[published Online First: Epub Date]|.
55. Berghofer B, Frommer T, Haley G, et al. TLR7 ligands induce higher IFN-alpha production in females. Journal of immunology (Baltimore, Md : 1950), 2006; **177**(4): 2088-96.
56. Afshan G, Afzal N, Qureshi S. CD4+CD25(hi) regulatory T cells in healthy males and females mediate gender difference in the prevalence of autoimmune diseases. Clinical laboratory, 2012; **58**(5-6): 567-71.

57. Abdullah M, Chai PS, Chong MY, et al. Gender effect on in vitro lymphocyte subset levels of healthy individuals. Cellular immunology, 2012; **272**(2): 214-9. doi: 10.1016/j.cellimm.2011.10.009[published Online First: Epub Date]|.
58. Teixeira D, Longo-Maugeri IM, Santos JL, et al. Evaluation of lymphocyte levels in a random sample of 218 elderly individuals from Sao Paulo city. Revista brasileira de hematologia e hemoterapia, 2011; **33**(5): 367-71. doi: 10.5581/1516-8484.20110100[published Online First: Epub Date]|.
59. Furman D, Hejblum BP, Simon N, et al. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. Proceedings of the National Academy of Sciences of the United States of America, 2014; **111**(2): 869-74. doi: 10.1073/pnas.1321060111[published Online First: Epub Date]|.
60. Fan H, Dong G, Zhao G, et al. Gender differences of B cell signature in healthy subjects underlie disparities in incidence and course of SLE related to estrogen, 2014; **2014**: 814598. doi: 10.1155/2014/814598[published Online First: Epub Date]|.
61. Stepanichev M, Dygalo NN, Grigoryan G, et al. Rodent models of depression: neurotrophic and neuroinflammatory biomarkers. BioMed research international, 2014; **2014**: 932757. doi: 10.1155/2014/932757[published Online First: Epub Date]|.
62. Grippo AJ, Sullivan NR, Damjanoska KJ, et al. Chronic mild stress induces behavioral and physiological changes, and may alter serotonin 1A receptor function, in male and cycling female rats. Psychopharmacology, 2005; **179**(4): 769-80. doi: 10.1007/s00213-004-2103-4[published Online First: Epub Date]|.
63. Cattaneo A, Macchi F, Plazzotta G, et al. Inflammation and neuronal plasticity: a link between childhood trauma and depression pathogenesis. Frontiers in cellular neuroscience, 2015; **9**: 40. doi: 10.3389/fncel.2015.00040[published Online First: Epub Date]|.
64. Chapman DP, Whitfield CL, Felitti VJ, et al. Adverse childhood experiences and the risk of depressive disorders in adulthood. Journal of affective disorders, 2004; **82**(2): 217-25. doi: 10.1016/j.jad.2003.12.013[published Online First: Epub Date]|.
65. Hammen C, Henry R, Daley SE. Depression and sensitization to stressors among young women as a function of childhood adversity. Journal of consulting and clinical psychology, 2000; **68**(5): 782-7.
66. Heim C, Binder EB. Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics.

Experimental neurology, 2012; **233**(1): 102-11. doi: 10.1016/j.expneurol.2011.10.032[published Online First: Epub Date]|.

67. Mazure CM, Bruce ML, Maciejewski PK, et al. Adverse life events and cognitive-personality characteristics in the prediction of major depression and antidepressant response. The American journal of psychiatry, 2000; **157**(6): 896-903. doi: 10.1176/appi.ajp.157.6.896[published Online First: Epub Date]|.
68. Nemeroff CB. Neurobiological consequences of childhood trauma. The Journal of clinical psychiatry, 2004; **65(1)**: 18-28.
69. Bowe WP, Logan AC. Acne vulgaris, probiotics and the gut-brain-skin axis - back to the future? Gut pathogens, 2011; **3**(1): 1. doi: 10.1186/1757-4749-3-1[published Online First: Epub Date]|.
70. Maes M, Kubera M, Leunis JC. The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. Neuro endocrinology letters, 2008; **29**(1): 117-24.
71. Edgar VA, Cremaschi GA, Sterin-Borda L, et al. Altered expression of autonomic neurotransmitter receptors and proliferative responses in lymphocytes from a chronic mild stress model of depression: effects of fluoxetine. Brain Behav Immun, 2002; **16**(4): 333-50.
72. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biological psychiatry, 2009; **65**(9): 732-41. doi: 10.1016/j.biopsych.2008.11.029[published Online First: Epub Date]|.
73. Viamontes G NC. Brain-Body Interactions: The Physiological Impact of Mental Processes The Neurobiology of the Stress Response Psychiatr Ann, 2009. doi: 10.3928/00485718-20091124-03 [published Online First: Epub Date]|.
74. Black PH. Stress and the inflammatory response: a review of neurogenic inflammation. Brain Behav Immun, 2002; **16**(6): 622-53.
75. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav Immun, 2007; **21**(7): 901-12. doi: 10.1016/j.bbi.2007.03.011[published Online First: Epub Date]|.
76. Elenkov IJ, Wilder RL, Chrousos GP, et al. The sympathetic nerve--an integrative interface between two supersystems: the brain and the immune system. Pharmacological reviews, 2000; **52**(4): 595-638.

77. Felten SY, Felten DL, Bellinger DL, et al. Noradrenergic and peptidergic innervation of lymphoid organs. Chemical immunology, 1992; **52**: 25-48.
78. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. The New England journal of medicine, 1995; **332**(20): 1351-62. doi: 10.1056/nejm199505183322008[published Online First: Epub Date]|.
79. Besedovsky HO, Del Rey AE, Sorkin E. What do the immune system and the brain know about each other? Immunology today, 1983; **4**(12): 342-6. doi: 10.1016/0167-5699(83)90171-8[published Online First: Epub Date]|.
80. Weigent DA, Blalock JE. Production of peptide hormones and neurotransmitters by the immune system. Chemical immunology, 1997; **69**: 1-30.
81. Gibbison B, Spiga F, Walker JJ, et al. Dynamic pituitary-adrenal interactions in response to cardiac surgery. Critical care medicine, 2015; **43**(4): 791-800. doi: 10.1097/ccm.0000000000000773[published Online First: Epub Date]|.
82. Nance DM, Sanders VM. Autonomic innervation and regulation of the immune system (1987-2007). Brain Behav Immun, 2007; **21**(6): 736-45. doi: 10.1016/j.bbi.2007.03.008[published Online First: Epub Date]|.
83. Sanders VM. Adrenergic Regulation of Adaptive Immunity. In: Welsh CJ, Meagher MW, Sternberg EM, eds. Neural and Neuroendocrine Mechanisms in Host Defense and Autoimmunity. Boston, MA: Springer US, 2006: 81-100.
84. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol, 2011; **11**(9): 625-32. doi: 10.1038/nri3042[published Online First: Epub Date]|.
85. Berkenbosch F, van Oers J, del Rey A, et al. Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. Science (New York, NY), 1987; **238**(4826): 524-6.
86. Kovacs KJ, Elenkov IJ. Differential dependence of ACTH secretion induced by various cytokines on the integrity of the paraventricular nucleus. Journal of neuroendocrinology, 1995; **7**(1): 15-23.
87. Ehrhart-Bornstein M, Hinson JP, Bornstein SR, et al. Intraadrenal interactions in the regulation of adrenocortical steroidogenesis. Endocrine reviews, 1998; **19**(2): 101-43. doi: 10.1210/edrv.19.2.0326[published Online First: Epub Date]|.
88. Ashwell JD, Lu FW, Vacchio MS. Glucocorticoids in T cell development and function*. Annual review of immunology, 2000; **18**: 309-45. doi: 10.1146/annurev.immunol.18.1.309[published Online First: Epub Date]|.

89. Caramori G, Adcock I. Anti-inflammatory mechanisms of glucocorticoids targeting granulocytes. Current drug targets Inflammation and allergy, 2005; **4**(4): 455-63.
90. Vandevyver S, Dejager L, Tuckermann J, et al. New insights into the anti-inflammatory mechanisms of glucocorticoids: an emerging role for glucocorticoid-receptor-mediated transactivation. Endocrinology, 2013; **154**(3): 993-1007. doi: 10.1210/en.2012-2045[published Online First: Epub Date]|.
91. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. The New England journal of medicine, 2005; **353**(16): 1711-23. doi: 10.1056/NEJMra050541[published Online First: Epub Date]|.
92. Cruz-Topete D, Cidlowski JA. One hormone, two actions: anti- and pro-inflammatory effects of glucocorticoids. Neuroimmunomodulation, 2015; **22**(1-2): 20-32. doi: 10.1159/000362724[published Online First: Epub Date]|.
93. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. Neuroimmunomodulation, 2009; **16**(5): 300-17. doi: 10.1159/000216188[published Online First: Epub Date]|.
94. Galon J, Franchimont D, Hiroi N, et al. Gene profiling reveals unknown enhancing and suppressive actions of glucocorticoids on immune cells. FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 2002; **16**(1): 61-71. doi: 10.1096/fj.01-0245com[published Online First: Epub Date]|.
95. Homma T, Kato A, Hashimoto N, et al. Corticosteroid and cytokines synergistically enhance toll-like receptor 2 expression in respiratory epithelial cells. American journal of respiratory cell and molecular biology, 2004; **31**(4): 463-9. doi: 10.1165/rcmb.2004-0161OC[published Online First: Epub Date]|.
96. Chinenov Y, Rogatsky I. Glucocorticoids and the innate immune system: crosstalk with the toll-like receptor signaling network. Molecular and cellular endocrinology, 2007; **275**(1-2): 30-42. doi: 10.1016/j.mce.2007.04.014[published Online First: Epub Date]|.
97. Busillo JM, Azzam KM, Cidlowski JA. Glucocorticoids sensitize the innate immune system through regulation of the NLRP3 inflammasome. The Journal of biological chemistry, 2011; **286**(44): 38703-13. doi: 10.1074/jbc.M111.275370[published Online First: Epub Date]|.
98. Ma Q. Role of nrf2 in oxidative stress and toxicity. Annual review of pharmacology and toxicology, 2013; **53**: 401-26. doi: 10.1146/annurev-pharmtox-011112-140320[published Online First: Epub Date]|.

99. Slocum SL, Kensler TW. Nrf2: control of sensitivity to carcinogens. Archives of toxicology, 2011; **85**(4): 273-84. doi: 10.1007/s00204-011-0675-4[published Online First: Epub Date]|.
100. Schuijs MJ, Willart MA, Hammad H, et al. Cytokine targets in airway inflammation. Current opinion in pharmacology, 2013; **13**(3): 351-61. doi: 10.1016/j.coph.2013.03.013[published Online First: Epub Date]|.
101. Panossian A, Wikman G. Effects of Adaptogens on the Central Nervous System and the Molecular Mechanisms Associated with Their Stress-Protective Activity. Pharmaceuticals (Basel, Switzerland), 2010; **3**(1): 188-224. doi: 10.3390/ph3010188[published Online First: Epub Date]|.
102. Salminen A, Kaarniranta K. Control of p53 and NF-kappaB signaling by WIP1 and MIF: role in cellular senescence and organismal aging. Cellular signalling, 2011; **23**(5): 747-52. doi: 10.1016/j.cellsig.2010.10.012[published Online First: Epub Date]|.
103. Zhang K, Kaufman RJ. From endoplasmic-reticulum stress to the inflammatory response. Nature, 2008; **454**(7203): 455-62. doi: 10.1038/nature07203[published Online First: Epub Date]|.
104. Cubillos-Ruiz JR, Silberman PC, Rutkowski MR, et al. ER Stress Sensor XBP1 Controls Anti-tumor Immunity by Disrupting Dendritic Cell Homeostasis. Cell., 2015; **161**(7): 1527-38. doi: 10.1016/j.cell.2015.05.025[published Online First: Epub Date]|.
105. Krysko DV, Garg AD, Kaczmarek A, et al. Immunogenic cell death and DAMPs in cancer therapy. Nature reviews Cancer, 2012; **12**(12): 860-75. doi: 10.1038/nrc3380[published Online First: Epub Date]|.
106. Garg AD, Agostinis P. ER stress, autophagy and immunogenic cell death in photodynamic therapy-induced anti-cancer immune responses. Photochemical & photobiological sciences : Official journal of the European Photochemistry Association and the European Society for Photobiology, 2014; **13**(3): 474-87. doi: 10.1039/c3pp50333j[published Online First: Epub Date]|.
107. Muralidharan S, Mandrekar P. Cellular stress response and innate immune signaling: integrating pathways in host defense and inflammation. Journal of leukocyte biology, 2013; **94**(6): 1167-84. doi: 10.1189/jlb.0313153[published Online First: Epub Date]|.
108. Gonzalez S, Lopez-Soto A, Suarez-Alvarez B, et al. NKG2D ligands: key targets of the immune response. Trends in immunology, 2008; **29**(8): 397-403. doi: 10.1016/j.it.2008.04.007[published Online First: Epub Date]|.

109. Raulet DH, Guerra N. Oncogenic stress sensed by the immune system: role of natural killer cell receptors. Nat Rev Immunol, 2009; **9**(8): 568-80. doi: 10.1038/nri2604[published Online First: Epub Date]|.
110. Antoni MH, Lutgendorf SK, Cole SW, et al. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. Nature Reviews Cancer, 2006; **6**(3): 240-48.
111. Chida Y, Hamer M, Wardle J, et al. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nature clinical practice Oncology, 2008; **5**(8): 466-75.
112. Sood AK, Lutgendorf SK. Stress influences on anoikis. Cancer prevention research, 2011; **4**(4): 481-85.
113. Thaker PH, Han LY, Kamat AA, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nature medicine, 2006; **12**(8): 939-44.
114. Kim-Fuchs C, Le CP, Pimentel MA, et al. Chronic stress accelerates pancreatic cancer growth and invasion: a critical role for beta-adrenergic signaling in the pancreatic microenvironment. Brain Behav Immun, 2014; **40**: 40-7. doi: 10.1016/j.bbi.2014.02.019[published Online First: Epub Date]|.
115. Magnon C, Hall SJ, Lin J, et al. Autonomic nerve development contributes to prostate cancer progression. Science (New York, NY), 2013; **341**(6142): 1236361.
116. Sloan EK, Priceman SJ, Cox BF, et al. The sympathetic nervous system induces a metastatic switch in primary breast cancer. Cancer research, 2010; **70**(18): 7042-52.
117. Andersen BL, Yang HC, Farrar WB, et al. Psychologic intervention improves survival for breast cancer patients. Cancer, 2008; **113**(12): 3450-58.
118. He Y, Rajantie I, Pajusola K, et al. Vascular endothelial cell growth factor receptor 3–mediated activation of lymphatic endothelium is crucial for tumor cell entry and spread via lymphatic vessels. Cancer research, 2005; **65**(11): 4739-46.
119. Alitalo A, Detmar M. Interaction of tumor cells and lymphatic vessels in cancer progression. Oncogene, 2012; **31**(42): 4499-508.
120. Hayashi K, Jiang P, Yamauchi K, et al. Real-time imaging of tumor-cell shedding and trafficking in lymphatic channels. Cancer research, 2007; **67**(17): 8223-28.
121. Le CP, Nowell CJ, Kim-Fuchs C, et al. Chronic stress in mice remodels lymph vasculature to promote tumour cell dissemination. Nature communications, 2016; **7.**
122. Kripke ML. Ultraviolet radiation and immunology: something new under the sun-presidential address. Cancer research, 1994; **54**(23): 6102-05.

123. Saul AN, Oberyszyn TM, Daugherty C, et al. Chronic stress and susceptibility to skin cancer. Journal of the National Cancer Institute, 2005; **97**(23): 1760-67.
124. Levi B, Benish M, Goldfarb Y, et al. Continuous stress disrupts immunostimulatory effects of IL-12. Brain, behavior, and immunity, 2011; **25**(4): 727-35.
125. Goldfarb Y, Sorski L, Benish M, et al. Improving postoperative immune status and resistance to cancer metastasis: a combined perioperative approach of immunostimulation and prevention of excessive surgical stress responses. Annals of surgery, 2011; **253**(4): 798-810.
126. Dhabhar F, Saul A, Holmes T, et al. High anxiety is associated with higher chronic stress burden, lower protective immunity, and increased cancer progression. PloS one, 2012; **7**(4): 1-14.