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Effects of stress on immune function: the good, the bad, and the beautiful

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Abstract Although the concept of stress has earned a bad reputation, it is important to recognize that the adaptive purpose of a physiological stress response is to promote survival during fight or flight. While long-term stress is generally harmful, short-term stress can be protective as it prepares the organism to deal with challenges. This review discusses the immune effects of biological stress responses that can be induced by psychological, physiological, or physical (including exercise) stressors. We have proposed that short-term stress is one of the nature's fundamental but under-appreciated survival mechanisms that could be clinically harnessed to enhance immunoprotection. Short-term (i.e., lasting for minutes to hours) stress experienced during immune activation enhances innate/primary and adaptive/secondary immune responses. Mechanisms of immuno-enhancement include changes in dendritic cell, neutrophil, macrophage, and lymphocyte trafficking, maturation, and function as well as local and systemic production of cytokines. In contrast, long-term stress suppresses or dysregulates innate and adaptive immune responses by altering the Type 1–Type 2 cytokine balance, inducing low-grade chronic inflammation, and suppressing numbers, trafficking, and function of immunoprotective cells. Chronic stress may also increase susceptibility to some types of cancer by suppressing Type 1 cytokines and protective T cells and increasing regulatory/suppressor T cell function. Here, we classify immune responses as being protective, pathological, or regulatory, and discuss "good" versus "bad" effects of stress on health. Thus, short-term stress can enhance the acquisition and/or expression of immunoprotective (wound healing, vaccination, anti-infectious agent, anti-tumor) or immuno-pathological (pro-inflammatory, autoimmune) responses. In contrast, chronic stress can suppress protective immune responses and/or exacerbate pathological immune responses. Studies such as the ones discussed here could provide mechanistic targets and conceptual frameworks for pharmacological and/or biobehavioral interventions designed to enhance the effects of "good" stress, minimize the effects of "bad" stress, and maximally promote health and healing.

Keywords Psychological/physical/physiological stress · Endocrinology/Hormones · Immune cell trafficking · Exercise · Psycho-Neuro-Immunology · Neuro-Endocrine-Immunology · Stress-reduction interventions

Introduction

Chronic or long-term stress is known to have numerous adverse effects on health [1, 2]. Many of these effects are mediated through stress actions on the immune system [3–5]. It is important to elucidate the psychological and biological mechanisms by which chronic stressors weaken health or exacerbate disease because that could enable the development of biobehavioral and pharmacological treatments designed to ameliorate or eliminate the harmful effects of chronic stress. However, it is also important to appreciate that the process of evolution did not select for the biological stress response to kill us, but rather to help us survive [6]. Thus, a psychophysiological stress response is one of nature's fundamental survival mechanisms. Without a fight-or-flight stress response, a lion

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has no chance of catching a gazelle, just as the gazelle has no chance of escape. During short-term stress, multiple physiological systems are activated to enable survival. Dhabhar et al. [7–9] hypothesized that just as the short-term stress response prepares the cardiovascular, musculoskeletal, and neuroendocrine systems for fight-or-flight, under certain conditions, stress may also prepare the immune system for challenges (e.g., wounding or infection) that may be imposed by a stressor (e.g., predator, or, in modern times, a medical/surgical procedure). Since then, numerous studies have shown in humans and non-human species that short-term stress experienced at the time of immune activation induces a significant enhancement of the ensuing immune response. Depending on the conditions of immune activation and the nature of the activating agent, short-term stress can enhance innate and adaptive, primary and secondary immune responses. We suggest that it is important to study, and clinically harness, the immuno-enhancing effects of the short-term stress response, that evolution has finely sculpted as a survival mechanism, even as we continue to study the deleterious effects of long-term stress. Here, we evaluate the range of effects of stress on immune function and discuss how these effects may promote immunoprotection versus immunopathology.

Stress

Even though the word "stress" generally has negative connotations, stress is a familiar and ubiquitous aspect of life, being a stimulant for some, but a burden for many others. Numerous definitions have been proposed for the concept of stress, each focusing on aspects of an internal or external challenge, disturbance, or stimulus; on stimulus perception by an organism; or on a physiological response to the stimulus [10–12]. An integrated definition states that stress is a constellation of events, consisting of a stimulus (stressor), that precipitates a reaction in the brain (stress perception), that activates physiological fight-or-flight systems in the body (stress response) [9]. It is important to understand that the only way that a stressor can affect the brain or body is through the biological stress response. Although many factors are involved, the major mediators of stress effects are norepinephrine and epinephrine that are released by the sympathetic nervous system, and corticotropin releasing hormone, adrenocorticotropin, and cortisol, that arise following activation of the hypothalamic–pituitary–adrenal axis. Since virtually every cell in the body expresses receptors for one or more of these factors, stress hormones can induce changes in almost all cells and tissues and inform them about the presence of a stressor.

Stress can be harmful when it is chronic or long lasting [1, 13–15]; however, it is often overlooked that a stress response has salubrious adaptive effects in the short run [16, 17]. Therefore, a major distinguishing characteristic of stress is the duration of the biological effects of stress. *Short-term stress* has been defined as stress that lasts for a period of minutes to hours, and *chronic stress* as stress that persists for several hours per day for weeks or months [9]. Dysregulation of the circadian cortisol rhythm is one maker that appears to coincide with the deleterious effects of chronic stress [9, 18, 19]. The intensity of stress may be gauged by the peak levels of stress hormones, neurotransmitters, and other physiological changes, such as increases in heart rate and blood pressure, and could affect the amount of time for which these changes persist during stress and following the cessation of stress. It is important to note that there are significant individual differences in stress perception, processing, appraisal, and coping [17, 20]. Individual differences become especially salient while studying human subjects because stress perception, processing, appraisal, and coping mechanisms can have significant effects on the kinetics and peak levels of circulating stress hormones and on the duration for which these hormone levels are increased. Animal studies showing strain differences in stress hormone receptors, reactivity and peak levels [21, 22], adaptation to stress [23], and in distribution and activation of adrenal steroid receptors and corticosteroid-binding globulin levels [21, 24], suggest that genetic as well as environmental factors play a role in establishing individual differences [21, 23–25]. The ability of humans to generate and experience psychological stressors in the absence of external stressors can result in long-term activation of the physiological stress response that often has deleterious effects. The magnitude and duration of stress-induced increases in catecholamine and glucocorticoid hormones can have significant effects on immune cell distribution and function [4, 8, 26, 27].

The immune triad: immunoprotection, immunopathology, and immunoregulation

While discussing immune responses, it is useful to categorize them in terms of their principal cellular and molecular components. For example, innate, adaptive, Th1, Th2, Th17 immune responses are all defined in terms of their cellular and cytokine components. In addition to these categories, it is also useful to define immune responses in terms of their integrated, functional, end-effects. Therefore, we have proposed that immune responses can be categorized as being immunoprotective, immunopathological, and immunoregulatory/inhibitory [3, 28]. It is important to bear in mind that while such categories provide useful constructs with which to organize ideas, concepts, and models, an overall in vivo immune response is likely to consist of several types of responses with varying amounts of dominance from each category. The composition and nature of an immune

response is also affected by, and changes with, time. Three major types of immune responses are defined below in terms of their functional end-effects:

Immunoprotective responses are defined as responses that promote efficient wound healing, eliminate infections and cancer, and mediate vaccine-induced immunological memory [3, 28]. Key characteristics of immunoprotection involve active immune surveillance, a rapid and robust response upon immune activation, efficient clearance of the activating agent or pathogen, followed by rapid resolution. Immunoprotective responses are critical for completion of the proliferative and remodeling phases of wound healing. Wound healing is important not only for frank wounds where the initiating event is tissue damage itself, but also for tissue-intrinsic "wounds" where the initiating event is an immune response precipitated by intracellular infection during which there can be collateral tissue damage. Innate and/or adaptive Type 1 or Type 2 immune responses can all confer immunoprotection depending on the type of the pathogen (viral, bacterial, protozoan, fungal, helminthic), on whether it is intra- or extracellular, and on the accompanying wounding conditions (sterile, infected, external, or internal wounds).

Immunopathological responses are defined as those that are directed against self- (autoimmune disease like multiple sclerosis, arthritis, lupus) or innocuous antigens (asthma, allergies) and responses that involving chronic, non-resolving inflammation [3, 28]. Immunopathology is also involved during low-level, long-term increases in local and/or systemic inflammatory mediators (e.g., CRP or IL-6) that are thought to contribute to disorders like cardiovascular disease, obesity, and depression [29–31].

Immunoregulatory responses are defined as those that involve immune cells and factors that regulate (mostly down-regulate) the function of other immune cells [3, 28]. Although the previous concept of suppressor T cells became mired in controversy, recent studies suggest that there is an arm of the immune system that functions to inhibit immune responses [32–34]. For example, regulatory CD4+CD25+FoxP3+ T cells, IL-10, and TGF-beta have been shown to have immunoregulatory/inhibitory functions. The physiological function of these factors is to keep pro-inflammatory, allergic, and autoimmune responses in check [34, 35]. However, it has also been suggested that immunoregulatory/inhibitory factors may suppress anti-tumor immunity and be indicative of negative prognosis for cancer [19, 36–38].

Acute stress induced enhancement of immune function: an adaptive response

Dhabhar et al. [7, 39, 40] hypothesized that short-term or acute stress induced enhancement of immune function may be an adaptive psychophysiological mechanism that confers increased immune protection following wounding or infection. Although this hypothesis sounds similar to Selye's concept of "eustress," it must be noted that Selye defined "eustress" largely in terms of the nature of the stressor (i.e., whether it was pleasant as opposed to noxious) and stated that eustress and distress both cause "damage," the former causing less damage than the latter [41]. Dhabhar et al. [3, 4, 7, 17, 28, 39, 40] have distinguished "good" versus "bad" stress in terms of the duration of the biological stress response and have stated that stress does not necessarily induce damage.

When viewed from an evolutionary perspective, immunosuppression under all stress conditions would not be adaptive because stress is an intrinsic part of life for most organisms, and dealing successfully with stressors enables survival. Moreover, most selection pressures, the chisels of evolution, are stressors. The brain perceives stressors, warns the body of danger, and promotes survival (e.g., when a gazelle sees a charging lion, the gazelle's brain detects a threat and orchestrates a physiological response that enables the gazelle to flee). Since stressful experiences often result in wounding or infection, immunoenhancement, rather than immunosuppression, would be adaptive during acute stress because it is unlikely that eons of evolution would select for a system exquisitely designed to escape the jaws and claws of a lion only to succumb to wounds and pathogens [7, 39, 40]. In other words, just as an acute stress response prepares the cardiovascular, musculoskeletal, and neuroendocrine systems for fight-or-flight, it should also prepare the immune system for challenges (wounding or infection) that are likely to result from stressful encounters (attack by a predator).

In contrast to the above discussion, it was previously believed that stress-induced suppression of immune function may be adaptive because immunosuppression may conserve energy that is required to deal with the immediate demands imposed by the stressor. However, most mechanisms of immunosuppression are likely to expend, rather than conserve, energy. Moreover, the immune system may often be critically needed for responding immediately to the actions of the stress-inducing agent (e.g., wounding by a predator). Thus, while ovulation, copulation, or digestion can wait for the cessation of stress, the immune response may not be similarly dispensable during times of stress. Immune activation may be critical for responding to the immediate demands of a stressful situation, especially if the situation results in wounding or infection. Furthermore, the time course for many proposed mechanisms for stress-induced immunosuppression, such as inhibition of prostaglandin synthesis, cytokine production, or leukocyte proliferation [42], is significantly longer than that seen during acute stress. While conservation of energy may play a role

in stress-induced immunosuppression under some conditions, it would not do so under all conditions of stress.

The energy-conservation hypothesis has also been invoked to suggest that adaptive immunity is suppressed and that only innate immunity is enhanced during acute stress [43, 44]. The underlying assumption for this hypothesis is that only innate immune responses are required for, and capable of, effective immunoprotection on a short-time scale, and that suppressing adaptive immune function would make more energy available to the innate immune system. There are several reasons for considering a revision of these assumptions and hypotheses: First, while classifications such as "innate" and "adaptive" are useful for conceptualization of different types of immune responses, it is now increasingly apparent that in vivo immune responses consist of intricate and synchronous interactions among numerous proteins, cytokines, and cell types that include components of what were traditionally thought to be separate "innate" versus "adaptive" systems [45]. In general, most, if not all, components of an immune response are galvanized following immune activation although different components may predominate during different phases of the response. Second, it must be appreciated that suppressing an immune response does not necessarily conserve energy and, in fact, may even require additional expenditure of energy (e.g., energy is consumed during synthesis and/or release of immunosuppressive factors or during apoptosis). Third, the "adaptive" immune system is not designed solely to fight challenges that the "innate" system fails to overcome. An important function of adaptive immunity is to "memorize" previously encountered antigens/pathogens and to increase the overall efficiency with which a total, in vivo immune response is mounted against the antigen/pathogen upon subsequent exposure. In many instances, antigens and pathogens that activate an immune response may be those that the organism has previously encountered. In such cases, surveillance memory T cells may play a critical role in conferring protection by initiating the immune response cascade and the sooner they are activated the more robust the protection. It would make no sense from an evolutionary standpoint to specifically waste energy resources during stress to suppress the specific and powerful adaptive immune responses that are driven by memory lymphocytes that the organism has invested considerable amounts of energy to acquire in the first place, and then to maintain for most if not all of its life span.

A variant of the energy-conservation hypothesis has been proposed to explain a transient acute stress induced decline in immune function observed in some invertebrate species like crickets [46]. It has been suggested that high-intensity short-term stressors (e.g., a cricket being tied to a stick) lead to immunosuppression in crickets because of octopamine (the insect analog of norepinephrine)-driven competition for specific factors that are required for both lipid-derived mobilization of energy as well as for immune activation. However, octopamine suppresses immune function in crickets, but enhances immunity in the tobacco hornworm and in cockroaches [47], suggesting that the relationship between octopamine and immune function in insects is diverse and complex. It is also important to recognize that stress-induced immunosuppression in some organisms may simply reflect the fact that these organisms have not experienced selection pressures for long-term survival following wounding or infection (which could be due to their very short life spans), and therefore have not evolved independent mechanisms to simultaneously support both the mobilization of energy and immune function.

Factors that determine whether stress will enhance or suppress immune function and the potential health consequences of these effects of stress

Key factors (discussed in the following sections) that determine whether stress enhances or suppresses immune function include the following: (1) the effects of stress on leukocyte distribution in the body. (2) The duration of stress. (3) The differential effects of physiologic versus pharmacologic concentrations of glucocorticoids, and the differential effects of endogenous (e.g., cortisol, corticosterone) versus synthetic (e.g., dexamethasone) glucocorticoids. (4) The timing of stressor or stress hormone exposure relative to the time of activation and ensuing time course of the immune response. It is important to recognize that factors, such as gender, genetics, age, the route of administration and nature of the immunizing antigen, and time during the circadian cycle, additionally affect immune function and could also affect the nature of the relationship between stress and immune function. It is also important to bear in mind that whether a stressor enhances or suppresses immune function, it is the end-effect of the immune response that determines whether the stress–immune interactions have beneficial or harmful effects on health (Fig. 1).

Stress-induced changes in immune cell distribution

Effective immunoprotection requires rapid recruitment of leukocytes into sites of wounding, infection, surgery, or vaccination. Immune cells circulate continuously on surveillance pathways that take them from the blood, through various organs, lymphatic vessels and nodes, and back into the blood. This circulation is essential for the maintenance of an effective immune defense network [48]. The numbers and proportions of leukocytes in the blood provide an

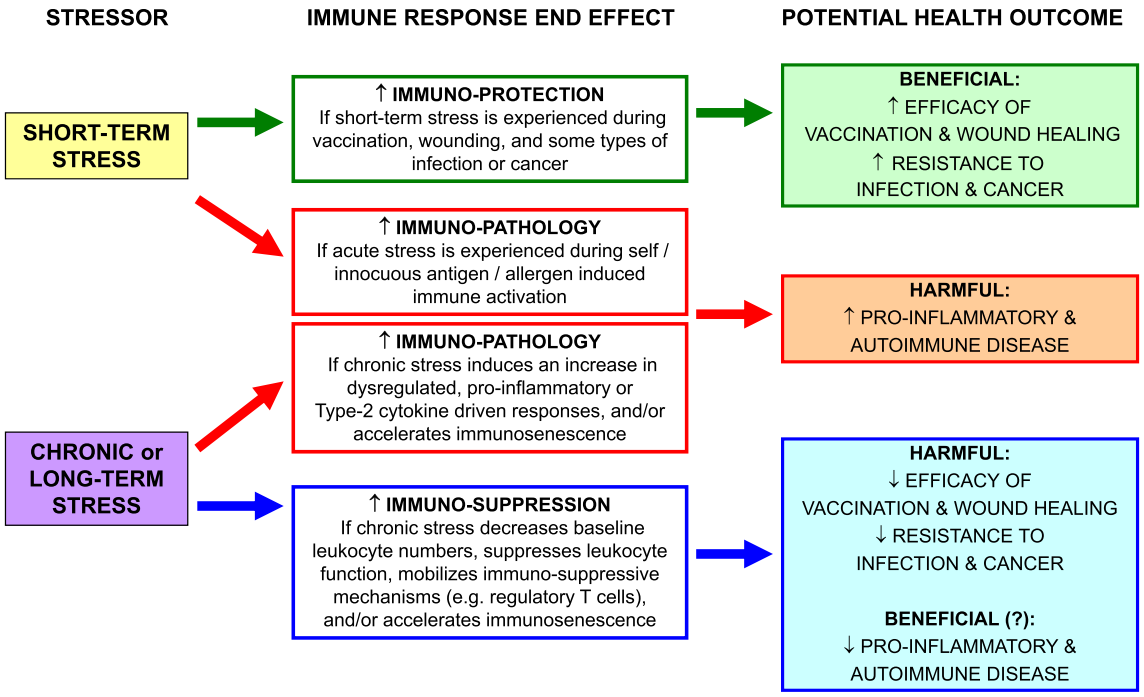

Fig. 1 Enhancing versus suppressive effects of stress on immune function and potential consequences for health outcomes. Short-term stress experienced during vaccination, wounding, or infection may enhance immunoprotective responses. Short-term stress experienced during immune activation in response to self/innocuous antigens or allergens may exacerbate pro-inflammatory and autoimmune disorders. Chronic stress induced increases in pro-inflammatory or Type 2 cytokine-mediated immune responses may also exacerbate inflammatory and autoimmune disease. Chronic stress induced suppression of immune responses may decrease the efficacy of vaccination and wound healing and decrease resistance to infection and cancer (Figure reproduced from [3] with permission from S. Karger AG, Basel)

important representation of the state of distribution of leukocytes in the body and of the state of activation of the immune system. The ability of short-term stress to induce changes in leukocyte distribution within different body compartments is perhaps one of the most under-appreciated effects of stress and stress hormones on the immune system [3, 4, 7, 9, 27].

Numerous studies have shown that short-term stress induces significant changes in absolute numbers and relative proportions of leukocytes in the blood. Stress-induced changes in blood leukocyte numbers have been reported in fish [49], hamsters [50], mice [51, 52], rats [7, 39, 53, 54], rabbits [55], horses [56], non-human primates [57], and humans [58–63]. This suggests that the phenomenon of stress-induced leukocyte redistribution has a long evolutionary lineage, and that perhaps it has important functional significance. Interestingly, changes in blood leukocyte numbers were used as a measure of stress before methods were available to directly assay stress hormones [64]. Studies have also shown that glucocorticoid [53, 65, 66] and catecholamine [27, 60, 67–70] hormones induce rapid and significant changes in leukocyte distribution and that these hormones are the major mediators of the effects of stress.

Short-term stress induces an initial increase followed by a decrease in blood lymphocyte and monocyte numbers and an increase in blood neutrophil numbers [4, 63]. Soon after the beginning of stress (order of minutes) or during mild short-term stress or exercise, stress hormones induce the body's "soldiers" (leukocytes), to exit their "barracks" (spleen, lung, marginated pool, and other organs) and enter the "boulevards" (blood vessels and lymphatics). This results in an increase in blood leukocyte numbers, the effect being most prominent for NK cells and granulocytes. As the stress response continues, stress hormones, acting largely through normal immune cell surveillance and trafficking mechanisms, induce leukocytes to exit the blood and take position at potential "battle stations" (skin, mucosal lining of gastrointestinal and urinogenital tracts, lung, liver, and lymph nodes) in preparation for immune challenges which may be imposed by the actions of the stressor [4, 7, 8, 40]. Such a redistribution of leukocytes results in a decrease in blood leukocyte numbers. Thus, short-term stress induces a redistribution of leukocytes from the *barracks*, through the *boulevards*, and to *potential battlefields* [3, 4, 9, 52]. It was hypothesized that such a leukocyte redistribution may enhance immune function in compartments to which immune cells traffic during stress and subsequently demonstrated that a stress-induced redistribution of leukocytes from the blood to the skin and subcutaneous tissues is accompanied by a significant enhancement of skin immunity [40, 71, 72].

Since the blood is the most accessible and commonly used compartment for human studies, it is important to carefully evaluate how changes in blood immune parameters might affect in vivo immune function in the context of the specific experiment or study at hand even when stress is not the focus of a study. Moreover, because most blood collection procedures involve a certain amount of stress, because all patients or subjects will have experienced short-term and chronic stress, and because many studies of psychophysiological effects on immune function focus on stress, the effect of stress on blood leukocyte distribution becomes a factor of considerable importance.

Short-term stress induced enhancement of innate/primary immune responses

In view of the skin being one of the target organs to which leukocytes traffic during stress, studies were conducted to examine whether skin immunity is enhanced when immune activation/antigen exposure takes place following a stressful experience. Short-term stress experienced at the time of novel or primary antigen exposure resulted in a significant enhancement of the ensuing immune response [16]. Compared to controls, mice restrained for 2.5 h before primary immunization with keyhole limpet hemocyanin (KLH) showed a significantly enhanced immune response when re-exposed to KLH nine months later. This immuno-enhancement was mediated by an increase in numbers of memory and effector helper T cells in sentinel lymph nodes at the time of primary immunization. Further analyses showed that the early stress-induced increase in T cell memory may have stimulated the robust increase in infiltrating lymphocyte and macrophage numbers observed months later at a novel site of antigen re-exposure. Enhanced leukocyte infiltration was driven by increased levels of the Type 1 cytokines, IL-2 and IFN-γ, and TNF-α, observed at the site of antigen re-exposure in animals that had been stressed at the time of primary immunization. Given the importance of inducing long lasting increases in immunological memory during vaccination, Dhabhar et al. [3, 4, 6, 16, 17] have suggested that the neuroendocrine stress response is nature's adjuvant that could be psychologically and/or pharmacologically manipulated to safely increase vaccine efficacy.

A similar enhancement of the sensitization/immunization/induction phase of cell-mediated immunity by different types of stressors administered at the time of antigen exposure has been observed in mice, rats, and non-human primates [73–75]. A series of elegant experiments also showed that short-term stress experienced at the time of sensitization resulted in a significant increase in the contact hypersensitivity (CHS) response [76]. Other studies further elucidated the molecular and cellular mediators of the immuno-enhancing effects of short-term stress [77]. They showed that compared to non-stressed mice, acutely stressed animals showed significantly greater pinna swelling, leukocyte infiltration, and upregulated macrophage chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-3α (MIP-3α), IL-1α, IL-1β, IL-6, TNF, and IFN-γ gene expression at the site of primary antigen exposure. Stressed animals also showed enhanced maturation and trafficking of dendritic cells from skin to lymph nodes, higher numbers of activated macrophages in skin and lymph nodes, increased T cell activation in lymph nodes, and enhanced recruitment of surveillance T cells to skin. These findings showed that important interactive components of innate (dendritic cells and macrophages) and adaptive (surveillance T cells) immunity are mediators of the stress-induced enhancement of a primary immune response. Such immuno-enhancement during primary immunization may induce a long-term increase immunologic memory resulting in subsequent augmentation of the immune response during secondary antigen exposure.

Short-term stress induced enhancement of adaptive/secondary immune responses

In addition to enhancing primary cutaneous immune responses, short-term stress experienced at the time of antigen re-exposure can also enhance secondary or recall responses in skin [40]. Compared to non-stressed controls, mice that were acutely stressed at the time of antigen re-exposure showed a significantly larger number of infiltrating leukocytes at the site of the immune reaction. These results demonstrated that a relatively mild behavioral manipulation can enhance an important class of immune responses that mediate harmful (allergic dermatitis) as well as beneficial (resistance to certain viruses, bacteria, and tumors) aspects of immune function. Other studies have similarly shown enhancement of the elicitation/recall phase of cell-mediated immunity by different stressors administered at the time of antigen re-exposure, in mice, rats, hamsters, and non-human primates [50, 73–75]. It has also been shown that short-term stress enhanced CHS responses in both male and female mice [78]; however, these authors did not observe the stress-induced enhancement of the sensitization phase of CHS [79] that has been reported by several independent groups as described above [16, 73–77, 80].

Short-term stress induced enhancement of anti-tumor immunity

Given the importance of cutaneous cell-mediated immunity in elimination of immuno responsive tumors like squamous

cell carcinoma (SCC) [81, 82], and given the immuno-enhancing effects of short-term stress, studies have examined the effects of short-term stress administered at the time of ultraviolet light (UV) exposure (minimum erythemal dose, thrice/week) on gene expression of chemokines and cytokines, infiltration of helper and cytolytic T cells that are critical for controlling and/or eliminating SCC and on tumor incidence, number and size [83]. Compared to controls, the short-term stress group showed greater cutaneous T cell attracting chemokine (CTACK)/CCL27, RANTES, IL-12, and IFN-γ gene expression, higher infiltrating T cell numbers, lower tumor incidence, and fewer tumors early, but not later during tumor development. These results suggest that activation of short-term stress physiology increased chemokine expression and T cell trafficking and/or function during/following UV exposure, and enhanced Type 1 cytokine-driven cell-mediated immunity that is crucial for resistance to SCC [83]. A stress-induced reduction in tumor burden has similarly been reported for murine sarcoma virus-induced tumors [84]. These findings raise the tantalizing possibility that the physiological fight-or-flight stress response and its adjuvant-like immuno-enhancing effects may provide a novel and important mechanism for enhancing immune system-mediated tumor detection/elimination that merits further investigation.

Endocrine mediators of stress-induced enhancement of immune function

Although much work remains to be done to identify molecular, cellular, and physiological mechanisms mediating the adjuvant-like, immuno-enhancing effects of short-term stress, studies have shown that corticosterone and epinephrine are important mediators of a short-term stress induced immuno-enhancement [71]. Adrenalectomy, which eliminates the glucocorticoid and epinephrine stress response, eliminated the stress-induced enhancement of cell-mediated immunity. Low-dose corticosterone or epinephrine administration significantly enhanced the immune response [71]. In contrast, high-dose corticosterone, chronic corticosterone, or low-dose dexamethasone were potently anti-inflammatory effects [71] as would be expected from their well-known use in the clinic [42]. These results suggested a novel role for physiological doses of adrenal stress hormones as endogenous immuno-enhancing agents. They also showed that hormones released during a short-term stress response may help prepare the immune system for potential challenges (e.g., wounding or infection) for which stress perception by the brain may serve as an early warning signal. Other studies have also suggested that physiological concentrations of glucocorticoid hormones mediate stress-induced enhancement of interferon production [85], skin CHS [78], and that the adjuvant-like effects of stress on dendritic cell and CD8+ T cell migration and function, that mediate immuno-enhancement are driven by norepinephrine [76]. In a series of elegant studies, Sanders and colleagues have elucidated the role of the beta-adrenergic receptor in regulating lymphocyte function and have shown that the level of activation is influenced by the time of receptor engagement relative to the state of activation and/or differentiation of the lymphocyte and by the cytokine milieu [86, 87]. Taken together, these studies suggest that endogenous stress hormones in physiological concentrations can have immuno-enhancing effects, while endogenous hormones at pharmacologic concentrations, and synthetic hormones, are immunosuppressive.

Cytokine mediators of stress-induced enhancement of immune function

Since gamma interferon (IFN-γ) is a critical cytokine mediator of cell-mediated immunity as well as delayed, and CHS, studies were conducted to elucidate the role of IFN-γ as a local mediator of the stress-induced enhancement of skin immunity [72]. The effect of short-term stress on skin immunity was examined in wild-type and IFN-γ receptor gene knockout mice (IFN-γR-/-). Acutely stressed wild-type mice showed a significantly larger cell-mediated immune response than non-stressed mice. In contrast, IFN-γR-/- mice failed to show a stress-induced enhancement of skin immunity. Immunoneutralization of IFN-γ in wild-type mice significantly reduced the stress-induced enhancement of skin immunity [72]. In addition to IFN-γ, stress-induced increases in gene expression of TNF, MCP-1, MIP-3α, IL-1α, IL-1β, and IL-6 (but not IL-4) have also been associated with enhancement of the immunization phase of cell-mediated immunity [16, 77].

Another important immunological effect of short-term stress is to induce a significant increase in concentrations of circulating cytokines such as IL-6 and IL-1β [88–93]. Importantly, this increase is observed in response to psychological stressors such as the Trier Social Stress Test (TSST) and in the absence of immune activating events such as a wound, or antigen/pathogen inoculation. We suggest that such short-term stress induced increases in circulating cytokines may be an additional systemic mechanism mediating stress-induced enhancement of immune function. Interestingly, short-term stress induced increases in circulating cytokines are related to changes in emotional states experienced during stress. For example, IL-1β reactivity during stress is a significant mediator of the relationship between a decline in positive affect and cognitions during stress, and an increase in depressive symptoms one year later [91]. Such mediation is

particularly salient given the known role of pro-inflammatory cytokines in inducing sickness behavior, depressive states, and depression [30, 94–97] and in important reciprocal immune-to-neural signaling [30, 98–100].

In another interesting example, anger experienced during a stressor is related to a stress-induced increase in circulating IL-6; however, perceived social support mitigates the effects of anger on IL-6 stress reactivity such that the greater the amount of social support the lower the stress reactivity of IL-6 [92]. In light of these findings, it has been suggested that short-term stress induced increases in IL-6 and other pro-inflammatory cytokines may confer a survival advantage by facilitating short-term stress induced immuno-enhancement [92]. We have speculated that individuals with low social support may be more likely to be "out on their own," and have to fend for themselves, and as a result be more susceptible to attack and/or injury [92]. Therefore, such individuals may mount a more robust immunological stress response. Furthermore, an angry individual may be more likely to engage in an aggressive encounter, i.e., choose to fight rather than flee, and as a result may be more likely to need enhanced immune defenses to heal wounds (incurred during the fight) and to defend against accompanying pathogen entry. Such evolutionary underpinnings may at least partially explain the association among emotional states and stress reactivity of pro-inflammatory cytokines. As with most psychological and biological processes, activating this response too frequently or for too long (especially in the absence of a wound or infection) may result in greater long-term exposure to pro-inflammatory factors resulting in their deleterious health consequences. Such chronic effects may underlie the pro-inflammatory milieu that is often observed during various disorders, [30, 101] such as major depression [89, 102–105], alcohol addiction [106], and post-traumatic stress disorder [107–109], and in some cases may be facilitated by the genetic makeup of an individual [110].

Chronic stress induced suppression/dysregulation of immune function

In contrast to short-term stressors, chronic stress has been shown to suppress or dysregulate immune function. This topic has been the subject of many excellent reviews (such as: [5, 14, 111–117]). In addition to significant personal and health-related costs of chronic stress, the economic cost to industry arising from work-related stress in the USA alone is thought to be more than $300 billion [118].

Studies have investigated the effects of increasing the intensity and duration of short-term stress as well as the transition from short-term to chronic stress on skin immune function [9]. Short-term stress administered for 2 h prior to antigenic challenge significantly enhanced skin cell-mediated immunity [9]. Increasing the duration of stress from 2 to 5 h produced the same magnitude immuno-enhancement. Interestingly, increasing the intensity of short-term stress produced a significantly larger enhancement of the immune response that was accompanied by increasing magnitudes of leukocyte redeployment. In contrast, immunosuppression was observed when chronic stress exposure was begun 3 weeks before primary immunization and either discontinued following immunization, or continued an additional week until re-exposure to the antigen, or extended for one week after re-exposure [9]. Interestingly, short-term stress induced redistribution of peripheral blood lymphocytes was attenuated with increasing duration of stressor exposure and correlated with attenuated glucocorticoid responsivity. These results suggested that stress-induced alterations in lymphocyte redeployment may play an important role in mediating the bidirectional effects of stress on cutaneous cell-mediated immunity [9]. An association between chronic stress and reduced skin cell-mediated immunity has also been reported in human subjects [119, 120].

A chronic stress induced decrease in leukocyte mobilization from the blood to other body compartments is thought to be one of the mediators of this stress-induced suppression of skin CMI [9]. In human and animal studies, chronic stress has also been shown to suppress different immune parameters examples of which include CMI [121], antibody production [122, 123], NK activity [13, 124–126], leukocyte proliferation [124, 126, 127], skin homograft rejection [128], virus-specific T cell and NK cell activity [129], and anti-mycobacterial activity of macrophages from susceptible mouse strains [130].

Acceleration of immuno-senescence is another important mechanism through which chronic stress suppresses/dysregulates immune function. In a seminal study, Epel et al. [131] showed that blood lymphocytes and monocytes from women reporting high chronic stress levels have significantly shorter telomeres compared to leukocytes from women reporting low stress. Immune cell telomerase activity was also lower in the high-stress women indicating a chronic stress induced decrease in their ability to rebuild shortened telomeres [131]. The study concluded that "women with the highest levels of perceived stress had telomeres that were shorter on average by the equivalent of at least one decade of additional aging compared to low-stress women [131]." Epel et al. have also shown that the rate of telomere shortening predicts death from cardiovascular disease [132] and has significant deleterious effects [133]. Thus, chronic stress induced acceleration of immune cell aging can have significant deleterious effects on immune function because it is likely to result in suppression of immunoprotection and exacerbation of immune dysregulation and immunopathology.

Chronic stress and cancer

Numerous studies have investigated the effects of chronic stress in the context of cancer [134–136]. In light of the immunosuppressive effects of long-term stress, and given the importance of cell-mediated immunity in elimination of immuno responsive tumors like SCC [81], studies have also investigated the effects of chronic stress on cancer emergence [19] and progression [19, 137–140]. Chronic stress significantly accelerated the emergence and progression of SCC. Compared to non-stressed controls, chronically stressed mice had lower IFN-γ, CCL27/CTACK, and CD3ε gene expression and lower CD4+ and CD8+ T cells infiltrating within and around tumors. Chronically stressed mice also showed a shorter median time to first tumor and reached 50 % incidence 6 weeks earlier than controls. Interestingly, stressed mice had higher numbers of tumor infiltrating and circulating regulatory/suppressor T cells than non-stressed mice. These studies showed that chronic stress increased susceptibility to UV-induced SCC by suppressing skin immunity, Type 1 cytokines, and protective T cells, and increasing active immunosuppressive mechanisms mediated by regulatory/suppressor T cells [19]. Similarly, studies have shown that a high-anxious behavioral phenotype, that is likely to be associated with increased susceptibility to chronic stress, is associated with suppressed anti-tumor immunity and increased susceptibility to the emergence and progression of SCC [141].

Chronic stress and autoimmune disease

Given the immunosuppressive effects of chronic stress, it may be hypothesized that under certain conditions, chronic stress could ameliorate autoimmune diseases. A few preclinical studies suggest that this may be the case. Levine and Saltzman [142] demonstrated that the administration of prolonged restraint stress to rats before the induction of experimental allergic encephalomyelitis (EAE) resulted in a suppression of the incidence and severity of disease. Rogers et al. [143] showed that exposure of rats to a variety of stressors results in a marked suppression of the clinical and histological manifestations of type II collagen-induced arthritis. Similarly, Griffin et al. [144] demonstrated suppression of EAE by chronic stress. In an elegant series of experiments, Stefanski et al. [145] recently showed that severe (but not moderate) social stress significantly reduced susceptibility to collagen-induced arthritis in Wistar rats, and that this effect was mediated by decreases in CD4, CD8 T cell numbers and macrophage infiltration at the site of collagen injection.

One would not recommend chronically stressing anyone, leave alone patients with autoimmune disease; however, there may be lessons to be learned from the above-mentioned studies. Important questions for future studies include as follows: (1) What are the physiological conditions and mechanisms under which chronic stress can exert immunosuppressive effects in the absence of inducing pro-inflammatory effects? (2) Does a chronic stress induced increase in regulatory/suppressor T (Tregs) [19], regulatory B cells [141], NK cells, dendritic cells or monocytes/macrophages mediate suppression of autoimmune responses? (3) Is chronic stress induced amelioration of autoimmune disease observed in human subjects? (4) If so, could some of the biological mechanisms mediating chronic stress induced amelioration of autoimmune reactions be safely and selectively harnessed to treat autoimmune diseases without administering chronic stress? Clearly, more research is warranted into investigating whether chronic stress ameliorates autoimmune reactions in humans, delineating the conditions under which such amelioration is observed, and elucidating mechanisms with the goal of identifying targets for pharmacological or biobehavioral interventions.

Importantly, it has also been suggested that chronic stress induced exacerbation of inflammatory diseases such as rheumatoid arthritis may be mediated by a loss of immunosuppression that is normally driven by sympathetic nerves that innervate the inflamed tissue, and by systemic secretion of cortisol through cytokine-induced activation [146, 147] of the hypothalamic–pituitary–adrenal axis [148, 149]. Sternberg et al. [22, 150] initially showed that a defect in inflammation-induced activation of the HPA-axis, resulting in a reduction/loss of the anti-inflammatory effects of endogenous glucocorticoids, is an important factor in the progression of autoimmune diseases.

Immunomodulatory effects of timing of stress or stress hormone administration relative to the timing of immune activation and the time course of the ensuing immune response

Under certain conditions, endogenous glucocorticoids have immuno-enhancing effects, while under other conditions, these hormones suppress autoimmune and inflammatory reactions. It is possible that these differential effects are achieved by differences in overall glucocorticoid sensitivity of the affected immune response. At the beginning of an immune response, certain components such as leukocyte trafficking, antigen presentation, helper T cell function, leukocyte proliferation, cytokine and chemokine function, and effector cell function may be receptive to glucocorticoid-mediated immuno-enhancement. In contrast, at a

later, more advanced stage of an immune response, these components may be more receptive to glucocorticoid-mediated immunosuppression. While this hypothesis needs to be tested through further experiments, studies examining the effects of corticosterone on T lymphocyte proliferation in vitro [151] support the hypothesis that there may be temporal differences in the receptivity of an immune response to the enhancing versus suppressive effects of endogenous glucocorticoid hormones. Thus, studies have shown that during the early stages of T cell activation, low levels of corticosterone potently enhance anti-TCR-induced lymphocyte proliferation. However, during later stages of culture, the same levels of corticosterone suppress T lymphocyte proliferation [151]. Furthermore, it has been shown that corticosterone had to be present during the process of TCR activation in order to enhance the proliferative response. If corticosterone was added to the culture system more than 2 h after the initiation of TCR activation, the enhancement of lymphocyte proliferation was not observed. Sanders and colleagues have elegantly elucidated the role of the beta-adrenergic receptor in regulating lymphocyte function, showing that the level of activation is influenced by the time of receptor activation relative to the state of activation and/or differentiation of the lymphocyte and by the cytokine milieu [86, 87]. Similar bimodal effects of catecholamines dependant on the state (early versus late) of progression of rheumatic disease have also been shown [116]. It has been proposed that energy and volume regulation may be one important aspect of interactions between stress (and other) hormones and the immune system and that these factors may take on additional significance during chronic inflammatory conditions [152, 153].

Exercise, stress, and immune function

The process of exercising induces a physiological stress response and increases circulating concentrations of adrenaline (epinephrine), noradrenaline (norepinephrine), cortisol, and other stress-related factors including cytokines [154–156]. Understanding the psychological, physiological, and health effects of exercise in the context of stress and stress physiology is critical for several important reasons: (1) A hitherto unappreciated but critical mechanism mediating the salubrious effects of exercise could be through its optimization of the beneficial, survival-promoting effects of the short-term or acute stress response [3]. Regular exercise may help keep the short-term stress response "well-oiled," fine-tuned, and ready for fight-or-flight. This idea also makes sense from an evolutionary perspective because regular and robust physical activity is an intrinsic part of life in nature. The "conveniences" of modern societies might cause unintended harm by decreasing our activity levels and making physical activity optional in our day-to-day lives. Studies have shown that physical activity can modulate cancer-related pathways and improve some biomarkers associated with better prognosis [157]. In keeping with this idea, recently conducted mouse studies have shown that exposure to short-term stress (thrice per week) in a manner that mimics exercise-induced activation of short-term stress physiology significantly enhanced anti-tumor immunity and decreased tumor burden [83]. These findings suggest that regular activation of the short-term stress response, in a frequency that does not induce chronic stress, may be one mechanism mediating findings from human studies showing that moderate and regular physical activity reduces the risk of cancer occurrence [158, 159], progression, and mortality [160]. (2) Intense prolonged exercise [161] or exercising under extreme environmental conditions [162] may lead to chronic exposure to stress hormones that make the individual susceptible to the deleterious health effects of chronic stress. Exercise-induced pain, exhaustion, or injury could also induce psychological stress. (3) When performed regularly and in moderation, exercise could be a factor in ameliorating the deleterious health effects of chronic stress and increased allostatic load (namely the physiological cost that results from ongoing adaptive efforts to maintain homeostasis in response to stressors) [1, 163–165]. The type, intensity, duration and frequency of exercise, and the conditions under which it should be performed in order to effectively reduce the stress burden of different individuals need to be better understood and defined. It is likely that one would need different strokes for different folks, i.e., running could serve as a "de-stressor" for some while others would benefit from aerobics, swimming, dancing, or yoga. The most desirable results are likely to arise when the physical as well as psychosocial aspects of the exercise are matched with factors such as the fitness, capability, temperament, personality of the exercising individual. (4) The psychosocial stress status of an individual may positively or negatively affect the relationship between exercise and health. For example, compared to a low-stress individual, a chronically stressed individual may react differently to the effects of exercise [166]. This is an area of research that is ripe for investigation and is relevant for the well-being of recreational and elite athletes as well as armed forces and other professions for whom exercise is a critical aspect of training and job performance.

Thus, physical activity and exercise are potent stimulators of the physiological stress response. Therefore, many health effects of exercise are likely to be mediated through stress and immune factors in addition to cardiovascular, neuromuscular, and other factors.

Short-term stress induced immuno-enhancement: from bench to bedside

It has been proposed that a psychophysiological stress response is one of the nature's fundamental survival mechanisms that could be therapeutically harnessed to augment immune function during vaccination, wound healing, or infection [3, 4, 16, 28, 167]. These adjuvant-like immuno-enhancing effects of short-term stress may have evolved because many stressful situations (aggression, accident) result in immune activation (wounding, infection) and vice versa. Interestingly, in modern times, many medical procedures involving immune activation (vaccination, surgery) also induce a stress response. Preclinical findings initially lent support to this hypothesis and have since been replicated in studies involving human subjects. Human subject's studies have shown that patients undergoing knee surgery, who show a robust and adaptive immune cell redistribution profile during the short-term stress of surgery, also show significantly enhanced recovery [63]. Similarly, preclinical studies initially demonstrated that short-term stress experienced during primary [16, 77] or secondary [40, 71, 72, 76] antigen exposure significantly enhances the ensuring immune response. Based on these laboratory studies, an elegant series of clinical studies have shown that adjuvant effects of short-term psychological stress, or exercise stress, and can enhance vaccine-induced immunity in human subjects [168–170]. In terms of further mechanistic parallels between basic and human subjects studies, it has been shown that a short-term stress induced enhancement of skin immunity in mice is mediated by enhanced maturation and trafficking of dendritic cells from skin to draining lymph nodes, larger numbers of activated macrophages in skin and lymph nodes, and increased T cell activation in lymph nodes [77]. These findings are in agreement with studies that showed that short-term psychological stress in human participants induces a significant decrease in epidermal Langerhans' cells that the authors suggest represents a trafficking of these cells from the skin to draining lymph nodes [171], a phenomenon that has elegantly been said to have striking similarities in "mice and men" [172].

While short-term stress induced enhancement of immunoprotective responses has been appreciated relatively recently, stress-induced exacerbations of pro-inflammatory (e.g., dermatitis [173, 174], cardiovascular disease [175, 176], periodontal disease [177], and asthma [173, 178, 179]) and autoimmune (e.g., psoriasis [180, 181], arthritis [182], multiple sclerosis [183]) diseases are well-known and frequently observed in the clinic. It has been suggested that stress-induced exacerbation of pro-inflammatory and autoimmune diseases may be partially mediated by mechanisms that are similar to those that enhance protective immune responses during stress [3, 4, 167]. Therefore, it would be beneficial for future studies to (1) determine the extent to which stress-induced exacerbation of such disorders is mediated by immuno-enhancing mechanisms activated during short-term stress versus immuno-dysregulatory mechanisms activated during chronic stress, (2) determine the extent to which stress induces the onset of disease, and the extent to which stress exacerbates ongoing disease, (3) use more standardized psychological and physiological measures of stress and where possible also of the stress-affected immune parameters.

Staying on the good side of the stress spectrum

In order to reconcile the potentially beneficial versus harmful effects of stress, Dhabhar et al. [3, 6, 8, 9] proposed that a stress response and its effects on immune function be viewed in the context of a STRESS SPECTRUM (Fig. 2). One end of this spectrum is characterized by GOOD STRESS or EUSTRESS, i.e., conditions of short-duration stress that may result in immuno-preparatory, or immuno-enhancing physiological conditions. An important characteristic of short-term stress is a rapid physiological stress response mounted in the presence of the stressor, followed by a rapid shutdown of the response upon cessation of the stressor. The opposite end of the spectrum is characterized by BAD STRESS or DISTRESS, i.e., chronic or long-term stress that can result in dysregulation or suppression of immune function. An important characteristic of chronic stress is that the physiological response either persists long after the stressor has ceased or is activated repeatedly to result in an overall increase in exposure to stress hormones and/or dysregulation of stress-related and other physiological processes (e.g., circadian rhythms). The concept of "allostatic load" has been proposed to define the "psychophysiological wear and tear" that takes place while different biological systems work to stay within a range of equilibrium (allostasis) in response to demands placed by internal or external chronic stressors (for review see: [1, 11, 184, 185]). We suggest that conditions of high allostatic load would result in dysregulation or suppression of immune function. Importantly, a disruption of the circadian cortisol rhythm is an important indicator and/or mediator of the deleterious effects of chronic stress [9]. The stress spectrum also proposes that short- or long-term stressors are interspersed by a RESTING ZONE of low/no stress that also represents a state of health maintenance/restoration (Fig. 2). The extent and efficiency with which an organism returns to its resting zone after stress depends on RESILIENCE, which we define as the capacity of psychophysiological systems to

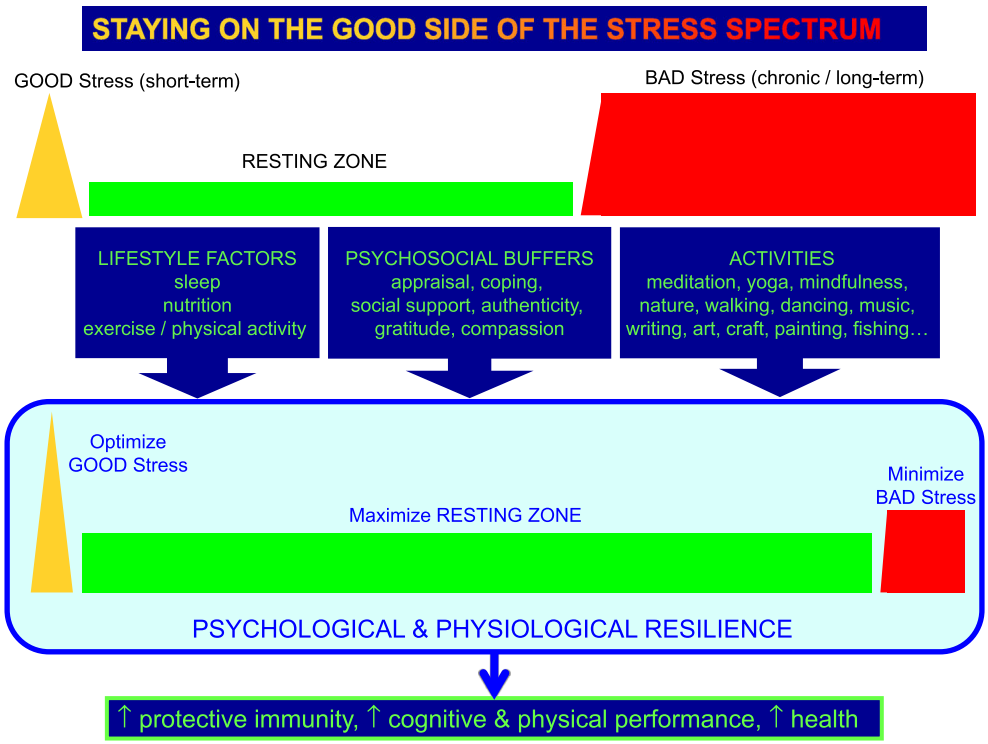

Fig. 2 Stress spectrum [3, 6, 17, 167]. One end of the spectrum is represented by GOOD stress which involves a rapid biological stress response mounted in the presence of the stressor, followed by a rapid shutdown of the response upon cessation of the stressor. Such responses induce physiological conditions that are likely to enhance protective immunity, cognitive and physical performance, and overall health. The opposite end of the spectrum is represented by BAD stress which involves chronic or long-term biological changes that are likely to result in dysregulation or suppression of immune function, a decrease in cognitive and physical performance, and an increased likelihood of disease. Short- and/or long-term stress is generally superimposed on a psychophysiological RESTING ZONE of low/no stress that also represents a state of health maintenance/restoration. In order to maintain health, one needs to optimize GOOD stress, maximize the RESTING ZONE, and minimize BAD stress. This is likely to involve a multi-pronged approach [3, 6, 17]: Sleep of a quality and duration that helps one feel rested in the morning, a moderate and healthy diet, and consistent and moderate exercise or physical activity are three LIFESTYLE FACTORS that are likely to enable one to stay on the "good" side of the stress spectrum. Effective appraisal and coping mechanisms, genuine gratitude, social support, and compassion toward others and oneself are likely to provide PSYCHOSOCIAL BUFFERS against bad stress and to enable one to stay on the "good" side of the stress spectrum. Additionally, depending on individual preferences, ACTIVITIES, such as, meditation, yoga, being in nature, exercise/physical activity, music, art, craft, dance, fishing, painting, may also reduce BAD stress, extend the RESTING ZONE, and optimize GOOD stress. Such personal activities are likely to involve different strokes for different folks and need not always be meditative or reflective in nature

recover from challenging conditions. Psychological and physiological resilience factors determine the overall effects of stress on an individual [3, 17].

The longer one experiences chronic stress, the higher the chances of there being detrimental health effects. However, because most organisms are stress resilient, it often takes prolonged exposure to chronic stress to break down physiological systems. In order to stay healthy, one needs to minimize chronic stress, maximize the resting zone of low/no stress, and optimize the short-term/fight-or-flight stress response so that it is mounted rapidly and robustly when needed and shutdown immediately after the cessation of stress (Fig. 2). Implementation of such a strategy involves a multi-pronged approach [3, 6, 186]: Sleep of a quality and duration that helps one feel rested in the morning, a moderate and healthy diet, and consistent and moderate exercise or physical activity are three lifestyle factors that are likely to enable one to stay on the "good" side of the stress spectrum. Effective appraisal and coping mechanisms, genuine gratitude, compassion toward others and oneself, and social support are likely to be powerful psychosocial buffers against chronic stress and enable one to stay on the "good" side of the stress spectrum. In addition to lifestyle and psychosocial factors, depending on the personality and preferences of the individual, activities, such as, meditation, yoga, nature walks or hikes, exercise/physical activity, music, art, craft, dance, fishing, painting, may also reduce BAD stress, maximize the RESTING ZONE, and optimize GOOD stress. Such personal activities are likely to involve different strokes for different folks, and they need not all be meditative or contemplative in nature.

The Stress Spectrum, taken together with the preceding discussions, shows that *the duration, intensity/concentration, and timing of exposure to stressor-induced physiological activation (neurotransmitters, hormones, and their molecular, cellular, organ-level and systemic effects) are critical for determining whether stress will enhance or suppress/dysregulate immune function*. While there is significant evidence in support of our stress spectrum model (Fig. 2) [3, 6, 17], different aspects of the model need to be further investigated in preclinical studies and studies involving human subjects.

Effects of stress on immune function: the good, the bad, and the beautiful

The GOOD

Natural, endogenous, stress-induced immuno-enhancement may naturally increase immunoprotection during surgery, vaccination, infection, or cancer. An important function of physiological mediators released under conditions of short-term psychological stress may be to ensure that appropriate leukocytes are present in the right place, at the right time, and activated in the right manner, to optimize response to an immune challenge which could be initiated by the stress-inducing agent (e.g., attack by a predator, accidental wounding, or a surgeon's scalpel). The modulation of immune cell distribution by short-term stress is an adaptive response designed to enhance immune surveillance and increase the capacity of the immune system to respond to challenge in immune compartments (such as the skin, and mucosal and epithelial linings of the gastrointestinal and urinogenital tracts) which serve as major defense barriers for the body, and at other sites of immune activation.

The BAD

Under some conditions, immune-enhancement driven by short-term stress or immune dysregulation driven by long-term stress can exacerbate pro-inflammatory (dermatitis, cardiovascular disease, gingivitis) and autoimmune diseases (psoriasis, arthritis, multiple sclerosis) diseases that are known to be worsened by stress [180, 187–189]. Moreover, immunosuppression by chronic stress can delay wound healing [14], suppress vaccine responses [14], and increase susceptibility to infections [190] and cancer [19, 137, 138, 141].

The BEAUTIFUL

Preclinical and clinical studies showing short-term stress induced enhancement of immune function during surgery [52, 63], vaccination [16, 40, 71, 72, 76, 77, 170] and cancer [83] raise the tantalizing possibility that the physiological fight-or-flight stress response and its adjuvant-like immuno-enhancing effects may provide a novel and important mechanism for enhancing immunoprotection. This could lead to the development of treatments that induce a short-term stress response (e.g., consistent moderate exercise, virtual-reality stressors, or pharmacological agents) to boost protective immunity when needed.

Much work remains to be done to further elucidate mechanisms and translate findings from bench to bedside. However, this work is important because stress is a ubiquitous part of life. Chronic stress has long been known to play a role in the etiology of numerous diseases, and extracts a tremendous cost from society. In contrast, it has recently been appreciated that short-term stress is one nature's fundamental survival mechanisms that could be clinically harnessed to safely and effectively enhance immunoprotection. It is hoped that studies such as the ones discussed here will identify specific factors/targets that may be therapeutically manipulated to enhance protective immune responses, or to ameliorate/eliminate stress-induced exacerbation of pro-inflammatory or autoimmune diseases, and to induce conditions that maximally promote health and healing.

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