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Psychological stress and immunoprotection versus immunopathology in the skin

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Abstract Stress is thought to suppress immune function and increase susceptibility to infections and cancer. Paradoxically, stress is also known to exacerbate autoimmune/proinflammatory disorders (eg, psoriasis, atopic dermatitis) that should be ameliorated by immunosuppression. Here we review studies showing that although chronic stress (lasting for weeks/months/years) can suppress/dysregulate immune function, acute stress (lasting for minutes to hours) can have immunoenhancing effects. Short-term stress experienced at the time of immune activation enhances dendritic cell, neutrophil, macrophage, and lymphocyte trafficking, maturation, and function, and has been shown to augment innate and adaptive immunity; therefore, depending on the conditions of immune activation, and the nature of the activating antigen, short-term stress can enhance the acquisition and expression of immunoprotection or immunopathology. In contrast, chronic stress suppresses or dysregulates innate and adaptive immune responses by altering the Type 1-Type 2 cytokine balance, inducing low-grade chronic increases in proinflammatory factors, and suppressing numbers, trafficking, and function of immunoprotective cells. Chronic stress also increases susceptibility to skin cancer by suppressing Type 1 cytokines and protective T cells while increasing regulatory/suppressor T cell number/function. It is important to recognize that the adaptive function of a physiological stress response is to promote survival. Stress-related neurotransmitters, hormones, and factors act as biological alarm signals that prepare the immune and other physiological systems for potential challenges (eg, wounding or infection) perceived by the brain (eg, detection of an attacker); however, this may exacerbate immunopathology (eg, psoriasis, atopic dermatitis) if the enhanced immune response is directed against innocuous or self-antigens, or if the system is chronically activated as seen during long-term stress. In view of the ubiquitous nature of stress and its significant effects on immunoprotection and immunopathology, it is important to further elucidate the mechanisms mediating both the salubrious and the harmful effects of stress, and to meaningfully translate findings from bench to bedside.

Introduction

Numerous studies have demonstrated adverse effects of stress on health.[1,2] These studies show that chronic or long-term stressors can have harmful effects, some of which are mediated through immune mechanisms; however, it is also important to appreciate that a psycho-physiological stress response is one of nature's fundamental survival mechanisms. Without a fight-or-flight stress response, a lion has no chance of catching a gazelle, just as the gazelle has no chance of escape. During such short-term stress responses, multiple physiological systems are activated to enable survival. We have hypothesized that just as the stress response prepares the cardiovascular, musculoskeletal, and neuroendocrine systems for fight or flight, under certain conditions, stress

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may also prepare the immune system for challenges (eg, wounding or infection) that may be imposed by a stressor (eg, predator, or, in modern times, a medical/surgical procedure).[3,4] Studies have shown that short-duration stressors induce a redistribution of immune cells within the body and that immune function is significantly enhanced in organs like the skin to which leukocytes traffic during acute stress. Studies have also identified mechanisms involving dendritic cell, neutrophil, macrophage, and lymphocyte trafficking, maturation, and function through which acute stressors may enhance innate as well as adaptive immunity. Acute stress response may serve as an endogenous psychophysiological adjuvant that enhances immune responses and may have evolved by virtue of the fact that stressful situations (aggression or accident) often result in immune activation (wounding or infection) and immune activating events (accidental wounding) can often trigger a stress response (resulting from pain and the realization that one has been wounded).[5-7] Interestingly, many clinical situations involving immune activation (eg, vaccination, surgery) also induce a stress response. Although acute stress-induced immunoenhancement may serve to increase immunoprotection during exposure to infectious agents or wounding, it may also exacerbate immunopathology if the enhanced immune response is directed against innocuous or self-antigens, or dysregulated following prolonged activation as seen during chronic stress. In contrast to acute stress, chronic stress has been shown to dysregulate immune responses[8,9] by altering the cytokine balance from Type-1 to Type-2 cytokine-driven responses[10] and accelerating immunosenescence[11,12] and to suppresses immunity by decreasing numbers,[13] trafficking,[13] and function of protective immune cells while increasing regulatory/suppressor T cells.[14] We discuss the effects of stress on immune function and implications of these effects for immunoprotection versus immunopathology. We propose that it is important to study, and if possible, to harness clinically, the immunoenhancing effects of the acute stress response that evolution has finely sculpted as a survival mechanism, just as we study its maladaptive ramifications (chronic stress) that evolution yet has to catch up with.

Stress: definition, mediators, and individual differences

Although 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 definition focuses on aspects of an internal or external challenge, disturbance, or stimulus; on perception of a stimulus by an organism; or on a physiological response of the organism to the stimulus.[15-17] 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).[13] The only way that a stressor can affect the brain or body is through the physiological stress response. The major mediators of stress effects are norepinephrine and epinephrine, which are released by the sympathetic nervous system and corticotrophin-releasing hormone, adrenocorticotropin, and cortisol, which arise following activation of the hypothalamic-pituitary-adrenal axis. Because 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.

Although stress can be harmful when it is chronic or long lasting,[1,8,9,18] it is often overlooked that a stress response has salubrious adaptive effects in the short run.[6,19] Major distinguishing characteristics of stress are duration and intensity. *Acute 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.[13] Dysregulation of the circadian cortisol rhythm is one maker that appears to coincide with the deleterious effects of chronic stress.[13,14,20] 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 by the amount of time for which these changes persist during stress and following the cessation of stress. There are significant individual differences in stress perception, processing, and coping.[19,21]. Individual differences become particularly relevant while studying human subjects because stress perception, processing, 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 elevated. Animal studies showing strain differences in stress reactivity and peak hormone levels,[22,23] adaptation to stress,[24] and in distribution and activation of adrenal steroid receptors and corticosteroid binding globulin levels,[22,25] suggest that genetic as well as environmental factors play a role in establishing individual differences.[22,24-26] 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, which often has deleterious effects. The magnitude and duration of stress-induced elevations in catecholamine and glucocorticoid hormones can have significant effects on immune cell distribution and function.[4,27,28]

The immune triad: immunoprotection, immunopathology, and immunoregulation

When 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, and so on, immune responses are all defined in terms of their cellular and cytokine components. Although 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. Therefore, in addition to these categories, it is also useful to define immune responses in terms of their end-effects. We suggest that immune responses can be categorized as being immunoprotective, immunopathological, and immunoregulatory/suppressive (for review see[7,29]). Immunoprotective responses are defined as responses that promote efficient wound healing, eliminate viral infections and cancer, and mediate vaccine-induced immunological memory. Immunopathological responses are defined as those that are directed against self- (autoimmune diseases like psoriasis, multiple sclerosis, arthritis, lupus) or other antigens (skin hypersensitivities, allergies, asthma), as well as responses that involve chronic, nonresolving inflammation. Immunopathology is also involved in low-grade, chronic elevations in local and/or systemic inflammatory mediators that are thought to contribute to disorders like cardiovascular disease, obesity, and depression. Immunoregulatory/suppressive responses are defined as those that involve immune cells and factors that regulate/inhibit the function of other immune cells. Although the previous concept of suppressor T cells became mired in controversy, recent studies suggest that a critical arm of the immune system functions to inhibit immune responses.

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

Critical factors that are likely to influence the direction (enhancing versus suppressive) of the effects of stress or stress hormones and the nature of the immune response (immunoprotective, immunopathological, or immunoregulatory/suppressive) that is affected include (1) the effects of stress on leukocyte distribution in the body, (2) the duration (short-term/acute versus long-term/chronic) of stress, (3) the differential effects of physiologic versus pharmacologic concentrations of glucocorticoids and the differential effects of endogenous (eg, cortisol, corticosterone) versus synthetic (eg, dexamethasone) glucocorticoids, and (4) the timing of stressor or stress hormone exposure relative to the time of activation and ensuing time course of the immune response. Factors, such as gender, genetics, age, the route of administration and nature of the immunizing antigen, and time during the circadian cycle, may additionally affect the relationship between stress and immune function.

Whether a stressor enhances or suppresses immune function, the end-effect of the immune response determines whether the stress-immune interactions have beneficial or harmful effects on health (Figure 1). Given the definitions in the preceding section, stress-induced enhancement of immunoprotection is likely to have beneficial effects, whereas stress-induced suppression of immunoprotection is likely to be harmful. Similarly, stress-induced enhancement of immunopathology or long-term proinflammation is also likely to be harmful. Finally, stress-induced enhancement of active immunoregulation/inhibition is likely to be beneficial in cases of autoimmune and proinflammatory disorders and harmful in cases of infections and cancer.

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.[30] The numbers and proportions of leukocytes in the blood provide an 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 acute stress to induce changes in leukocyte distribution within different body compartments is perhaps one of the most underappreciated effects of stress and stress hormones on the immune system.[3,13]

Numerous studies have shown that acute or 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,[31] hamsters,[32] mice,[33,34] rats,[3,35-37] rabbits,[38] horses,[39] nonhuman primates,[40] and humans.[41-46] 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.[47] Studies have also shown that glucocorticoid[36,48,49] and catecholamine[28,43,50-53] hormones induce rapid and significant changes in leukocyte distribution and that these hormones are the major mediators of the effects of stress.

Acute stress induces an initial increase followed by a decrease in blood lymphocyte and monocyte numbers, and an increase in blood neutrophil numbers.[46] Stress conditions that result in activation of the sympathetic nervous system, especially conditions that induce high levels of norepinephrine, generally induce an increase in circulating leukocyte numbers. These conditions may occur during the beginning

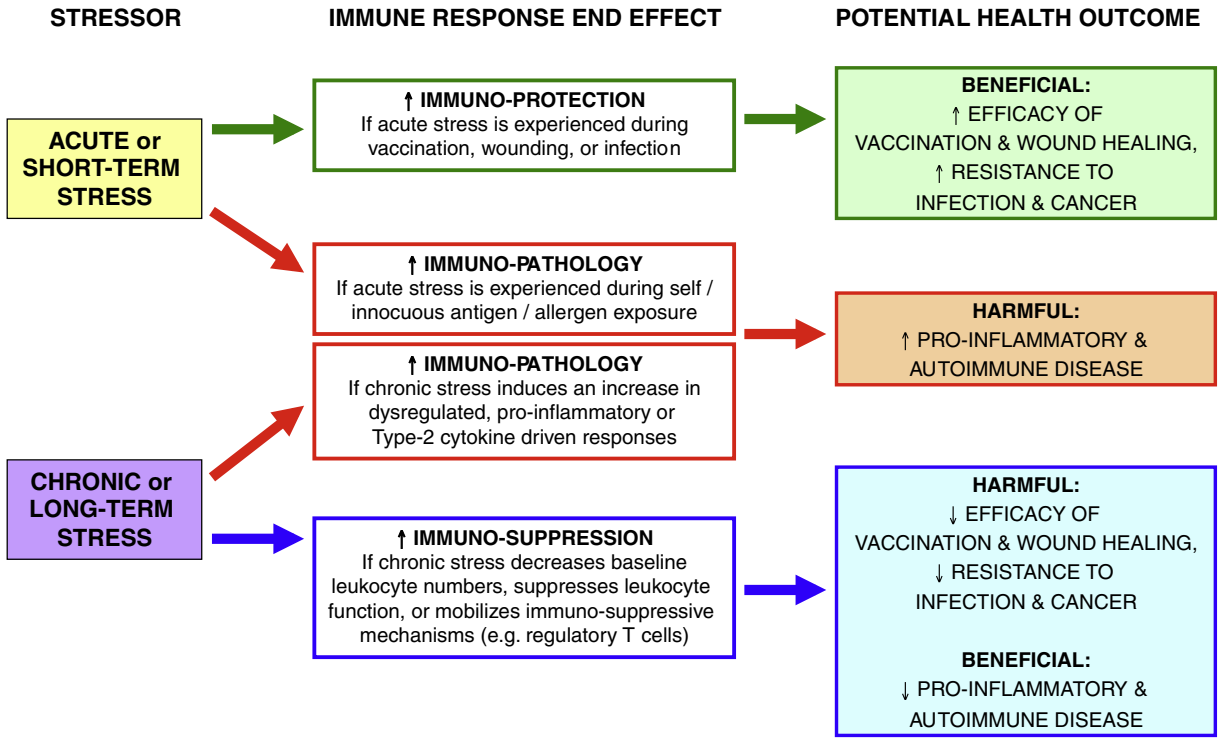

Fig. 1 Effects of acute/short-term and chronic/long-term stress on immunoprotection, immunopathology, and immunoregulation/suppression, and their implications for wound healing, vaccination, resistance to infections/cancer, and proinflammatory and autoimmune diseases. (Reprinted with permission of S. Karger AG, Basel from Dhabhar FS.[7])

of a stress response, very short duration stress (order of minutes), mild psychological stress, or during exercise. In contrast, stress conditions that result in the activation of the hypothalamic-pituitary-adrenal (HPA) axis generally induce a decrease in circulating leukocyte numbers. These conditions often occur during the later stages of a stress response, long duration acute stressors (order of hours), or during severe psychological, physical or physiological stress. Thus, an acute stress response induces bidirectional changes in blood lymphocyte and monocyte numbers. Soon after the beginning of stress (order of minutes) or during mild acute stress, or exercise, catecholamine hormones and neurotransmitters 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, activation of the HPA axis results in the release of glucocorticoid hormones that induce leukocytes to exit the blood and take position at potential "battle stations" (skin, mucosal lining of gastrointestinal and urinary-genital tracts, lung, liver, and lymph nodes) in preparation for immune challenges which may be imposed by the actions of the stressor.[3,4,54] Such a redistribution of leukocytes results in a decrease in blood leukocyte numbers. Thus, acute stress may result in a redistribution of leukocytes from the barracks, through the boulevards, and to potential battle stations within the body.[7,13] Such a leukocyte redistribution may enhance immune function in compartments to which immune cells traffic during stress, and subsequently demonstrate 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.[54-56]

Because the blood is the most accessible and commonly used compartment for human studies, it is important to evaluate carefully how changes in blood immune parameters might affect in vivo immune function in the context of the specific experiment or study at hand. Because most blood-collection procedures involve a certain amount of stress, because all patients or subjects will have experienced acute 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 clinical importance.

Effects of acute stress on leukocyte trafficking to a site of surgery or immune activation

Subcutaneously implanted surgical sponges have been used as clinically relevant in vivo arenas to elucidate the effects of stress on the kinetics, magnitude, subpopulation,

and chemoattractant specificity of leukocyte trafficking to a site of immune activation or surgery.[34] Mice that were acutely stressed before sponge implantation showed a two to threefold higher neutrophil, macrophage, NK cell, and T-cell infiltration than nonstressed animals. Enhanced leukocyte infiltration was evident as early as 6 hours and peaked between 24 and 48 hours. Importantly, sponges from nonstressed and acutely stressed mice had comparable and significantly lower leukocyte numbers at 72 hours, indicating effective resolution of inflammation in both groups. These authors also examined the effects of stress on early (6 hours) leukocyte infiltration in response to a predominantly proinflammatory cytokine, tumor necrosis factor (TNF)-α, and lymphocyte-specific chemokine, lymphotactin (LTN). Acute stress significantly increased infiltration of macrophages, in response to saline, LTN or TNF-α; neutrophils, only in response to TNF-α; and NK and T cells only in response to LTN. These results showed that acute stress significantly enhances the kinetics and magnitude of leukocyte infiltration into a site of immune activation or surgery in a subpopulation and chemoattractant specific manner with tissue damage, antigen-, or pathogen- driven chemoattractants synergizing with acute stress to further determine the specific subpopulations that are recruited.[34] Depending on the primary chemoattractants driving an immune response, acute stress may selectively mobilize specific leukocyte subpopulations into sites of surgery, wounding, or inflammation. Such a stress-induced increase in leukocyte trafficking may be an important mechanism by which acute stressors alter the course of different (innate versus adaptive, early versus late, acute versus chronic) protective or pathological immune responses.

Acute stress-induced enhancement of innate/primary immune responses in skin

In view of the skin's 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. Studies showed that acute stress experienced at the time of novel or primary antigen exposure results in a significant enhancement of the ensuing skin immune response.[6] Compared with controls, mice restrained for 2.5 hours before primary immunization with keyhole limpet hemocyanin (KLH) showed a significantly enhanced immune response when reexposed to KLH 9 months later. This immunoenhancement 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 reexposure. Enhanced leukocyte infiltration was driven by increased levels of the Type-1 cytokines, interleukin (IL)-2 and interferon (IFN)- γ, and TNF-α, observed at the site of antigen reexposure 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, we have suggested that the neuroendocrine stress response is nature's adjuvant that could be psychologically and/or pharmacologically manipulated to safely increase vaccine efficacy.[6,7,19]

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 nonhuman primates.[57-59] A series of elegant experiments also showed that acute stress experienced at the time of sensitization resulted in a significant increase in the contact hypersensitivity (CHS) response.[60] Other studies further elucidated the molecular and cellular mediators of the immunoenhancing effects of acute stress.[61] They showed that compared with nonstressed 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-α, 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 immunoenhancement during primary immunization may induce a long-term increase immunologic memory resulting in subsequent augmentation of the immune response during secondary antigen exposure.

Acute stress-induced enhancement of adaptive/secondary immune responses in skin

In addition to enhancing primary cutaneous immune responses, acute stress experienced at the time of antigen reexposure can also enhance secondary or recall responses in skin.[54] Compared with nonstressed controls, mice that were acutely stressed at the time of antigen reexposure 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 reexposure, in mice, rats, hamsters, and nonhuman primates.[32,57-59] It has also been shown that acute stress-enhanced CHS responses in both male and female mice[62]; however, they failed to observe the stress-induced enhancement of the sensitization phase of CHS[63] that has been reported by several independent groups as described previously.[6,57-61,64]

Hormone and cytokine mediators of stress-induced enhancement of immune function

Although much work remains to be done to identify molecular, cellular, and physiological mechanisms mediating the adjuvantlike, immunoenhancing effects of acute stress, studies have shown that corticosterone and epinephrine are important mediators of an acute stress-induced immunoenhancement.[55] Adrenalectomy, which eliminates the glucocorticoid and epinephrine stress response, eliminated the stress-induced enhancement of skin cell mediated immunity. Low-dose corticosterone or epinephrine administration significantly enhanced skin cell–mediated immunity.[55] In contrast, high-dose corticosterone, chronic corticosterone, or low-dose dexamethasone administration significantly suppressed skin cell–mediated immunity.[55] These results suggested a novel role for adrenal stress hormones as endogenous immunoenhancing agents. Stress hormones released during a circumscribed or acute stress response may help prepare the immune system for potential challenges (eg, wounding or infection) for which stress perception by the brain may serve as an early warning signal. Other studies have also suggested that corticosterone is a mediator of the stress-induced enhancement of skin CHS[62] and that the adjuvantlike effects of stress on dendritic cell and CD8+ T-cell migration and function are mediated by norepinephrine.[60] Taken together, these studies suggest that endogenous stress hormones in physiological concentrations can have immunoenhancing effects, whereas endogenous hormones at pharmacologic concentrations, and synthetic hormones, are immunosuppressive.

Because IFN-γ is a critical cytokine mediator of cell-mediated immunity and delayed as well as contact hypersensitivity, studies were conducted to examine its role as a local mediator of the stress-induced enhancement of skin cell–mediated immunity.[56] The effect of acute stress on skin cell–mediated 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 immunity response than nonstressed 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. These results showed that IFN-γ is an important local mediator of a stress-induced enhancement of skin cell–mediated immunity.[56] In addition to IFN-γ, TNF-α, MCP-1, MIP-3α, IL-1, and IL-6 have also been associated with a stress-induced enhancement of the immunization/sensitization phase of skin cell–mediated immunity.[6,61] Given the importance of stress effects on skin immune function, further investigation is necessary to identify the molecular, cellular, and physiological mediators of a stress-induced enhancement of skin immunity.

Fight-or-flight physiology as an adjuvant for protective and pathological immune responses—clinical implications

It has been proposed that a psycho-physiological stress response is nature's fundamental survival mechanism that could be therapeutically harnessed to augment immune function during vaccination, wound healing, or infection.[6,7,29] These adjuvantlike immunoenhancing effects of acute 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. In keeping with this hypothesis, studies have shown that patients undergoing knee surgery, who show a robust and adaptive immune cell redistribution profile during the acute stress of surgery, also show significantly enhanced recovery.[46] Similarly, an elegant series of studies has shown that adjuvant effects of acute mental or exercise stress can enhance vaccine-induced humoral and cell-mediated immunity in human subjects.[65,66]

While short-term stress-induced enhancement of immunoprotective responses have been appreciated relatively recently, stress-induced exacerbations of proinflammatory (eg, dermatitis,[67,68] cardiovascular disease,[69,70] periodontal disease,[71] and asthma[67,72,73]) and autoimmune (eg, psoriasis,[74,75] arthritis,[76] multiple sclerosis[77]) diseases are well known and frequently observed in the clinic. It will be important for future studies to (1) determine the extent to which stress-induced exacerbation of such disorders is mediated by immunoenhancing mechanisms activated during acute stressors versus immunodysregulatory mechanisms activated during chronic stressors, (2) determine the extent to which stress induces the onset of disease versus exacerbating preexisting conditions, And (3) to use more standardized and homogeneous psychological and physiological measures of stress and, where possible, also of the affected immune mediators.

In terms of 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.[61] These findings are in agreement with studies that showed that acute 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,[78] a phenomenon that has elegantly been shown to have striking similarities in "mice and men."[79]

Taken together, results from numerous studies show that stress can significantly enhance innate as well as adaptive immunity and can potentiate the immunization/sensitization/induction as well as the elicitation/recall phases of an immune response. These mechanisms may contribute to stress-induced enhancement of immunoprotection, but could also mediate clinically well-known examples of stress-induced exacerbation of proinflammatory and autoimmune disorders and may also be of relevance to psychodermatology.[80] Further investigation of mechanisms mediating stress-induced enhancement of immune function is critical for identifying specific biological factors/targets that may be therapeutically manipulated to enhance protective immune responses, or ameliorate/eliminate stress-induced exacerbation of proinflammatory or autoimmune diseases.

Chronic stress-induced suppression/dysregulation of skin immunity

In contrast to acute stressors, chronic stress has been shown to suppress or dysregulate immune function including skin immunity (for review see[8,81-87]). Studies have investigated the effects of increasing the intensity and duration of acute stress as well as the transition from acute to chronic stress on skin immune function.[13] These studies showed that acute stress administered for 2 hours before antigenic challenge significantly enhanced skin cell–mediated immunity.[13] Increasing the duration of stress from 2 to 5 hours produced the same magnitude immunoenhancement. Interestingly, increasing the intensity of acute stress produced a significantly larger enhancement of the cell-mediated immune response that was accompanied by increasing magnitudes of leukocyte redeployment. In contrast, suppression of the skin immune response was observed when chronic stress exposure was begun 3 weeks before primary immunization and either discontinued following immunization, or continued an additional week until reexposure to the antigen, or extended for 1 week after reexposure.[13] Interestingly, acute 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.[13] An association between chronic stress and reduced skin cell–mediated immunity has also been reported in human subjects.[88,89]

Effects of acute versus chronic stress on squamous cell carcinoma

Given the importance of cutaneous cell-mediated immunity in elimination of immunoresponsive tumors like squamous cell carcinoma (SCC),[90,91] and given the skin-immunoenhancing effects of acute or short-term stress, studies have examined the effects of acute stress administered at the time of ultraviolet light (UV) exposure (minimum erythemal dose, 3 times per 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.[92] Compared with controls, the short-term stress group showed greater cutaneous T-cell–attracting chemokine (CTACK)/CCL27, RANTES, IL-12, and IFN-γ gene expression (at weeks 7, 20, and 32 after the beginning of UV exposure), higher skin-infiltrating T-cell numbers (weeks 7 and 20), lower tumor incidence (weeks 11-20), and fewer tumors (weeks 11-26). 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.[92] Therefore, the physiological fight-or-flight stress response and its adjuvantlike immunoenhancing effects may provide a novel and important mechanism for enhancing immune system–mediated tumor-detection/elimination that merits further investigation.

In light of the immunosuppressive effects of chronic stress, studies were conducted to investigate the effects of chronic stress on the emergence and progression of SCC.[14] Compared with nonstressed 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 (15.0 versus 16.5 weeks) and reached 50% incidence earlier than controls (15 weeks versus 21 weeks). Interestingly, stressed mice had higher numbers of tumor-infiltrating and circulating regulatory/suppressor T cells than nonstressed 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.[14]

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 immunoenhancing effects, whereas 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 or receptivity 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 immunoenhancement. In contrast, at a later, more advanced stage of an immune response, these components may be more receptive to glucocorticoid-mediated immunosuppression. Although this hypothesis needs to be tested through further experiments, studies examining the effects of corticosterone on T-lymphocyte proliferation in vitro 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.[93] These 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.[93] It has been shown that corticosterone had to be present during the process of TCR T-cell receptor activation to enhance the proliferative response. If corticosterone were added to the culture system more than 2 hours after the initiation of TCR activation, the enhancement of lympho-proliferation was not observed.

Other potential mediators of the effects of stress on skin immune function

Although the preceding discussion has focused on the role of psychological stress and stress hormones in mediating changes in skin cell–mediated immunity, numerous other studies have examined other mediators of the effects of changes in central nervous system activity on skin immunity as well as cutaneous wound healing, and changes in skin barrier function.[94-96] Although the principal stress hormones appear to play a major role, additional factors that could mediate the effects of stress and other emotional states on skin immunity include the actions of cutaneous nerves and the release of peptides like calcitonin gene–related peptide, substance P, vasoactive intestinal peptide,[97,98] and proopiomelanocortin peptides[99,100] such as alpha-melanocyte stimulating hormone, local and systemic release of corticotrophin-releasing hormone,[101,102] mast cell factors,[101,103] and mediators that also induce neurogenic inflammation.[104] Therefore, it is clear that much research remains to be done to identify the various psychophysiological factors that may mediate the effects of stress and other emotional states on skin immune reactivity.

The stress-immune spectrum

It is often overlooked that a stress response has salubrious adaptive effects in the short run,[3,6,7,19,34,54,55,105] although stress can be harmful when it is long-lasting.[1,8,13] To reconcile these seemingly contradictory effects of stress, we proposed that a stress response and its effects on immune function be viewed in the context of a STRESS SPECTRUM[4,7,13] (Figure 2). One region of this spectrum is characterized by ACUTE STRESS or EUSTRESS, ie, conditions of short-duration stress that may result in immunopreparatory, or immunoenhancing physiological conditions. An important characteristic of acute stress is a rapid physiological stress response mounted in the presence of the stressor, followed by a rapid shut-down of the response upon cessation of the stressor. The opposite region of the stress spectrum is characterized by CHRONIC STRESS or DISTRESS, ie, repeated or prolonged stress that may 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 integrated increase in exposure of the organism to stress hormones. 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[1,16]). Conditions of high allostatic load are likely to result in dysregulation or suppression of immune function. Importantly, a disruption of the circadian corticosterone/cortisol rhythm may be an indicator and/or mediator of distress or high allostatic load.[13] The STRESS SPECTRUM also proposes that acute or chronic stress is generally superimposed on a psycho-physiological HEALTH MAINTENANCE EQUILIBRIUM (Figure 2). The extent and efficiency with which an organism returns to its health maintenance equilibrium after stress depends on RESILIENCE, which we define as the capacity of psychophysiological systems to recover from challenging conditions (Figure 2). Factors such as coping mechanisms, sense of control, optimism, social support, early life experiences, learning, genetics, and sleep may be important mediators of PSYCHOLOGICAL RESILIENCE (Figure 2). Factors such as neuro-endocrine reactivity, genetics, environment, nutrition, and sleep may be important mediators of PHYSIOLOGICAL RESILIENCE (Figure 2). The

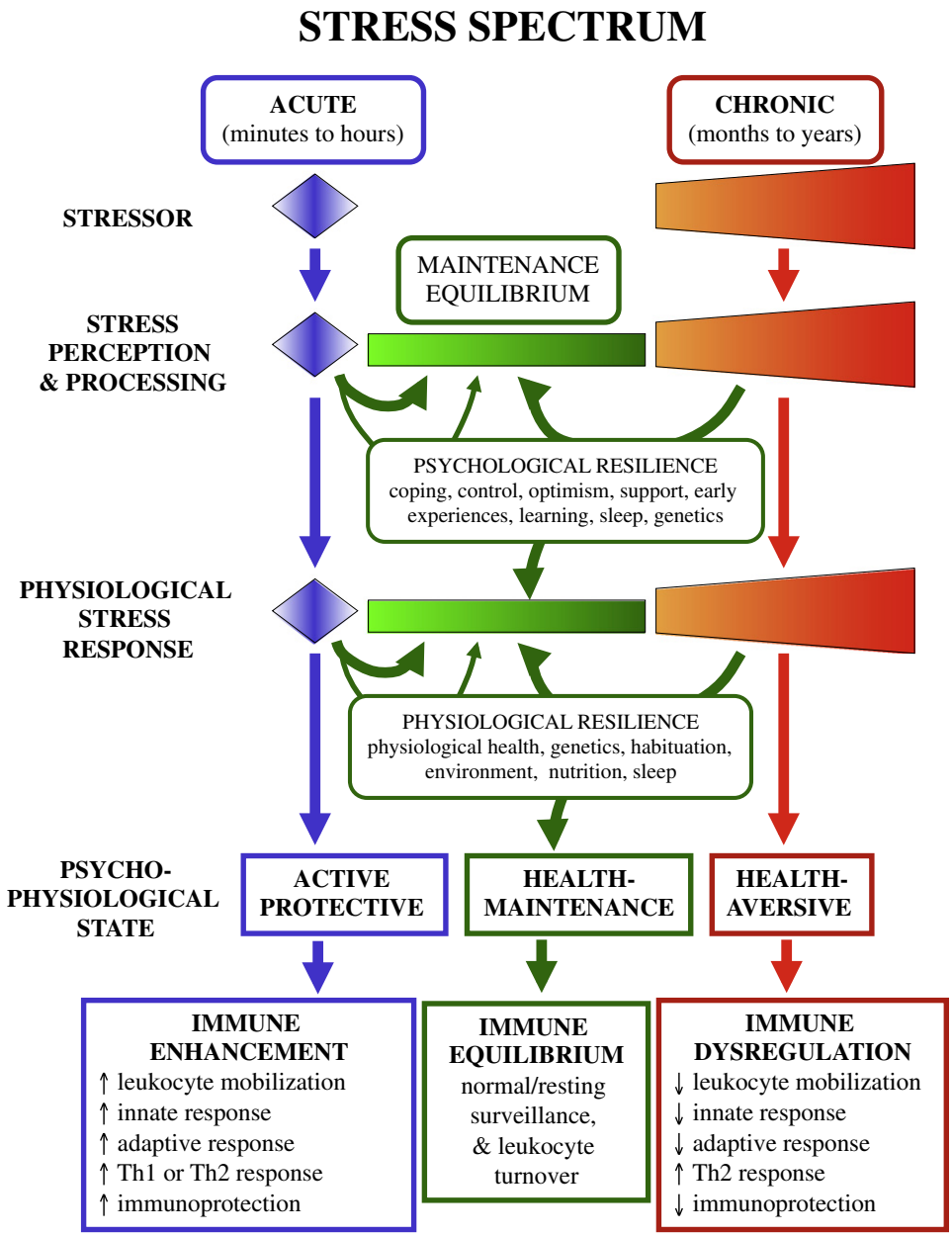

Fig. 2 The Stress Spectrum Model describes the relationships among the duration (acute or chronic) of stress, psychological and physiological resilience mechanisms, and immune and health outcomes. (Reprinted with permission from Dhabhar and McEwen.[19])

psychophysiological basis of resilience are underinvestigated and provide an important opportunity for future research.

This model suggests that an effective strategy for health maintenance would be to stay within the "good stress" and psycho-physiological equilibrium regions of the stress-spectrum while minimizing the time spent on the chronic stress side. Personal strategies for returning to equilibrium following stressor exposure are likely to involve different strokes for different folks, ie, different individuals may need/use different means (eg, walking, running, dancing, yoga, meditation, reading, music, painting, sleeping, or other de-stressors) to return to their psycho-physiological equilibrium after a stressful experience. The longer one experiences chronic stress, the higher the chances of there being detrimental effects on health; however, biological organisms, including humans, are resilient. It takes long exposures to chronic stress to critically break down physiological systems. Getting sufficient sleep, engaging in moderate exercise, and establishing a moderate but healthy diet may increase stress resilience.

The Stress Spectrum, taken together with the preceding discussion, 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. The model shows that the stressor itself can be acute or chronic (Figure 2). Stress perception and processing by the brain and mechanisms mediating psychological and physiological resilience are critical for determining the duration and magnitude of the physiological stress response (Figure 2). Psychological resilience mechanisms are especially important in humans because they can limit the duration and magnitude of chronic stress responses. Psychogenic stressors are also very important in human subjects because they can generate stress responses long after stressor exposure (eg, posttraumatic stress disorder following a severe traumatic experience, or in a milder form, lingering anger/mood disturbance following a social altercation) or even in the absence of a physical stressor or salient threat (eg, worrying about whether one's romantic feelings will be reciprocated). Following stressor exposure and its processing by the brain, there ensues a PHYSIOLOGICAL STRESS RESPONSE. This response may consist of acute or chronic physiological activation (neurotransmitters, hormones, and their molecular, cellular, organ-level, and systemic effects), which results in PSYCHO-PHYSIOLOGICAL STATES that have different effects on overall health and immune function, as shown in Figure 2. Although there is significant evidence from animal studies to support this model, it needs to be further examined in studies involving human subjects.

Conclusions

An important function of physiological mediators released under conditions of acute or 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 respond to an immune challenge that could be initiated by the stress-inducing agent (eg, attack by a predator, invasion by a pathogen). The modulation of immune cell distribution by acute stress may be 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 urinary-genital tracts) that serve as major defense barriers for the body. Thus, neurotransmitters and hormones released during stress may increase immune surveillance and help enhance immune preparedness for potential (or ongoing) immune challenge. Stress-induced immunoenhancement may increase immunoprotection during surgery, vaccination, or infection, but may also exacerbate immunopathology during inflammatory (dermatitis, cardiovascular disease, gingivitis) or autoimmune (psoriasis, arthritis, multiple sclerosis) diseases that are known to be negatively affected by stress.[74,106-108]

The relationships between immune function and the physiological manifestations of stress are complex. Clinically, the important connection between stress and the exacerbation of skin disorders has been known for a long time[96,109,110] and is an important aspect of psychodermatology.[80] The studies described here shed light on potential mechanisms that may mediate the bidirectional effects of stress on skin immune function, and provide targets for clinical interventions that may be designed to dampen or eliminate stress-induced exacerbation of skin immunopathology. Although decades of research have examined the pathological effects of stress on immune function and on health, the study of salubrious or health-promoting effects of stress is relatively new.[6,7,19,29] Therefore, the studies presented here also provide a framework for developing therapeutic interventions that harness the mind and body's endogenous health-promoting mechanisms to enhance protective immunity during vaccination, infection, wound healing, or cancer. Much work remains to be done to elucidate the mechanisms mediating the salubrious versus health-aversive effects of stress and to translate findings from bench to bedside. This work is extremely important because stress is a ubiquitous aspect of life and although chronic stress is thought to play a role in the etiology of numerous diseases, acute or short-term stress is one of nature's fundamental survival mechanisms that could be clinically harnessed to enhance immunoprotection.

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