

## SCIENCE AND SOCIETY

# Stress-induced immune dysfunction: implications for health

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Abstract | Folk wisdom has long suggested that stressful events take a toll on health. The field of psychoneuroimmunology (PNI) is now providing key mechanistic evidence about the ways in which stressors — and the negative emotions that they generate — can be translated into physiological changes. PNI researchers have used animal and human models to learn how the immune system communicates bidirectionally with the central nervous and endocrine systems and how these interactions impact on health.

The central nervous system (CNS), the endocrine system and the immune system are complex systems that interact with each other. Various stressors — from parachute jumping to academic examinations to bereavement — can dysregulate the immune response by affecting the interplay of these systems. Psychoneuroimmunology (PNI) is the broad interdisciplinary research field that addresses the interactions of these three systems<sup>1,2</sup>. Studies undertaken during the past two decades have provided evidence that immune alterations that are stimulated by stressful events, ranging from commonplace daily hassles to chronic calamities, can provoke health changes. One definition of a stressor is a stimulus that activates the hypothalamic–pituitary–adrenal (HPA) axis and/or the sympathetic nervous system (SNS) to help an organism to adapt physiologically to deal with a threat<sup>3</sup>. More broadly, psychological stress ensues when events or environmental demands exceed an individual's perceived

ability to cope<sup>4</sup>. Researchers often categorize stressors by their duration and course (discrete versus continuous)<sup>5</sup> (BOX 1). For example, chronic stressors, such as suffering a traumatic injury that leads to physical disability, can force people to restructure key aspects of their daily lives. Whereas chronic stressors are deleterious to immune function, some investigators have suggested that very brief stressors, lasting less than 2 hours, might enhance some aspects of immune function, such as trafficking of cells from lymphoid organs to the peripheral blood and the skin (BOX 2).

Stressors can increase susceptibility to infectious agents, influence the severity of infectious disease, diminish the strength of immune responses to vaccines, reactivate latent herpesviruses and slow wound healing. Moreover, stressful events and the distress that they evoke can also substantially increase the production of pro-inflammatory cytokines that are associated with a spectrum of age-related diseases. Accordingly, stress-related immune dysregulation might be one core mechanism behind a diverse set of health risks<sup>1,3</sup>.

### CNS–immune–endocrine interactions

Modulation of the immune response by the CNS is mediated by a complex network of bidirectional signals between the nervous, endocrine and immune systems (FIG. 1). The HPA axis and the autonomic nervous system provide two key pathways for immune-system dysregulation: stressors can activate the sympathetic–adrenal–medullary (SAM) axis, as well as the HPA axis, and thereby provoke the release of pituitary and adrenal

### Box 1 | How is stress assessed?

When events or environmental demands exceed an individual's ability to cope, the ensuing psychological stress response typically includes negative thoughts and emotions<sup>4</sup>. Studies of stress and immunity often use measures of negative mood that assess symptoms of general distress, anxiety or depression. Researchers might also assess the number and type of recent significant stressful life changes, or they might ask participants to rate their perceptions of stress on a scale by answering certain questions, such as how frequently in the past week did you feel you could not control important things in your life, or how often did you feel that things were piling up so high that you could not overcome them<sup>4</sup>.

In addition, researchers often study the psychological and immunological responses of individuals who are experiencing a distress-generating event (for example, students taking an examination or spouses going through a divorce) or a more chronic stressor (such as caring for a husband or wife who has Alzheimer's disease)<sup>5</sup>. Other longer-term stressors that are associated with immune alterations have included 'burnout' at work, job strain, unemployment, and isolation and exposure to the hostile climate of Antarctica<sup>81</sup>. Adverse immunological changes have also been documented for weeks or months following such natural disasters as earthquakes and hurricanes, with more persistent immune dysregulation among those who suffered greater personal losses<sup>82</sup>. Stressors that are perceived as unpredictable and/or uncontrollable might continue to be associated with increased levels of stress hormones, even after repeated exposures<sup>83</sup>. The ability to 'unwind' after stressful events — that is, to return to one's neuroendocrine baseline in a relatively short time — is thought to influence the total burden that stressors place on an individual<sup>84</sup>.

hormones. For example, the catecholamines (adrenaline and noradrenaline), adrenocorticotrophic hormone (ACTH), cortisol, growth hormone and prolactin are all influenced by negative events and negative emotions (BOX 1), and each of these hormones can induce quantitative and qualitative changes in immune function. Furthermore, depression can substantially boost cortisol levels, and increases in cortisol levels can provoke multiple adverse immunological changes.

Almost all immune cells have receptors for one or more of the hormones that are associated with the HPA and SAM axes; these are called 'stress' hormones (TABLE 1). Immune modulation by these hormones might proceed through two pathways: directly, through binding of the hormone to its cognate receptor at the surface of a cell; or indirectly — for example, by inducing dysregulation of the production of cytokines, such as interferon- $\gamma$  (IFN- $\gamma$ ), interleukin-1 (IL-1), IL-2, IL-6 and tumour-necrosis factor (TNF). Cytokines such as IFN- $\gamma$  have many functions and affect different target cells. Therefore, there are secondary effects of many stress hormones on the immune response<sup>6,7</sup>.

Moreover, communication between the CNS and the immune system is bidirectional. For example, IL-1 influences the production of corticotropin-releasing hormone (CRH) by the hypothalamus. In turn, CRH can affect the HPA axis and thereby trigger increases in stress hormone levels, which results in dysregulation of immune function (FIG. 1). In addition, lymphocytes can synthesize hormones such as ACTH, prolactin and growth hormone<sup>8</sup>. The role of lymphocyte-derived hormones in immune responses is not well understood, although they might have a role in modulating cell function within the microenvironment of lymphoid organs. Furthermore, studies that show nerve fibres in the spleen and thymus provide evidence of direct connections or 'hard-wiring' between the SNS and lymphoid organs<sup>9</sup>. Therefore, there are many pathways through which stressors might influence immune function<sup>1,6</sup>. Moreover, many individuals working in the field of PNI are now focusing their efforts on immune-system-to-brain communication and how the activation of inflammatory-cytokine networks might shape mood, cognition and behaviour<sup>10,11</sup>.

In addition to the direct influences of psychological states on endocrine and immune function, stressed individuals are more likely to have health habits that put them at greater risk, including poorer sleep patterns, poorer nutrition, less exercising and a greater propensity for abuse of alcohol, cigarettes and other

## Box 2 | Can stress be beneficial?

The best evidence that stress might be good for the immune system comes from studies of mice that are exposed to very brief stressors. Delayed-type-hypersensitivity skin responses following either primary or secondary cutaneous antigen exposure were augmented following stressors lasting 2 hours, compared with the response of non-stressed control animals. These effects seem to be mediated by glucocorticoid- and adrenaline-induced stress responses<sup>85</sup>. It has been argued that such immunoenhancement would be beneficial to survival, because skin wounding and infection can result from brief aggressive encounters in nature<sup>85</sup>. In humans, short-term stressors, such as public speaking, briefly increase natural-killer-cell activity<sup>5,86</sup> and increase the numbers of some types of leukocyte<sup>5</sup>. The latter change probably reflects transient alterations in lymphocyte migration from lymphoid organs and peripheral blood, which is mediated by receptors at the cell surface of lymphocytes (TABLE 1) or through sympathetic-nervous-system innervation of lymphoid organs such as the spleen<sup>9</sup>. However, the same short-term stressors also produce transitory changes in humans that would generally be seen as maladaptive: they reduce lymphocyte proliferation<sup>5</sup>, increase pro-inflammatory cytokine production<sup>86</sup> and impair the ability of the skin to repair abrasions<sup>86</sup>. Further studies need to be carried out to help to clarify health outcomes that are associated with short-term acute stressors.

drugs. Although these health behaviours have immune and endocrine consequences, these indirect effects of stress are not addressed here; we focus on immune dysregulation by stressors and the health consequences of these changes.

### Stress and infectious-disease risks

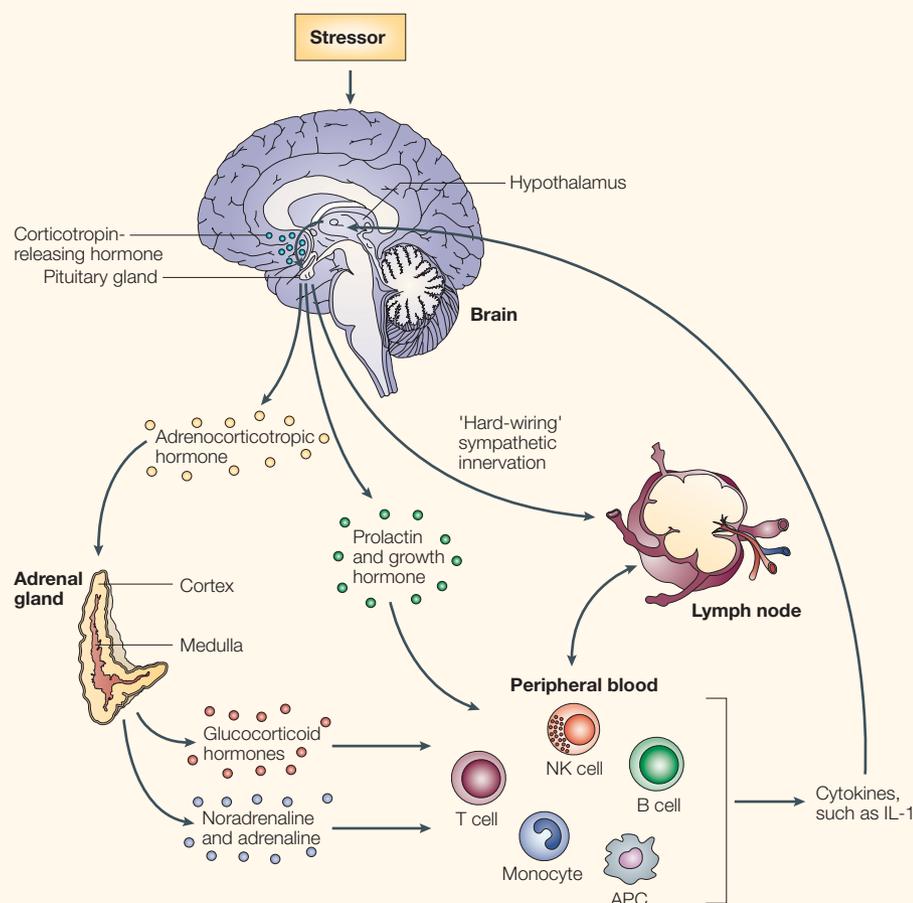
Stressors can enhance the risk of developing infectious disease, and they can also prolong infectious illness episodes. For the mouse models used to explore this relationship, restraint is a commonly used stressor. Mice are placed in tubes such that they can move forwards or backwards but cannot turn around; holes in the tubes ensure that the mice do not overheat. Restraint is often applied overnight, because this is the most active time for mice. One example of data obtained using a mouse model of influenza-virus infection shows that restraint stress altered the immune response to the virus, including the kinetics of the antibody response and suppression of both pro-inflammatory and anti-inflammatory cytokine responses<sup>12,13</sup>. Mononuclear-cell trafficking to virus-infected lungs was significantly reduced in stressed animals, as was the size of the draining lymph nodes. Virus-specific cytokine responses of T cells in restraint-stressed mice were restored in the draining lymph nodes by pharmacological blockade of the glucocorticoid receptor with the glucocorticoid receptor antagonist RU486. These and related studies have shown that the HPA axis and the SNS are the main immunoregulatory pathways that can influence the pathophysiology of a viral infection<sup>12,13</sup>.

Consistent with the mouse data on stress and influenza-virus infections, influenza-virus vaccine studies with human participants show that stress can influence infectious-disease

risks. For example, men and women who were chronically stressed by caring for a spouse with dementia showed clear deficits in both their cellular and humoral immune responses to an influenza-virus vaccine compared with well-matched control individuals who were not carers<sup>14,15</sup>. The protective capacity of antiviral vaccines depends on their ability to induce both humoral and cell-mediated immune responses<sup>16</sup>, both of which were poorer in the stressed carers compared with control individuals. Stress-associated impairments in antibody responses after vaccination with influenza virus have also been shown in younger adults<sup>17</sup>.

Further studies have confirmed the finding that stressful events and the negative emotions, such as anxiety and depression, that accompany them can modulate the antibody and T-cell responses to other antiviral vaccines, including the vaccines against infection with hepatitis B virus and rubella virus<sup>18,19</sup>. Moreover, antibody responses to antibacterial vaccines are also influenced by stress: for example, following vaccination, antibody titres to a pneumococcal vaccine decreased during a 6-month period in the carers of spouses with dementia, whereas antibody titres were stable in non-carers<sup>20</sup>. Similarly, undergraduates who had received a meningitis C conjugate vaccine and who reported greater stress had a poorer antibody response 1–12 months after vaccination<sup>21</sup>.

Responses to vaccines show clinically relevant alterations in immunological responses to challenge under well-controlled conditions; accordingly, they function as a proxy for a response to an infectious agent. Individuals who were more distressed and more anxious had immune responses to vaccines that were delayed, substantially weaker and/or shorter-lived. As a consequence, it is reasonable to



**Figure 1 | Stress-associated modulation of the hormone response by the central nervous system.** Experiencing a stressful situation, as perceived by the brain, results in the stimulation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic–adrenal–medullary (SAM) axis. The production of adrenocorticotropic hormone by the pituitary gland results in the production of glucocorticoid hormones. The SAM axis can be activated by stimulation of the adrenal medulla to produce the catecholamines adrenaline and noradrenaline, as well as by ‘hard-wiring’, through sympathetic-nervous-system innervation of lymphoid organs. Leukocytes have receptors for stress hormones that are produced by the pituitary and adrenal glands and can be modulated by the binding of these hormones to their respective receptors. In addition, noradrenaline produced at nerve endings can also modulate immune-cell function by binding its receptor at the surface of cells within lymphoid organs. These interactions are bidirectional in that cytokines produced by immune cells can modulate the activity of the hypothalamus. APC, antigen-presenting cell; IL-1, interleukin-1; NK, natural killer.

assume that these same individuals would also be slower to develop immune responses to pathogens; therefore, they could be at greater risk of developing more severe illness. Consistent with this argument, adults who show poorer responses to vaccines also experience higher rates of clinical illness<sup>22</sup>.

In agreement with these vaccine studies, researchers have also shown that distress can alter an individual’s susceptibility to infection with respiratory viruses<sup>4,23,24</sup>. In a group of 394 healthy volunteers who were inoculated with one of five strains of respiratory virus, severity of both respiratory infection and clinical cold symptoms increased in a dose–response relationship as scores increased on a psychological stress index. The stress index was a

compilation of three common measures: the number of stressful life events, the degree that a participant felt that current demands exceeded his or her ability to cope, and scores from a negative-emotion word list (including words such as sad, angry and nervous). Importantly, the risk did not differ across the five strains of respiratory virus studied. In further related work from the same laboratory, stressors that lasted for 1 month or more were the best predictors of developing colds; volunteers who reported more enduring interpersonal difficulties with family or friends were substantially more likely to develop a cold after inoculation with a rhinovirus<sup>23</sup>. Similarly, other researchers reported that individuals who

developed cold symptoms following inoculation with rhinovirus had higher numbers of recent stressful life events than those who did not<sup>24</sup>.

Studies carried out with human participants in which individuals have been exposed to a pathogen or a vaccine give researchers a means of controlling exposure and dosage; moreover, because immune function can be assessed before the infectious challenge, these studies provide excellent data on causality, thereby complementing evidence from research that addresses the course of naturally occurring infections<sup>25–35</sup>. The similarity of the data from human and rodent studies provides strong evidence that stress can dysregulate the humoral and cellular immune responses to pathogens and increase the risk of developing infectious disease.

HIV and the herpesviruses are different from many other viruses, such as rhinoviruses and influenza virus, in that they remain in a latent state in the body after primary infection. To investigate the possibility that social stress was a contributor to the rate of progression in HIV-associated disease, rhesus macaques were inoculated with simian immunodeficiency virus (SIV)<sup>36</sup>. Animals that were assigned to the stable social condition (the same three animals met every day) had lower concentrations of SIV RNA in plasma early after inoculation and survived longer than those in the unstable social condition (different two-, three- and four-member groups were formed every day).

Studies of HIV-infected men have also indicated that stress increases the rate of disease progression. For example, in a longitudinal study of HIV-positive men who were asymptomatic at entry to the study, faster progression to AIDS was associated with more stressful life events and less social or interpersonal support<sup>25</sup>; indeed, at 5.5 years after entry into the study, the probability of developing AIDS was two- to threefold higher in men who were above the median level for stress or below the median level for support compared with those who were below the median level for stress or above the median level for support. Other researchers reported that the course of HIV infection was accelerated in gay men who concealed their homosexual identity compared with men who did not<sup>26</sup>.

Considerable anecdotal evidence has supported the relationship between psychological stress and the development, duration and recurrence of herpesvirus infections. The cellular immune response has an important role in controlling the pathophysiology of both lytic herpesvirus infections and the expression

Table 1 | Interactions of hormones and immune cells

Hormone	Expression of receptors by immune cells	Examples of effects on cell function	References
Glucocorticoids	T and B cells, neutrophils, monocytes and macrophages	Inhibit inflammation; inhibit the production of IL-12 by antigen-presenting cells; induce a shift from production of T <sub>H</sub> 1 to T <sub>H</sub> 2 cytokines	87,88
Substance P	T and B cells, eosinophils, mast cells, monocytes and macrophages	Stimulates mitogen-induced blastogenesis; increases trafficking of cells from lymph nodes to peripheral blood; stimulates monocytes to produce several cytokines, such as IL-1, IL-6 and TNF	89
Neuropeptide Y	T and B cells, dendritic cells, monocytes and macrophages	Can downregulate antibody production to T-cell-dependent antigens by its effect on dendritic cells, and T and B cells	90
Corticotropin-releasing hormone	T cells, monocytes and macrophages	Increases production of IL-1 by monocytes; evidence for autocrine and/or paracrine modulation of inflammation	91
Prolactin	T and B cells, granulocytes, NK cells, monocytes and macrophages	Can stimulate lymphoid-cell clonal expansion; might function as an <i>in vitro</i> co-mitogen for NK cells and macrophages	92,93
Growth hormone	T and B cells, NK cells, monocytes and macrophages	Helps to maintain competence of T and B cells, and macrophages; stimulates antibody production and NK-cell activity	94
Catecholamines (adrenaline and noradrenaline)	T and B cells, NK cells, monocytes and macrophages	Induce a shift to a T <sub>H</sub> 2 response, involving antigen-presenting cells and T <sub>H</sub> 1 cells	95
Serotonin	T and B cells, NK cells, monocytes and macrophages	Modulates the synthesis of IFN- $\gamma$ by NK cells; stimulates the production of IL-16 (a chemotactic factor) by T cells	96

IFN- $\gamma$ , interferon- $\gamma$ ; IL, interleukin; NK, natural killer; T<sub>H</sub>, T helper; TNF, tumour-necrosis factor.

and/or replication of latent herpesviruses. When the cellular immune response is impaired, one or more herpesviruses can be reactivated, and herpesvirus infections are often more severe.

Herpes simplex virus (HSV) is a natural human pathogen that is characterized by its ability to cause an acute infection at a peripheral site and to establish a latent infection in the local sensory ganglia, and stress can exacerbate HSV lytic infection. Mouse models have been developed to study the effect of stress on the pathophysiology of HSV latent and lytic infections. Indeed, several studies carried out during the past 15 years have provided compelling experimental evidence that stress not only increases the development and severity of HSV infection, in both the peripheral nervous system<sup>13,37–39</sup> and the CNS, but also suppresses components of primary<sup>13,37,39–41</sup> and memory<sup>13,38,41</sup> cytotoxic T lymphocyte (CTL) responses to HSV infection.

Surgical and pharmacological approaches have shown the ability of both the HPA<sup>13</sup> and the SAM<sup>41</sup> axes to mediate stress-induced

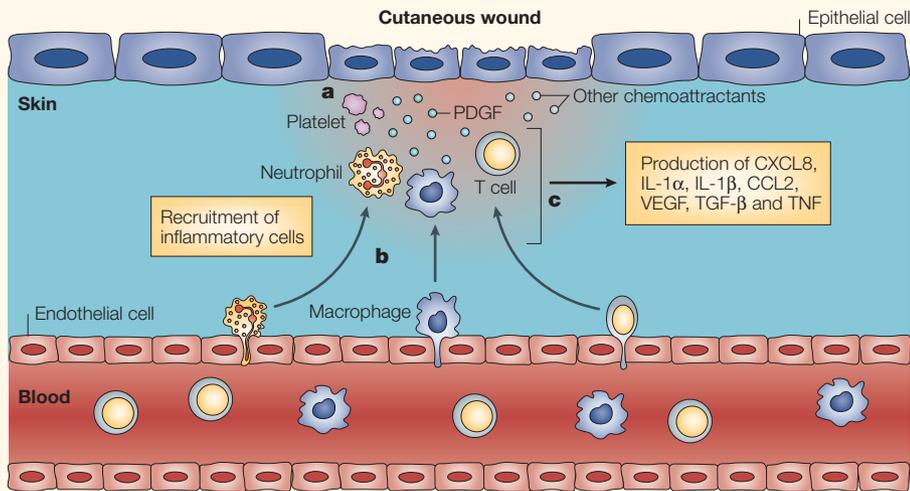
modulation of immunity and HSV-associated pathology. For example, mice treated with 6-hydroxydopamine (6-OHDA) to induce peripheral sympathetic denervation were inhibited in their ability to generate primary HSV-1-specific CTLs when infected with the virus<sup>41</sup>. The suppression of CTL production could result from a large release of noradrenaline induced by 6-OHDA and increased levels of corticosterone. In another study, surgical removal of the adrenal gland blocked the suppression of HSV-1-specific CTLs that was induced by restraint stress and also blocked the production of IL-6 and IFN- $\gamma$ <sup>13</sup>.

Relationships between neuroendocrine activity, immune function and latent HSV reactivation have also been documented<sup>42,43</sup>; infected mice that were exposed to a stressor showed reactivation of the latent virus, whereas non-stressed controls showed no reactivation<sup>43</sup>. It is important to keep in mind that these experiments were carried out using mice in a laboratory setting; however, the data still provide some insight into how stress

could modulate the immune response to HSV in humans.

Indeed, psychological stressors have been linked to more frequent recurrences of lesions in individuals who are latently infected with HSV-1 or HSV-2. For example, women who reported greater persistent stress from events that lasted longer than 1 week also had more recurrences of genital herpes<sup>28</sup>. Similarly, more chronically distressed individuals had more frequent recurrences of re-activation of HSV-1 (REF 29) and HSV-2 (REF 30).

The incidence of Herpes zoster (also known as shingles), which is caused by the reactivation of latent varicella-zoster virus (VZV), increases with age, presumably owing to a decline in cell-mediated immunity to VZV<sup>44</sup>. A case-control study indicated that psychological stress in healthy community-dwelling older adults was associated with the occurrence of herpes zoster<sup>31</sup>. Other researchers evaluated the possibility that VZV-specific immunity could be altered by means of a behavioural intervention, such as T'ai chi (also known as 'meditation through movement')<sup>44</sup>. Older adults who



**Figure 2 | Influence of stress on pro-inflammatory cytokine responses in wound healing.** Stress can influence key pro-inflammatory cytokine responses in the early phase (the first 24 hours) of the healing of skin wounds, through dysregulation of cytokine secretion at the wound site and recruitment and activation of circulating peripheral-blood leukocytes that traffic to the wound site<sup>48,52,54</sup>. Using a skin wound as an example, blood platelets at the wound site produce platelet-derived growth factors (PDGFs) (a). Other chemoattractants are also produced by activated parenchymal cells. A concentration gradient is established, with higher levels of chemoattractants at the wound site attracting immune cells, such as neutrophils and macrophages. These cells have important roles in the early phases of wound healing. For example, neutrophils clean the area of bacteria and, together with activated macrophages, they phagocytose the bacteria and produce cytokines that stimulate the growth of fibroblasts. The leukocytes transmigrate through the endothelium of the blood-vessel wall to the wound site in the skin (b) and are activated to proliferate and produce cytokines and chemokines, such as CXC-chemokine ligand 8 (CXCL8; also known as IL-8), IL-1 $\alpha$ , IL-1 $\beta$ , transforming growth factor- $\beta$  (TGF- $\beta$ ), vascular endothelial growth factor (VEGF), CC-chemokine ligand 2 (CCL2; also known as MCP1) and tumour-necrosis factor (TNF), at the wound site (c). These cytokines continue to function as chemoattractants for the continued migration of cells to the site. The proliferative phase of wound healing involves the recruitment and replication of cells that are required for tissue regeneration and capillary growth. Therefore, the downregulation of the early inflammatory response by an increase in serum cortisol levels can help to explain how stress affects wound healing<sup>49</sup>.

were randomly assigned to Tai chi showed a 50% increase in VZV-specific cellular immunity between the start and the end of the 15-week intervention compared with no change in the 'waiting-list' control group.

Epstein-Barr virus (EBV) — the aetiological agent of infectious mononucleosis — is another herpesvirus that establishes latent infection and can be modulated by psychological stressors. In one early study, West Point Military Academy (New York, United States) cadets who were seronegative for EBV on entry into the academy were followed for 4 years<sup>27</sup>. Men with particular psychosocial risk factors (high motivation for a military career in the face of poorer academic performance) were more likely to develop infectious mononucleosis and were likely to be hospitalized for longer periods. In addition, these risk factors were also associated with increased EBV-specific antibody titres in cadets who had been infected with EBV but had not developed obvious clinical symptoms.

A series of studies provided mechanistic data that revealed the effect of stress on EBV

latency. Medical students had substantially higher titres of IgG specific for EBV capsid antigen, and these were associated with more stressful examination periods compared with lower-stress periods<sup>45</sup>. In a further study of medical students, examination stress produced a significant decrease in the ability of EBV-specific CTLs to kill EBV-infected autologous B cells<sup>45</sup>. The results of several studies have shown that various psychological stressors — including examination stress, caring for a spouse with dementia and spaceflights by astronauts — can reactivate latent EBV and cytomegalovirus (CMV)<sup>32–35,45</sup>. Together, these human and animal studies show that stress can modulate the steady-state expression of latent HSV, EBV and CMV, downregulating the specific T-cell response to the virus to an extent that is sufficient to result in viral reactivation. Although the mechanisms that underlie stress-associated reactivation of latent herpesviruses are not fully understood, *in vitro* studies of cells that are latently infected with EBV have shown that glucocorticoid hormones can reactivate the virus.

For example, a glucocorticoid hormone, dexamethasone, can reactivate latent EBV and enhance the lytic replication of the virus in EBV-superinfected cells *in vitro*, but the catecholamine hormones do not induce such a response. Other stress hormones — CRH and ACTH — cannot induce reactivation of latent EBV, but they can enhance lytic replication in EBV-superinfected cells<sup>46</sup>.

Different types of stressor can have different effects on reactivation of latent HSV-1 and EBV<sup>43,47</sup>. For example, although restraint-stressed mice did not show evidence of reactivation of latent HSV-1, infectious HSV-1 was isolated from approximately 50% of the mice that were subjected to social reorganizational stress, despite both stressors resulting in similar increases in serum corticosterone levels<sup>43</sup>. Data from studies of students at West Point Military Academy also showed that different types of stress could have an impact on the reactivation of latent HSV-1 and EBV<sup>47</sup>. The mechanisms underlying these differences are not understood, but clearly, a factor as obvious as disparities in glucocorticoid hormone levels is not sufficient to explain variations in viral reactivation. Together, these studies highlight the complex interactions that underlie the relationships between stress, neuroendocrine activity, immune function and herpesvirus pathogenesis, and they indicate the many ways in which these relationships are central to a lifelong defence against herpesvirus infections.

### Stress and wound healing

Wound repair progresses through several overlapping stages<sup>48</sup>. In the initial inflammatory stage, vasoconstriction and blood coagulation are followed by platelet activation and the release of platelet-derived growth factors (PDGFs), as well as the release of chemoattractant factors by injured parenchymal cells. Cytokines and chemokines — such as IL-1 $\alpha$ , IL-1 $\beta$ , transforming growth factor- $\beta$  (TGF- $\beta$ ), vascular endothelial growth factor (VEGF), TNF and CXC-chemokine ligand 8 (CXCL8; also known as IL-8) — are important in the early stages of wound healing. These factors function as chemoattractants, promoting the migration of phagocytes and other cells to the wound site, thereby starting the proliferative phase, which involves the recruitment and replication of cells that are required for tissue regeneration and capillary regrowth. The final step, wound remodelling, might continue for weeks or months. So, the healing process is a cascade, and success in the later stages of wound repair depends to a large extent on initial events<sup>48</sup>.

Immune function has a key role in the early stages of this cascade (FIG. 2). CXCL8 and pro-inflammatory cytokines, such as IL-1 and TNF, are essential to this effort; they help to protect against infection and prepare injured tissue for repair by enhancing the recruitment and activation of phagocytes<sup>49</sup>. Furthermore, cytokines that are released by recruited cells regulate the ability of fibroblasts and epithelial cells to remodel the damaged tissue<sup>49</sup>. IL-1 that is produced early after tissue injury can regulate the production, release and activation of metalloproteinases that are important in the destruction and remodelling of the wound. IL-1 also regulates fibroblast chemotaxis and the production of collagen<sup>49</sup>. Moreover, IL-1 stimulates the production of other cytokines that are important for wound healing, including IL-2, IL-6 and CXCL8 (REF. 49). Accordingly, IL-1 deficits early in the wound-repair cascade can have adverse consequences downstream.

Stress disrupts the production of pro-inflammatory cytokines that are important for wound healing, a mechanism that produces substantial delays in wound repair. For example, in a clinical study, women who were experiencing the long-term stress of caring for a relative with Alzheimer's disease took 24% longer than sociodemographically matched controls to heal a small, standardized dermal wound. Consistent with these differences in wound repair, peripheral-blood leukocytes (PBLs) obtained from carers also produced less IL-1 $\beta$  in response to lipopolysaccharide (LPS) stimulation<sup>50</sup>. In a subsequent study in a different population, wounds produced in the hard palate 3 days before important examinations healed an average of 40% more slowly than identical wounds made during summer holidays: no student healed as rapidly during examinations as during the holiday period, and no student produced as much IL-1 $\beta$  when his or her PBLs were stimulated with LPS<sup>51</sup>.

Mouse models have also been developed to study the effect of stress on wound healing. These studies have confirmed and extended the data obtained by studying humans. Mice that were subjected to restraint stress and had a standardized 3.5-mm full-thickness cutaneous punch-biopsy wound healed this wound an average of 27% more slowly than control mice<sup>52</sup>. Analysis of the cellularity of wound sites using cross-sections of dermal and epidermal layers showed less leukocyte infiltration of the wound sites in restraint-stressed mice at 1 and 3 days after wounding, compared with controls<sup>52</sup>. Serum corticosterone levels in the restraint-stressed group were more than fourfold higher than those

of control animals<sup>52</sup>. Blocking glucocorticoid receptors in restraint-stressed animals, using RU40555, resulted in healing rates that were similar to those of control animals<sup>52</sup>. Accordingly, these data provide evidence that disruption of neuroendocrine homeostasis modulates the early stages of wound healing.

Higher levels of glucocorticoids have several adverse effects on various components of the wound-healing process. For example, they might slow wound healing by altering local levels of pro-inflammatory cytokines. Hübner *et al.*<sup>48</sup> showed that the strong and early induction of IL-1 $\alpha$ , IL-1 $\beta$  and TNF expression at the site after wounding was significantly reduced after pretreatment of mice with glucocorticoids. Similarly, human studies have also shown that stress-induced increases in glucocorticoids can transiently suppress IL-1 $\beta$ , TNF and PDGF production<sup>53</sup>. Accordingly, dysregulation of glucocorticoid secretion provides one obvious neuroendocrine pathway through which stress alters wound healing.

In humans, a suction-blister model enabled investigators to measure immune responses that are central to the early stages of wound healing *in vivo* and occur at the wound site, providing key data on the inflammatory response that have direct clinical relevance<sup>54,55</sup>. The suction-blister model provides an excellent mechanism to study the migration of neutrophils and macrophages and the production of cytokines at wound sites for the first 2 days after wounding. Commonly, after raising several blisters and removing their roofs (the epidermis), plastic templates with wells containing a salt solution and autologous serum are placed over the lesions, and cells migrate to the wound sites and collect in the wells. The serial collection of samples from the wells as time progresses allows for cell phenotyping and cytokine measurement as the local immune response evolves. Using this approach to study stress and wound healing, women who reported more stress produced significantly lower levels of two pro-inflammatory cytokines (IL-1 $\alpha$  and CXCL8) that are important for the early stages of wound healing<sup>54</sup>.

Therefore, convergent data from mouse and human studies have shown that stress has substantial adverse effects on wound repair. In agreement with these laboratory findings, several studies have shown that greater fear or distress before surgery is associated with poorer outcomes, including longer hospitalization, more post-operative complications and higher rates of rehospitalization<sup>56,57</sup>.

### Stress and inflammation

The pro-inflammatory cytokine IL-6, which is produced by T cells, B cells, monocytes and several non-lymphoid cell types, has an important role in the acute-phase response<sup>3</sup>. IL-6 is an important inducer of C-reactive protein (CRP) by the liver, and the combination of IL-6 and CRP is important in the process that leads to the development of cardiovascular disease<sup>3,58</sup>. As previously discussed, stress induces immune dysregulation partly through alterations in the production of pro-inflammatory cytokines. Both physical and psychological stressors can provoke transient increases in pro-inflammatory cytokines, particularly in IL-6 (REFS 53,59). In animal models, both stress and administration of adrenaline increase levels of IL-6 in the plasma, which is consistent with evidence that IL-6 production is stimulated by  $\beta$ -adrenergic receptors, as well as through other pathways<sup>3</sup>.

Importantly, negative emotions, such as depression and anxiety, augment the production of IL-6 (REFS 60–62). Indeed, both stressors and depression can sensitize the inflammatory response, thereby producing heightened responsiveness to subsequent stressful events, as well as to antigen challenge<sup>59,61–63</sup>. For example, individuals who reported more depressive symptoms showed increases in serum IL-6 levels 2 weeks after vaccination against influenza-virus infection, whereas there was little change in IL-6 levels in those individuals who reported few or no symptoms<sup>61</sup>. This is consistent with other evidence of cross-sensitization between cytokines and stressors in human and animal studies<sup>59,62,63</sup>. These stress-related changes have broad implications for health: increased levels of pro-inflammatory cytokines, such as IL-6, have been linked to various age-related diseases and conditions (including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, frailty and functional decline) and to certain cancers (such as chronic lymphocytic leukaemia)<sup>64</sup>.

### Stress, inflammation and ageing

One recent longitudinal study highlighted the deleterious longer-term immunological consequences of chronic stress: the average annual rate of increase in serum IL-6 was about fourfold higher in men and women who were chronically stressed by caring for a spouse with dementia than in similar individuals who did not have caring responsibilities<sup>65</sup>. Possible consequences of these different trajectories are indicated by epidemiological studies of individuals of 65 years of age or older<sup>64</sup>; within these population studies, individuals whose IL-6 values fell within the highest quartile had

a twofold greater risk of death within the following 4–5 years compared with those whose IL-6 values were in the lowest quartile<sup>64</sup>. Application of the epidemiological risk values to the data from carers indicated that carers would, on average, have values that crossed into the highest quartile around the age of 75, whereas the IL-6 values of control individuals would not reach that level until after the age of 90.

Another recent study also supports the hypothesis that chronic stress might be associated with premature ageing of immune cells. Telomerase activity and telomere length — two cellular markers that are associated with ageing — were measured in peripheral-blood mononuclear cells obtained from mothers caring for a chronically ill child, as well as from mothers of healthy children<sup>66</sup>. Carers reported greater stress than controls, but reports of a higher level of perceived stress were associated with lower telomerase activity and shorter telomere length, regardless of whether the mother's child was ill or healthy. Reports of high stress levels were also associated with higher oxidative-stress activity, as measured by levels of F<sub>2</sub>-isoprostanes, another independent measure associated with ageing<sup>66</sup>.

Taken together, the data regarding the IL-6 levels of carers of spouses with dementia<sup>65</sup> and the data regarding telomerase activity and length<sup>66</sup> provide evidence of mechanisms through which chronic stressors might accelerate the risk of developing many age-related diseases by 'premature ageing' of the immune response. Indeed, a prospective population-based cohort study found that the relative risk for all-cause mortality over a 4-year period in strained carers was 63% higher than in control individuals who were not carers<sup>67</sup>.

### Conclusions and future directions

Great strides have been made in the field of PNI towards understanding some of the interactions between the CNS, endocrine system and immune system, as well towards understanding how distress modulates these three complex systems. Although the mechanisms that underlie these interactions are complex, and although it will probably take many years to fully understand how these three systems interact, there are already clear translational implications from laboratory data.

Herpesvirus infections carry substantial human costs because the latent viruses are linked to considerable pain and suffering. Moreover, the evidence that psychological stressors can reactivate latent herpesviruses might have the most notable implications for

people who are already immunosuppressed (such as patients who have received an organ transplant or patients infected with HIV), owing to the risk of these individuals developing EBV-associated B-cell lymphomas. Indeed, reactivation of latent EBV, HSV-1 and CMV is associated with significant morbidity and mortality of immunosuppressed patients.

Furthermore, on the basis of speculation that chronic inflammation might be a contributing factor in up to 15% of all cancer cases<sup>68</sup>, stress-induced increases in the inflammatory response could be a broader pathway that links stress with cancer. Although it is beyond the scope of this article, the possibility that the physiological changes associated with stress could be key factors in cancer risk and progression has recently been reviewed<sup>69</sup>.

The results of the vaccine studies are particularly important for individuals who might be at a higher risk of developing complications that are associated with respiratory-virus infections, such as older individuals for whom increased susceptibility to pathogens is a serious health problem: together, influenza and pneumonia are the fifth leading cause of mortality in individuals aged 50 or older<sup>16</sup>. Biologically, the largest deleterious or enhancing consequences of stress are likely to occur when biological vulnerability is greatest: that is, early and late in life<sup>70</sup>. Older adults seem to show greater immunological impairments associated with distress or depression than younger adults<sup>14,57</sup>. However, the studies indicate that vaccine efficacy can be compromised by psychological stress, even in younger adults — an important public-health finding in its own right. These studies should be considered in the planning of clinical studies using cancer vaccines. The efficacy of such vaccines will depend on an optimum immune response.

The possibility that stressors might have a long-term impact on the developing endocrine and immune systems of infants and young children is an important question that has not been well studied in the PNI field. Indeed, excellent developmental studies of primates indicate that early stressors can reverberate for the life of an individual<sup>70</sup>.

In accordance with the evidence that stress delays wound healing, more than 200 studies published in the past 3 decades have shown beneficial effects from pre-surgical interventions. These beneficial effects include decreased anxiety and stress reductions when hospitalized, fewer post-operative complications, better treatment compliance, less pain and reduced use of analgesics, and alterations in various physiological indices<sup>56,57</sup>. Given the substantial consequences of stress for wound

repair, even small reductions in anxiety could have substantial clinical consequences, both directly and indirectly<sup>57</sup>.

More broadly, researchers have used several diverse strategies to modulate immune function, including relaxation, hypnosis, exercise, classical conditioning, self-disclosure and cognitive behavioural interventions. These interventions have generally produced positive endocrine and immune changes<sup>5,44,71–74</sup>. Although it is not yet clear to what extent these positive immunological changes translate into any concrete improvements in relevant aspects of health, such as alterations in the incidence, severity or duration of infectious and/or malignant disease, the preliminary evidence seems to be promising.

The role that genetics might have in these complex relationships is unknown, and this is an important new area that deserves exploration. For example, do individuals who have one or more variants of the polymorphisms associated with increased production of cortisol show greater immunological dysregulation when faced with stressful events?

Several studies have provided convincing evidence linking stress-induced immune dysregulation with morbidity and mortality. Animal models that involve viral infections have confirmed that stress can exacerbate morbidity that is associated with a viral infection<sup>37,75–77</sup>. Stress can also exacerbate bacterial infections, such as infections with *Listeria monocytogenes*<sup>78,79</sup>. In both humans and mice, studies of wound healing show a direct link between stress-associated immune dysregulation and health outcome, with well-documented relationships occurring between stress hormones, the immune response and the rate of wound healing<sup>50–52,54</sup>. Together, these studies support the hypothesis that morbidity can be directly linked to stress-induced immune dysregulation.

Using a mouse model, it was also shown that stress-induced immune dysregulation can cause mortality<sup>80</sup>. Restraint-stressed mice infected with Theiler's murine encephalomyelitis virus (TMEV) had an increased risk of dying. TMEV is a Picorna virus, which can cause CNS lesions. Higher titres of the virus were observed in the stressed mice compared with the control mice, and the underlying mechanism that accounted for the increased mortality in restraint-stressed mice was related to corticosterone-induced immune suppression.

The field of PNI is improving our understanding of the complex physiological changes that take place in stressful situations and providing new insights into various clinical applications. This research field is

also contributing to our knowledge of how the immune system operates in an environment in which there is bidirectional communication with other bodily systems. Despite the remarkable complexities of the interactions between the CNS, the immune system and the endocrine system, the researchers are making good progress at the molecular, cellular and organ-system levels. And, with that knowledge, the potential for new approaches to treatment is evident.

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doi:10.1038/nri1571

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## Acknowledgements

We thank J. Sheridan, D. Padgett, R. Bonneau, R. Nelson, N. Qian and V. Sanders for helpful suggestions. Work on this paper was supported, in part, by grants from the General Clinical Research Center (Columbus, United States) and the Comprehensive Cancer Center, (Columbus, United States).

## Competing interests statement

The authors declare no competing financial interests.

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## OPINION

## Consensual immunity: success-driven development of T-helper-1 and T-helper-2 responses

Pawel Kalinski and Muriel Moser

**Abstract** | Non-germline-encoded T- and B-cell receptors allow humans to effectively deal with rapidly mutating pathogens. Here, we argue that, in addition to determining the antigenic specificity of immune responses, the same receptor systems can also regulate the T-helper-1/T-helper-2 profile of immunity. Such a mechanism — based on feedback from distinct effector cells to dendritic cells, rather than on instruction from pathogens — uses the effectiveness of particular effector cells at targeting and destroying a pathogen as a reliable, experience-based criterion to induce and maintain the appropriately polarized response.

Distinct subsets of CD4<sup>+</sup> T cells preferentially support cell-mediated (type 1) versus humoral (type 2) immunity<sup>1</sup>. Type 1 T helper (T<sub>H</sub>1) cells promote the cytotoxic effector functions of natural killer (NK) cells, CD8<sup>+</sup> T cells and macrophages. They also promote antibody-dependent cell-mediated cytotoxicity (ADCC) by supporting B-cell production of IgG2a in mice and IgG1 in humans. By

contrast, T<sub>H</sub>2 cells promote humoral immunity, mediated by B-cell-produced IgG4 and IgE in humans (and IgG1 and IgE in mice). Although the proper balance of T<sub>H</sub>1 and T<sub>H</sub>2 immunity is as important for the success of an immune response as its specificity and overall magnitude<sup>1</sup>, it still remains unclear how the T<sub>H</sub>1/T<sub>H</sub>2-response profile is matched to distinct pathogens and to particular affected tissues.

The previously identified 'instructive' mechanisms of the induction of T<sub>H</sub>1- versus T<sub>H</sub>2-dominated responses by dendritic cells (DCs) use germline-encoded receptors to identify both distinct sets of conserved pathogen-specific motifs and endogenous mediators of tissue damage that are induced by different pathogen types invading distinct tissues<sup>2–6</sup>. Here, we discuss recent evidence for the existence of an additional highly reliable mechanism that assures the correctness of such a match. We propose that the intrinsic ability of different effector cells to discriminate between different pathogen classes and to differentially affect DC functions is a