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Depression and immune function
Central pathways to morbidity and mortality

Janice K. Kiecolt-Glaser[a,*], Ronald Glaser[b]

[a]Department of Psychiatry, The Ohio State University College of Medicine, 1670 Upham Drive, Columbus, OH 43210, USA
[b]Department of Molecular Virology, Immunology, and Medical Genetics, The Ohio State University College of Medicine, Columbus, OH 43210, USA

Abstract

Objective: The increased morbidity and mortality associated with depression is substantial. In this paper, we review evidence suggesting that depression contributes to disease and death through immune dysregulation. **Method:** This review focuses on recent human studies addressing the impact of depression on immune function, and the health consequences of those changes. **Results:** There is growing evidence that depression can directly stimulate the production of proinflammatory cytokines that influence a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, certain cancers, periodontal disease, frailty, and functional decline. Additionally, depression can down-regulate the cellular immune response; as a consequence, processes such as prolonged infection and delayed wound healing that fuel sustained proinflammatory cytokine production may be promoted by depression. **Conclusions:** These direct and indirect processes pose the greatest health risks for older adults who already show age-related increases in proinflammatory cytokine production. Thus, aging interacts with depression to enhance risks for morbidity and mortality.

Keywords: Proinflammatory cytokines; Interleukin 6; Psychoneuroimmunology; Stress

Depression is the most common psychiatric illness; both major depression and subthreshold depressive symptoms carry substantial health risks, reviewed in the articles in this issue of the journal and elsewhere [1–4]. Depression can affect health through many pathways; these influences may occur through health behaviors or compliance with medical regimens, as well as through alterations in the functioning of the central nervous system (CNS), immune, endocrine, and cardiovascular systems [5–8]. In this paper, we consider how depression may contribute to morbidity and mortality through immune dysregulation. We focus on a central immunological mechanism that serves as a gateway for a range of age-associated diseases, the dysregulation of proinflammatory cytokine production, particularly interleukin 6 (IL-6) [9].

Although we will not address the effects of disease on emotional distress in any detail, it is important to mention the bidirectional nature of the relationship. Unquestionably, cytokines have substantial effects on the CNS, including production and enhancement of negative moods, physical symptoms including lethargy and fatigue, and a range of sickness behaviors from shivering to loss of appetite [8,10,11]. Indeed, despite our focus on the impact of depression on immune responses and disease, there is also plausible evidence that the immune system has a role in the neuroendocrine and behavioral features of both depressive and anxiety disorders [8,11].

Morbidity, mortality, and aging: central immunological mechanisms

The immune system's inflammatory response can be triggered in a variety of ways, including infection and trauma. Inflammation is an important and constructive consequence of infection and injury; proinflammatory cytokines including IL-1, IL-6, and tumor necrosis factor (TNF) attract immune cells to the site of infection or injury, and prime them to become activated to respond. Anti-inflammatory cytokines such as IL-10 and IL-13 serve to dampen

* Corresponding author. Tel.: +1-614-292-0033; fax: +1-614-292-0038.
E-mail addresses: kiecolt-glaser.1@osu.edu (J.K. Kiecolt-Glaser), glaser.1@osu.edu (R. Glaser).

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this immune response, including decreased cell function and synthesis of other cytokines. Thus, broadly speaking, cytokines provide intercellular signals that help to regulate the immune system's response to injury and infection.

Although the mechanisms associated with inflammation are critical to resolving infections and repairing tissue damage, chronic or recurring infections can provoke pathological changes [12]. For example, low levels of persistent inflammation may result when chronic infectious processes such as periodontal disease, urinary tract infections, chronic pulmonary disease, and chronic renal disease persistently stimulate the immune system. Persistent stimulation of proinflammatory cytokine production has the greatest impact among older adults who already show age-related increases in IL-6 production [13].

Depression and immune system alterations

Depression enhances the production of proinflammatory cytokines, including IL-6 [14–18]. Importantly, both depressive symptoms and syndromal depression are associated with heightened plasma IL-6 levels [16]. Following successful pharmacologic treatment, elevated IL-6 levels decline in patients with a major depression diagnosis [19]. Moreover, both physical and psychological stressors can provoke transient increases in proinflammatory cytokines [20–22]; in animal models, both stress and administration of epinephrine elevate plasma IL-6, consistent with evidence that IL-6 production is stimulated through β-adrenergic receptors, among other pathways [23,24]. Thus, production of IL-6 and other proinflammatory cytokines can be directly stimulated by negative emotions and stressful experiences, providing one direct pathway.

Overproduction of proinflammatory cytokines may lead to subsequent maladaptive immune and endocrine changes. IL-6 is a potent stimulator of corticotropin-releasing hormone (CRH) production, a mechanism that leads to heightened HPA activity, including elevated levels of plasma ACTH, followed by increased cortisol levels [14]; elevations in ACTH and cortisol can provoke multiple adverse immunological changes [8]. The complexity of these potential interactions is further underscored by one line of research which suggests that once cortisol levels rise, they can initiate, perpetuate or aggravate syndromal depression, depression-like behaviors, and depressive symptoms such as anxiety, insomnia, and poor memory [25]. Thus, negative emotions that dysregulate IL-6 secretion may also promote adverse neuroendocrine alterations.

Indeed, in addition to their association with enhanced secretion of proinflammatory cytokines, depression and distress can also have direct adverse effects on a variety of other immunological mechanisms, including the downregulation of cellular and humoral responses [8], and these changes are large enough to be clinically significant. For example, vaccine responses demonstrate clinically relevant alterations in immune responses to challenge under well-controlled conditions; accordingly, they serve as a proxy for response to an infectious agent [26–29]. More distressed and more anxious individuals produce immune responses to vaccines that are delayed, substantially weaker, and/or shorter lived [26–29]; as a consequence, it is reasonable to assume these same individuals would also be slower to develop immune responses to pathogens; thus, they could be at greater risk for more severe illness. Consistent with this argument, adults who show poorer responses to vaccines also experience higher rates of clinical illness, as well as longer lasting infectious episodes [30]. In addition, other researchers have shown that distress can alter susceptibility to cold viruses [31]. Furthermore, distress also provokes substantial delays in wound healing [32,33], and enhances the risk for wound infection after injury [34].

Increased susceptibility to infectious disease and poorer recovery from infection are substantial and important problems; in addition, however, they carry additional risks. Repeated, chronic, or slow-resolving infections or wounds enhance secretion of proinflammatory cytokines, a process that can serve to further inhibit certain aspects of immune responses (e.g., IL-2, a cytokine important in protection against infection) [35]. Thus, depression can directly affect the cells of the immune system and modulate the secretion of proinflammatory cytokines; in addition, depression may also contribute to prolonged or chronic infections or delayed wound healing, processes that indirectly fuel proinflammatory cytokine production. We next consider evidence which suggests that the etiology and course of a very broad range of diseases may be altered by dysregulated inflammatory responses.

Morbidity, mortality, and inflammatory immune responses

Inflammation has been linked to a spectrum of conditions associated with aging, including cardiovascular disease [9]. The association between cardiovascular disease and IL-6 is related in part to the central role that this cytokine plays in promoting the production of C-reactive protein (CRP), an important risk factor for myocardial infarction [23]. For example, high concentrations of CRP predicted the risk of future cardiovascular disease in apparently healthy men [36]. Further studies provided mechanistic links: chronic infections amplified the risk for development of atherosclerosis fourfold in subjects who were free of carotid atherosclerosis at baseline, conferring increased risk even in subjects lacking conventional vascular risk factors [37]. Indeed, the increased risk for artery-clogging plaque was greater than that conferred by elevated blood pressure or cholesterol [37]. Cardiovascular disease is the leading cause of death, and individuals with high levels of both IL-6 and CRP were 2.6 times more likely to die over a 4.6-year period than those who had low levels of both [38].

In addition to cardiovascular disease, inflammation has been linked to a spectrum of conditions associated with aging, including osteoporosis, arthritis, type 2 diabetes, certain lymphoproliferative diseases and other cancers (including multiple myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia), Alzheimer's disease, and periodontal disease [9]. In fact, more globally, chronic inflammation has been suggested as one key biological mechanism that may fuel declines in physical function leading to frailty, disability, and, ultimately, death [12,39]. For example, elevated levels of CRP and IL-6 predicted the development of type 2 diabetes in a 4-year follow-up period in healthy women after adjustments for BMI, family history of diabetes, smoking, exercise, alcohol, and hormone replacement therapy; among women in the highest vs. lowest quartiles, the relative risk for developing diabetes was 7.5 for IL-6 and 15.7 for CRP [40].

In other work, elevated serum IL-6 levels predicted future disability in older adults, a finding that may reflect the effects of the cytokine on muscle atrophy, and/or to the pathophysiologic role played by the cytokine in particular diseases [41]. Proinflammatory cytokines including IL-6 may slow muscle repair following injury and accelerate muscle wasting [42]; indeed, IL-6 and CRP also play a pathogenic role in a range of diseases associated with disability among the elderly (osteoporosis, arthritis, and congestive heart failure, among others) [41]. In this context, it is interesting that IL-6 is also associated with self-rated health [43], a robust predictor of mortality [10]. Thus, the clinical importance of immunological dysregulation for older adults is highlighted by increased risks across diverse conditions and diseases.

Health behaviors

In addition to the direct influences of psychological states on physiological function, distressed individuals are more likely to have health habits that put them at greater risk, including poorer sleep, a greater propensity for alcohol and drug abuse, poorer nutrition, and less exercise, and these health behaviors have cardiovascular, immunological, and endocrinological consequences [44]. Higher plasma IL-6 and CRP levels are associated with adverse health habits: values for both are higher in smokers than nonsmokers, in individuals who report less physical activity, and in those with a higher body mass index [39,41]. However, health habits including smoking, physical activity, and alcohol use have typically explained only a small part of the excess mortality associated with depression among older adults [3]. Similarly, IL-6 has robust relationships with morbidity and mortality, even after controlling for health behaviors [39–41]. Thus, health behaviors, although obviously important, are not sufficient to explain the relationship between depression and disease.

Pharmacologic treatments hold promise. A prospective trial of statins produced reductions in CRP, providing evidence that these drugs have anti-inflammatory effects in addition to their ability to lower lipids [45]. Additionally, the use of antidepressants can normalize activation of the inflammatory response system in patients with a major depression diagnosis [19]. The question of whether cognitive or other psychological treatments for depression have similar positive consequences is an important arena for future research.

Conclusions

Many lines of evidence now indicate that IL-6 may function as a "...global marker of impending deterioration in health status in older adults" (p. 645) [41]. Indeed, even after the point at which risk factors such as cholesterol, hypertension, and obesity predict health deterioration less successfully among the very old, chronic inflammation continues to be an important marker [41]. We have argued that depression (both syndromal and subsyndromal) directly prompts immune dysregulation, and these processes may lead to subsequent maladaptive immune and endocrine changes [14,20–24]. Production of IL-6 and other proinflammatory cytokines can be directly stimulated by depression, providing one direct pathway. In addition, depression and stress may also contribute to prolonged infection or delayed wound healing, processes that fuel sustained proinflammatory cytokine production. Thus, research that addresses the dysregulation of the immune and endocrine systems associated with depression could substantially enhance our understanding of psychological influences on health, particularly among the elderly.

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