In immune defense: redefining the role of the immune system in chronic disease

Katya B. Rubinow, MD; David R. Rubinow, MD

The recognition of altered immune system function in many chronic disease states has proven to be a pivotal advance in biomedical research over the past decade. For many metabolic and mood disorders, this altered immune activity has been characterized as inflammation, with the attendant assumption that the immune response is aberrant. However, accumulating evidence challenges this assumption and suggests that the immune system may be mounting adaptive responses to chronic stressors. Further, the inordinate complexity of immune function renders a simplistic, binary model incapable of capturing critical mechanistic insights. In this perspective article, we propose alternative paradigms for understanding the role of the immune system in chronic disease. By invoking allostasis or systems biology rather than inflammation, we can ascribe greater functional significance to immune mediators, gain newfound appreciation of the adaptive facets of altered immune activity, and better avoid the potentially disastrous effects of translating erroneous assumptions into novel therapeutic strategies.

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Introduction

Depression and metabolic disease exhibit an interdependent relationship. Obesity and type 2 diabetes mellitus are associated with increased incidence of depression, and patients with depression are at increased risk for the development of metabolic disease.[1] Though this relationship is poorly understood, the presence of altered immune system activity in both disorders may provide a key pathophysiologic link. Indeed, over the past 2 decades, changes in immune system activity have been identified as a hallmark feature of many chronic diseases, including depression, obesity, type 2 diabetes mellitus, atherosclerosis, and cancer.[2-6] Common changes in immune function across these disorders may in part underlie their association in epidemiologic studies. These observations collectively have generated a novel paradigm, that of inflammation contributing to the initiation and progression of chronic disease. This paradigm has been pivotal for capturing critical insights about the dynamic regulation of immune function in a variety of disorders.

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Author affiliations: Diabetes Institute, Department of Medicine, University of Washington, Seattle, Washington, USA (Katya B. Rubinow); Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina, USA (David R. Rubinow)

Address for correspondence: Katya Rubinow, 850 Republican St, Box 358055, Seattle, Washington 98109, USA
(email: rubinow@uw.edu)

Nevertheless, use of the term inflammation in depression and metabolic disease may also inadvertently encourage the continued use of explanatory models deprived of context. Specifically, the "inflammation" model engenders a binary understanding of biology, wherein inflammation is detrimental and its attenuation beneficial. This construct of inflammation as a unitary process thus fails to account for the exquisite complexity of the immune system, which comprises multiple cell types, each with the capacity to acquire highly heterogeneous phenotypes in different biological contexts. Consequently, describing the role of inflammation rather than the immune system in depression and metabolic disease may create a falsely comprehensive sense of understanding pathophysiology where significant uncertainty persists. So, too, may it obscure important differences in immune function in these respective disease states. Finally, the paradigm of inflammation fails to distinguish between immune system involvement and aberrant immune function, a critical distinction when identifying potential targets for therapeutic interventions. In the following paragraphs, we first describe observations that are discordant with the current perceived associations between depression or metabolic disease and inflammation. We then discuss the limitations of inflammation as a paradigm for describing the role of the immune system in disease states. Next, we suggest the potential dangers inherent in the conceptualization of immune function as inflammation, a value-laden construct that may obscure physiologic insights and thereby generate therapeutic interventions with unintended, adverse effects. Finally, we introduce alternative models—allostasis and systems biology—that may facilitate a more textured understanding of immune regulation in metabolic and mood disorders.

Inflammation and disease: a dissociable association

A causal relationship between changes in immune activity and depression is supported by the high prevalence of depressive syndromes among patients on interferon-α therapy, with 25% to 50% of patients on high-dose therapy meeting *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition]) criteria for major depression.[7,8] Notably, many of these patients derive therapeutic benefit from selective serotonin reuptake inhibitors, offering further, indirect evidence that peripheral changes in cytokine exposure can alter central neurotransmitter signaling.[9] In humans, illness or experimental administration of endotoxin can produce changes in mood and behavior characteristic of major depression.[10-13] Similarly, animal studies demonstrate the precipitation of "depressive-like" behaviors after endotoxin administration in association with elevations of individual cytokines (eg, interleukin [IL]-1β, IL-6).[11] Hodes et al further demonstrated that susceptibility to chronic stress–induced social avoidance in mice appeared to be mediated by excess peripheral IL-6 production.[14] These observations are supported by extensive evidence of cytokine regulation of neurotransmitters central to mood and behavior.[10] Thus, primary activation of the immune system can generate many of the behavioral, affective, and biochemical features of major depression. In turn, major depression is associated with altered immune system activity, as illustrated by increased circulating levels of the cytokine tumor necrosis factor-α (TNF-α) and IL-6.[15,16] Elevated cytokine production is, unsurprisingly, not unique to depression but also has been reported for anxiety disorders including posttraumatic stress disorder.[17-20] These findings have collectively led to the pivotal recognition that immune function may be altered in depression and related mood disorders and the growing interest in the use of anti-inflammatory therapies as a novel treatment strategy for major depression.[9,20-23]

Despite these intriguing findings, dissociations between cytokine elevation and depression have been observed. For example, endotoxin administration to patients with severe depression resulted in the acute remission of depressive symptoms,[24] and exercise augmentation produced significant antidepressant effects in the absence of changes in serum levels of TNF-α or IL-6.[25] Similarly, in vitro and in vivo, pharmacologic antidepressant treatment has resulted in either paradoxical increases or no changes in the production of cytokines, including IL-6 and IL-1β.[14,26-29] Further, anti-inflammatory agents have been shown to antagonize the behavioral and biochemical effects of selective serotonin reuptake inhibitors in mice and the antidepressant effects of these agents in humans.[30] Observed dissociations between peripheral and central cytokine levels also underscore the limitations of making inferences about a local immune response on the basis of circulating markers.[30] Notably, too, the specific cytokines reported as significantly elevated in depressed

patients have differed across studies and may in part reflect the confounding effects of medical comorbidities commonly found among patients included in these studies. Finally, the overlap in serum cytokine levels between patients and controls is substantial.[31] Indeed, in their thoughtful review, Raison and Miller conclude that depression is not primarily an inflammatory disorder though they propose that inflammation probably contributes to a subset of depressive presentations.[31] Nonetheless, even these more nuanced views may risk conceptually collapsing dynamic changes in immune activity to "inflammation." This reductionist model could prevent more comprehensive understanding of underlying biology, including specificity with regard to cell type, time course, and, most critically, the adaptive and functional significance of an immune response.

As is true for depression, obesity and type 2 diabetes mellitus have been associated with elevated circulating cytokine levels and further may be characterized by increased infiltration of immune cells into metabolic tissues.[3,32-34] In animal models, deficiency of TNF-α or chemokine (C-C motif) ligand 2 (CCL2) confers protection from diet-induced insulin resistance,[35-37] and TNF-α can directly inhibit insulin signaling in vitro.[38,39] These and similar observations have led to an analogous paradigm of metabolic disease as a state of chronic inflammation, with the attendant suggestion that immune function is dysregulated; therefore, immunomodulatory therapies may hold promise as treatment strategies. Again, however, the development of such treatments posits aberrant immune function as a driving etiologic force of metabolic disorders, a problematic concept for several reasons. First, the capacity to generate insulin resistance through pharmacologic cytokine exposures does not definitively demonstrate that dysregulated immune activity drives the insulin resistance associated with obesity. Second, an etiopathogenic role of inflammation is undermined by the failure to date of immune-targeted therapies in the treatment of metabolic disease.[40,41] Third, as in depression, changes in serum cytokine levels are dissociable from the predicted metabolic phenotype. Thus, lipid infusion in human subjects generated insulin resistance in the absence of changes in circulating cytokines.[42] In mice, IL-6 deficiency led to glucose intolerance and insulin resistance not seen in wild-type controls.[43] In a model of diet-induced obesity, IL-6–deficient mice exhibited the same metabolic phenotype as wild-type controls, despite attenuated leukocytosis and serum amyloid A-1 (SAA-1) generation.[44] In parallel, clinical use of an IL-6 receptor (IL-6R) neutralizing antibody led to metabolic dysregulation characterized by markedly increased weight, hypertriglyceridemia, and hypercholesterolemia.[45] Collectively, these observations undermine existing, simplistic models that identify inflammation as both hallmark feature and pathogenic origin of metabolic and mood disorders. Moreover, they underscore the importance of determining not only a clinical syndrome but also the underlying disease, as defined by a distinct pathophysiology.

Immune alterations: adaptation and maladaptation

The inference that the immune system behaves aberrantly in metabolic disorders disregards the critical question of why altered immune function is observed in these disease states. As an alternative construct, the immune system could be mounting an adaptive response to the chronic stress of excess energy intake; the prolipolytic and antiadipogenic effects of TNF-α could be viewed as protective, antiobesity functions that may attenuate lipotoxicity or glucotoxicity at the cellular level.[41] Indeed, obesity itself has been described as an adaptive effort to prevent lipotoxicity in extra-adipose tissue.[46] Thus, even if one by-product of this response were the promotion of insulin resistance, immune-directed therapies could target adaptive responses rather than pathogenic triggers and pose a potential for harm magnified by the almost inevitable compromise of host defense conferred by such treatments. The complexity of physiologic responses to stressors is well illustrated by glucocorticoid activity in affective disorders. Thus, it is generally assumed that elevated glucocorticoid release corresponds to the relative physiologic overwhelm conferred by a stressor. This presumption, however, breaks down with consideration of the individual calibration of the hypothalamic-pituitary-adrenal (HPA) axis or the timing of cortisol elevation. The isolated use of serum cortisol levels, for example, would fail to capture the physiologic overwhelm of stress-dependent disorders like posttraumatic stress disorder, which commonly is associated with low cortisol levels but increased glucocorticoid receptor signaling in target tissues.[47,48] Further, in striking contrast to the presumed deleterious effects of glucocorticoids, increased glucocorticoid exposure during or immediately before acute immobili-

zation stress was shown to protect male rats from the subsequent development of anxiety-like behaviors and spinogenesis in the basolateral amygdala.[49] These latter findings would suggest an unequivocally adaptive role for glucocorticoids. This distinction between adaptive and dysregulated responses is not always clear and may evolve with greater insights into disease pathophysiology. The possibility also exists that a single mediator or process may effect both adaptive and maladaptive changes. The evolution of insulin resistance in obesity, for example, could be seen as a transition point from allostatic load to allostatic overload, the point at which physiology undergoes a sustained recalibration, as described further below; however, insulin resistance could well play a concurrent role in protecting cells from glucose- or lipid-associated toxicity. Analogously, the phenomenon of post-ischemic stroke depression occurs in association with increased cytokine production.[50] Yet even as this immune activation could potentiate depression, it also might play a key role in neuronal protection and recovery from ischemic injury.[51] This duality of benefit and harm is illustrated further by glucocorticoid signaling in the hippocampus, which exerts acute, protective effects on neurons by inhibiting excessive glucose uptake but nonetheless also can contribute directly to neuronal death.[52] Similarly, elimination of IL-1β or TNF reduces the pain of peripheral nerve injuries but markedly impairs healing,[53] and both TNF-α and IL-6 display complex, context-dependent effects on learning, memory, and synaptic regulation, which may be beneficial (even critical) or detrimental depending upon context.[54]

The occurrence of adaptive and maladaptive sequelae also may be separated temporally. Obesity itself may be adaptive in certain contexts, as overeating could confer protective, stress-alleviating effects that contribute immediately to reproductive success, albeit at the expense of the individual's long-term health.[55] Thus, the perspective from which the biological system is observed must first be defined, as the same mediators may appear to confer maladaptive changes with regard to systemic glucose metabolism or clinical symptoms but nonetheless continue to play protective, adaptive roles with regard to cellular function and survival. This dynamic approach to understanding adaptation reflects the intricate network of biologic systems involved in any stress response. Adaptation entails not a linear progression of events but rather extensive crosstalk among multiple regulatory arms, including the immune system, sympathetic and parasympathetic nervous systems, and neuroendocrine systems.[56] Yet, pharmacologic therapies are designed specifically to target a single locus within this vast regulatory framework. The attendant implication, then, is that such therapies are unlikely to restore an optimally adaptive state but have great potential to disrupt these signaling networks and thereby prevent or impede innate, adaptive responses.

Complexity of immune responses: defying a binary nomenclature

One obstacle to elucidating disease pathophysiology is the tendency to model disease states in terms of biological markers as opposed to biological mediators. Whereas mediators can play complex roles, markers are deprived of biological context and functional significance; they simply rise or fall, appear or disappear. As a result, markers fit neatly into paradigms predicated on binary or linear constructs, but the importance of assigning functional significance becomes increasingly evident as emergent data dismantle binary or linear understandings of immune function. Rather, a clear distinction between pro- and anti-inflammatory processes readily disappears when individual mediators and contextual variables are more closely examined. The dynamic functional properties of immune mediators are compellingly illustrated by prostanoid signaling. Induction of the enzyme cyclooxygenase 2 (COX-2), for example, generates lipid mediators that evolve both early and late in immune cell activation and function to both propagate and resolve the immune response. Although prostaglandin E_2 (PGE_2) promotes vasodilation and neutrophil chemotaxis, it also confers suppressive effects on T-cell proliferation and activation.[57] Further, progressive accumulation of PGE_2 may be critical for the generation of resolvins and protectins, the lipid signals that help terminate an immune response.[58] Thus, PGE_2 exerts complex effects and cannot be reduced to a simple pro- or anti-inflammatory designation as would be required by the rubric of inflammation.

As noted above, the effects of an individual immune mediator depend on critical variables, including the timing and magnitude of exposure, the specific cell and tissue type, and the presence of concurrent signals. The actions of an individual mediator, therefore, can only be understood within a defined biological context. The

time-dependent nature of paracrine signaling is illustrated by the adipokine adiponectin, which triggers an initial burst of nuclear factor-κB activity and cytokine secretion in macrophages. Subsequent to this transient activation, however, adiponectin-treated macrophages exhibit a substantially diminished response to endotoxin stimulation.[59] The phenomenon of macrophage tolerance to endotoxin similarly illustrates that the cellular response to a given stimulus can differ markedly on the basis of previous exposure.[60] Notably, too, endotoxin tolerance is characterized by reductions only in specific cytokines and can be abrogated completely when macrophages are pretreated with interferon-γ.[61] These observations are complemented by the recent demonstration that previous exposure to a stressor dramatically and persistently alters the gene-expression profile resulting from a subsequent stressor, evidence of a reprogrammed cellular response.[62] Even the kinetics of biological signaling are critical, as pulsatile versus sustained exposures elicit different genetic activation profiles, despite the same cumulative "dose of signal."[63] Further, as with PGE_2, the physiologic effects of other immune-derived mediators are concentration-dependent. In vitro data suggest that TNF-α diminishes insulin-stimulated glucose uptake at higher concentrations but actually augments adipocyte glucose uptake at lower concentrations.[64] Moreover, the metabolic effects of TNF-α may be divergent across different tissue types, as TNF-α–deficient mice exhibited reduced lipid accumulation in liver but not skeletal muscle during high-fat feeding.[65] Adding an additional layer of complexity, the magnitude of signal exposure encompasses not only the concentration of a mediator but also the relative expression of its receptor, cellular localization of the receptor, and flux in postreceptor pathways, which may undergo continual remodeling under different biological conditions. The heterogeneous effects of these individual mediators find parallel in the apparent paradox that metabolic and mood disorders represent states of both heightened immune system activity and relative immunosuppression.[66,67] Thus, an ever-growing body of data refuses to conform to the extant understanding of inflammation as a discrete, present-or-absent process. Instead, aggregate findings mandate a reformed framework that can accommodate the innumerable variables of biological context. Such a revised framework is essential to restore functional relevance to otherwise mere markers of disease.

Aberration versus adaptation: allostasis as an alternative construct to inflammation

The challenge then arises to develop alternative paradigms capable of incorporating these findings that appear discordant within the current conceptual framework of inflammation. One such alternative construct is that of allostasis, a model initially applied to cardiovascular physiology and hypertension and subsequently expanded to describe the effects of chronic stress.[55,56,68] In contradistinction to homeostasis, allostasis invokes continual adaptation and change rather than conservation of a single set point. Further, allostatic theory posits that these adaptations entail not only reactive but also anticipatory responses designed to optimize efficiency and, ultimately, survival and reproductive success.[55] Importantly, however, allostatic theory does not assume that the new state of equilibrium will be identical to that achieved before stress. Allostatic load also can transition to a state of allostatic overload if the stressors become sufficiently chronic or the attendant energy requirements exceed energy intake. In states of allostatic overload, maladaptive or dysregulated responses now become evident. Further, even the adaptive responses to stress, particularly with prolonged stress, may themselves lead to seemingly adverse consequences and thereby contribute to allostatic load. Thus, in contrast to models of homeostasis, allostasis allows for physiologic recalibration of the biological system and creates conceptual space for adaptive responses that may result in new biological set points. Whereas homeostasis invokes linear and binary designations, allostasis is an intrinsically nonlinear model of biology.[69,70] In contrast to allostatic theory, the reduction of immune system activation to a unitary concept—inflammation—and selected biomarkers can result in missed or erroneous biological insights and potentially dangerous translational efforts. Despite its putative anti-inflammatory effects, for example, the selective COX-2 inhibitor rofecoxib was found to confer a near doubling in cardiovascular event rate.[71] Analogously, the paradigm of oxidative stress in the pathogenesis of cancer and cardiovascular disease has led to a number of clinical trials evaluating the efficacy of antioxidants in disease prevention. Strikingly, however, beta carotene supplementation among smokers resulted in increased risk of both lung cancer and cardiovascular disease.[72] Such findings critically under-

score the potential dangers of prematurely translating observational or in vitro findings into clinical interventions and, moreover, highlight our relative paucity of mechanistic insight into the pathogenesis of many chronic diseases.

A second and related model, systems biology, views phenotype as the highly context-dependent output of integrated networks of cells and signaling molecules. Understanding these multipathway networks requires measurement of many targets across multiple cell types under many conditions.[73] The fundamental insight of systems biology is that a physiologic system cannot be understood if examined in isolation or assessed under only one condition, even if thousands of variables are quantified. As such, the same stimulus may elicit different or opposite responses as a function of the state of the network. This phenomenon characterizes the functioning of genetic and brain networks and has been well recognized in neuroscience research but is now inarguably not unique to the field; as a rule, then, biological signals simply cannot be reliably interpreted independent of context.

Conclusion

Cytokine signaling is of enormous physiologic and pathophysiologic importance, with a vast and continually expanding spectrum of described biological effects. The exquisite complexity of immune system function and its exquisitely complex relationship to the etiopathogenesis of metabolic and affective disorders simply cannot be captured through reductionist terms like "proinflammatory." Rather, binary and linear models become increasingly devoid of meaning as they fail to evolve with emergent findings. Whereas inflammation once captured previously unrecognized roles of the immune system, it now promotes a physiologically inaccurate model that at best impedes understanding and at worst may lead to premature and potentially destructive therapeutic strategies. Our efforts to understand the role of immune signaling in depression and metabolic disease will be advanced only if informed by models that encourage the assignment of functional significance to biological mediators and recognize dynamic changes in biological context. Thus, discrete mediators can and do exert different effects in the presence or absence of other local signals, and these effects exhibit variable kinetics that may result in a single mediator performing seemingly disparate functions at different time points. As conceptual frameworks inform therapeutic strategies, investigative questions, and the interpretation of data, they must be continually reexamined and refined, particularly when emergent data consistently challenge the existing constructs. This reformulation of the immune system's role in depression and metabolic disease is necessary to enable the continued growth of this extraordinarily promising area of investigation. Even more critical, our proposed reformulation offers a more textured approach to biology that could optimize treatment strategies and help avoid those with the potential to do greater harm than good. ❑

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Redefinición del papel del sistema inmunitario en la enfermedad crónica dentro de la defensa inmune

Durante la última década, el reconocimiento de la alteración de la función del sistema inmune en muchas enfermedades crónicas ha demostrado ser un avance central en la investigación biomédica. En diversos trastornos metabólicos y anímicos, esta actividad inmune alterada ha sido caracterizada como inflamación, asumiendo concomitantemente que la respuesta inmune es aberrante. Sin embargo, la evidencia acumulada desafía esta suposición y sugiere que el sistema inmune puede estar estructurando respuestas adaptativas a estresores crónicos. Además, un modelo simplista y binario no es capaz de dar cuenta de la excesiva complejidad de la función inmune ni hacer comprensibles los mecanismos internos esenciales. En este contexto, este artículo de perspectiva se propone entregar paradigmas alternativos para la comprensión del papel del sistema inmune en la enfermedad crónica. Al invocar la alostasis o la biología de sistemas antes que la inflamación, se puede atribuir un mayor significado funcional a los mediadores inmunes, obtener una nueva apreciación de los aspectos adaptativos de la actividad inmune alterada, y evitar mejor los efectos potencialmente desastrosos de traducir suposiciones erróneas en nuevas estrategias terapéuticas.

Vers une redéfinition du rôle du système immunitaire dans la maladie chronique

Ces 10 dernières années, l'identification d'une altération du système immunitaire dans de nombreuses maladies chroniques est au centre des avancées de la recherche biomédicale. Dans de nombreux troubles métaboliques ou de l'humeur, cette activité immunitaire modifiée se caractérise par une inflammation, ce qui suppose une réponse immunitaire anormale. Cette hypothèse est néanmoins mise en défaut car un nombre croissant d'arguments suggère que le système immunitaire développerait des réponses adaptatives aux facteurs de stress chroniques. De plus, un modèle simpliste, binaire, ne peut rendre compte de l'extraordinaire complexité de la fonction immunitaire et n'est pas suffisant pour en restituer les mécanismes fondamentaux. Dans ce contexte, nous proposons dans cet article d'autres modèles pour comprendre le rôle du système immunitaire dans la maladie chronique. En invoquant l'allostase ou la biologie de systèmes plutôt que l'inflammation, nous pouvons accorder une plus grande importance fonctionnelle aux médiateurs immunitaires, réviser notre conception des capacités d'adaptation d'une activité immunitaire altérée et mieux éviter les effets potentiellement désastreux d'une traduction d'hypothèses erronées en nouveaux traitements.