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Understanding inflammation, its regulation, and relevance for health: A top scientific and public priority

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One of the most important scientific discoveries in health research in recent years has involved the realization that inflammation plays a role in not just a few disorders, but many disease conditions that cause substantial morbidity and contribute to early mortality (Couzin-Frankel, 2010). Included in this list are several psychiatric conditions, such as anxiety, unipolar and bipolar depression, schizophrenia, and post-traumatic stress disorder, as well as numerous physical disease conditions including asthma, rheumatoid arthritis, cardiovascular disease, obesity, diabetes, osteoporosis, Alzheimer's disease, certain cancers, and stroke (Miller et al., 2011; Slavich and Irwin, 2014). All told, inflammation is involved in at least 8 of the top 10 leading causes of death in the United States today (Hoyert and Xu, 2012). Understanding how inflammation promotes poor health, and how and when we can intervene to reduce inflammation-related disease risk, should thus be a top scientific and public priority.

Although it is easy to characterize inflammation as bad, the story is complicated and several issues remain unresolved. The first issue involves *time course*. Time-limited increases in inflammation are important for promoting wound healing and recovery and for limiting the spread of communicable infections. Inflammation, therefore, is certainly not always bad and rather can be absolutely critical for survival, especially during times of injury and infection. Presently, however, we have only a limited understanding of when elevated levels of inflammatory activity are helpful versus harmful. The second issue involves *location*. Although classic theories conceptualized inflammation as a localized process, novel assays for detecting different inflammatory mediators have ushered in new ideas about “systemic inflammation”. At the same time, these advancements have shown that inflammatory activity occurring in different places, including in peripheral tissues, different organs, oral fluids, and the central nervous system, are usually not highly correlated and likely have different effects on health. Therefore, although it is convenient to characterize individuals as having “high” versus “low” levels of inflammation, these descriptions are overly crude and highlight a need to talk about “elevated inflammation” in more precise terms. A third issue concerns *conditional effects*. Although inflammation is a core feature of some diseases, in

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Conflicts of interest

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most instances inflammation is only one pathophysiologic mechanism that interacts with other factors, such as neural, cognitive, and emotional processes, diet, sleep, and exercise, genetic factors, and social-environmental adversity, to influence health. Nevertheless, most human studies do not yet examine factors that moderate or mediate the effects of inflammation on health. Finally, there is the important issue of *regulation*: inflammatory activity is not static, but rather changes over time as a result of a complex set of bidirectional regulatory interactions with other innate immune system and physiologic processes (Sternberg, 2006; Irwin and Cole, 2011).

This last issue of regulation is particularly important for at least two reasons. First, since not all individuals who exhibit elevated levels of inflammatory activity develop serious medical problems, understanding endogenous and exogenous processes that can cause aberrant regulatory dynamics and foster chronic inflammation may provide important insights into why some people develop inflammation-related diseases while others do not. Second, and relatedly, a better understanding of these regulatory processes may highlight new psychosocial, nutritional, and pharmacologic strategies that can be used to target inflammation and improve human health.

Researchers have just begun investigating how interactions between immune and related regulatory systems predict health outcomes, and an excellent example of this work is provided by Santarsieri et al. (in press) who examined how neuroendocrine and inflammatory factors in serum and from cerebrospinal fluid (CSF) interrelate and predict clinical outcomes in the context of traumatic brain injury (TBI). Among several findings, the authors reported that: (a) high cortisol levels over the six-day post-TBI period conferred a 3.5-fold increased odds of poorer clinical functioning six months later; (b) the effects of TBI-induced increases in CSF inflammatory activity were mediated by patients' post-TBI cortisol trajectories; and (c) associations between CSF cytokine-cortisol dynamics and subsequent clinical functioning differed for patients in the high-versus low-cortisol trajectory group, suggesting that "outcome prediction based solely on cortisol levels or solely on inflammation is incomplete and reductive" (Santarsieri et al., in press, p. 9).

Studies like this provide an excellent model for future research on inflammation and health. Such work could aim to meet several goals, including: simultaneously studying multiple markers of inflammatory activity; examining (when possible) inflammatory mediators in the central nervous system and not just in the periphery; collecting information on relevant regulatory mechanisms; assessing hypothesized moderating and mediating factors; and following individuals over time to evaluate the relevance of immune and related regulatory processes for subsequent health. Several multi-level theories of inflammation and health have been recently proposed (e.g., Kiecolt-Glaser et al., 2010; Miller et al., 2011; Raison and Miller, 2013; Slavich and Cole, 2013; Slavich and Irwin, 2014), and these frameworks have the potential to reveal new strategies for reducing the enormous social and economic burden caused by inflammation-related disease. To fully realize this potential, though, we must continue to push the boundaries of scientific enquiry by conducting studies that are increasingly integrated, multi-level, and multidisciplinary, and that link inflammatory and related processes with important health outcomes.

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