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Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters

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ABSTRACT

Behavioral researchers have increasingly become interested in the idea that chronic, low-grade inflammation is a pathway through which social and behavioral variables exert long-term effects on health. Much research in the area employs putative inflammatory biomarkers to infer an underlying state of inflammation. Interleukin 6 (IL-6) and C-reactive protein (CRP, whose production is stimulated by IL-6) are arguably the two most commonly assayed biomarkers. Yet, in contrast with near-universal assumptions in the field, discoveries in immunology over the past two decades show that neither IL-6 nor CRP are unambiguous inflammatory markers. IL-6 operates through two distinct signaling pathways, only one of which is specifically upregulated during inflammation; both pathways have a complex range of effects and influence multiple physiological processes even in absence of inflammation. Similarly, CRP has two isoforms, one of which is produced locally in inflamed or damaged tissues. The other isoform is routinely produced in absence of inflammation and may have net anti-inflammatory effects. We propose a functional framework to account for the multiple actions of IL-6 and CRP. Specifically, we argue that both molecules participate in somatic maintenance efforts; hence elevated levels indicate that an organism is investing in protection, preservation, and/or repair of somatic tissue. Depending on the state of the organism, maintenance may be channeled into resistance against pathogens (including inflammation), pathogen tolerance and harm reduction, or tissue repair. The findings and framework we present have a range of potential implications for the interpretation of empirical findings in this area—a point we illustrate with alternative interpretations of research on socioeconomic status, stress, and depression.

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1. Introduction

An important goal of the behavioral sciences is to understand the physiological mechanisms through which environmental factors influence behavior and health. Increasingly, researchers have focused on the immune system and particularly on *inflammation*, a nonspecific response against actual or potential infections. Inflammatory pathways are intertwined with those that regulate stress and metabolism; for this reason, inflammation can be a physiological nexus though which a wide range of psychosocial, socioeconomic, and nutritional factors exert their effects. These factors do not produce the high-intensity inflammatory responses that occur in acute infections but rather have been linked to chronic states of "low-grade" activation of the same biochemical pathways (see Fagundes and Way, 2014; Kuhlman et al., 2017; Miller et al., 2011; Minihane et al., 2015).

Inflammation is an intricate process involving dozens of molecules. The majority of studies in this area have employed two functionally linked biomarkers—the cytokine *interleukin 6* (IL-6) and the acute phase protein *C-reactive protein* (CRP), whose production in the liver is stimulated by IL-6. These molecules are easy to detect in serum and are secreted in large amounts during infections. In the behavioral literature, IL-6 and CRP are unanimously regarded as inflammatory biomarkers, and both are commonly used to assess the presence and severity of low-grade inflammation (e.g., Baumeister et al., 2016; Fagundes and Way, 2014; Miller et al., 2011). Recent examples with a focus on psychosocial factors include studies of the effects of financial stress on inflammation (Sturgeon et al., 2016), developmental trajectories of stress exposure and inflammation in adolescence (Ehrlich et al., 2016), and inflammation as a mediator between stressful life events across the life course and telomere length in middle age (Osler et al., 2016). Large-scale epidemiological studies and meta-analyses yield evidence for robust associations of IL-6 and CRP with mortality outcomes due to a variety of causes, including cancer, cardiovascular disease, and metabolic syndrome (e.g., Schnabel et al.,

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2013; Singh-Manoux et al., 2017; Li et al., 2017), with some associations likely being stronger in men (e.g., cancer; Li et al., 2017).

Despite scholars within the behavioral sciences treating and utilizing IL-6 and CRP as markers of inflammation, each with pro-inflammatory effects, recent research in immunology questions this assumption. As we discuss in detail below, IL-6 acts through two distinct signaling pathways; depending on which one operates, it may be part of an inflammatory response or have effects in absence of inflammation. Indeed, some effects of IL-6 are best described as *anti-* rather than pro-inflammatory. Likewise, CRP is involved in inflammation but also in many other processes related to tissue maintenance, and plays both pro- and anti-inflammatory roles within the immune system. Its varied roles partly stem from the fact that CRP exists in two isoforms with markedly different functions, only one of which (the one less strongly tied to inflammation) is routinely measured in the behavioral and biomedical literature. These important findings are widely recognized in the field of immunology but virtually never appreciated in the behavioral sciences.

Our first goal in this paper is to summarize relevant findings from the immunological literature concerning the multiple functions of IL-6 and CRP. These findings challenge the idea that IL-6 and CRP are simply "inflammatory biomarkers," and suggest that moderately elevated levels of these molecules may reflect physiological states other than low-grade chronic inflammation. To gain more insight into the possible alternative interpretations of elevated IL-6 and CRP, we then place the action of these molecules in a broader functional perspective by (a) framing immunity and tissue repair as two overlapping aspects of *somatic maintenance*, the organism's investment in the integrity and functionality of the body (Del Giudice et al., 2015; Roff, 2002); and (b) considering the key distinction between *resistance* and *tolerance* in the immune response to pathogens (Ayres and Schneider, 2012; Medzhitov et al., 2012). Drawing on this framework, we discuss the implications for research examining associations between environmental factors and elevated IL-6 and CRP. We illustrate our points by considering possible alternative interpretations of empirical findings on the immunological correlates of socioeconomic status, stress, and depression.

2. Inflammation

Inflammation is a nonspecific immune response to actual or potential infections (see Ashley et al., 2012; Lochmiller and Deerenberg, 2000; Parkin and Cohen, 2001). In an acute inflammatory reaction, molecular patterns that indicate microbial invasion, tissue damage, or exposure to foreign particles are detected and trigger an inflammatory response. The response is coordinated by a number of cytokines, the signaling proteins of the immune system. Among the most important cytokines involved in inflammation are *interleukin 1 beta* (IL-1β), *interleukin 17* (IL-17), *tumor necrosis factor alpha* (TNF-α), and IL-6. At a systemic level, acute inflammation triggers fever and sickness behaviors, as well as secretion of acute phase proteins by the liver (including CRP). Glucose levels in the blood are elevated through temporary insulin resistance; glycolysis, lipolysis, and proteolysis are accelerated to sustain the increase in metabolic rate caused by fever and upregulated protein synthesis. Locally, inflammation is marked by swelling (caused by increased vascular permeability), pain (caused by stimulation and damage to nerve endings), redness, and heat (caused by vasodilation). The presence of redness and heat gives rise to the name "inflammation," from Latin for "setting on fire".

More specifically, PAMPs (*pathogen-associated molecular patterns*; e.g., viral DNA, bacterial lipopolysaccharides) and DAMPs (*danger-associated molecular patterns*; e.g., uric acid, reactive oxygen species) are detected by inflammasomes present within a variety of cells including macrophages, neutrophils, and endothelial cells. When activated, these structures in turn activate IL-1β (Martinon et al., 2009). In the nervous system, this cytokine leads to fever and increased pain sensitivity. IL-1β also prompts vasodilation, and increases expression of adhesion molecules in the endothelium, which promotes infiltration of immune cells into affected tissue (Dinarello, 2009). PAMP and DAMP detection also leads to activation of TNF-α, another potent mediator of inflammation. TNF-α adheres to cell surfaces, and has autocrine and paracrine effects. Activation of the specialized metalloproteinase ADAM17 cleaves TNF- α from cell surfaces and renders it soluble in plasma. Like IL-1β, circulating TNF- α induces fever, increases blood glucose levels, and impairs insulin signaling, thereby leading to insulin resistance (which maintains high blood glucose levels available for immune cells; e.g., Straub et al., 2010).

At the cellular level, inflammatory cytokines recruit neutrophils and monocytes, which then differentiate into macrophages. Neutrophils ingest pathogens and infected cells, which they kill by releasing toxic chemicals such as proteinases and reactive oxygen and nitrogen species. In addition, neutrophils release antimicrobial compounds in the plasma and secrete cytokines that further amplify the inflammatory response. Inflammation also activates the *complement system*, a cascade of acute phase proteins that kill cells by forming pores in their membranes, increase vascular permeability, and perform other support functions. The early phase of inflammation entails marked collateral damage to surrounding tissues, which are attacked in a relatively indiscriminate fashion. It aims to rapidly destroy or isolate the source of threat, but does so at the cost of significant self-harm. In the resolution phase, neutrophils are replaced by monocytes and macrophages, wound healing is initiated, and homeostasis is eventually restored.

A notable feature of inflammation is its high energetic cost. During acute infections, the metabolic rate typically increases by 25–50%. About half of the extra energy is allocated to the synthesis of acute phase proteins in the liver. Severe infections with high fever can double the metabolic rate and, when persistent, lead to a 15–30% loss of body weight over time. Importantly, the costs of inflammation include the disposal and repair of damaged tissue in the resolution phase. Macrophages are energetically demanding cells; more generally, cell-mediated immunity is strongly compromised by malnutrition, a point to which we return below (Lochmiller and Deerenberg, 2000; McDade, 2003; Straub et al., 2010).

2.1. Chronic inflammation

In addition to these acute inflammatory responses, individuals may experience chronic inflammatory states. In such a condition, pro-inflammatory pathways fuel low-grade levels of inflammatory response, often in absence of a specific inflamed tissue (hence, in a systemic fashion). Multiple potential sources maintain chronic inflammation, including persistent low-level infections, autoimmune conditions, dietary components that upregulate pro-inflammatory pathways, and obesity. Chronic inflammatory conditions have recently received much attention in the psychological and behavioral literatures. They have been argued to be associated with exposure to stressors, including psychosocial stress, traumatic life events, and childhood adversity (e.g., Baumeister et al., 2016; Fagundes and Way, 2014; Kuhlman et al., 2017; Miller et al., 2011). They may be implicated in mental disorders, such as depression and schizophrenia (e.g., Berk et al., 2013; Fernandes et al., 2016; Miller and Raison, 2016). And they may arise from lifestyle factors, including unbalanced diet and lack of exercise (e.g., Bosma-den Boer et al., 2012; Minihane et al., 2015; Ruiz-Núñez et al., 2013). In many cases, the presence of chronic inflammation is inferred from moderate elevations in IL-6 and CRP, although

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