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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

other cytokines (such as IL-1β and TNF-α) are also sometimes assessed. Importantly, chronic inflammation involves processes similar to acute inflammation, albeit at reduced rates (and at systemic rather than local levels). Specifically, chronic inflammation causes tissue damage, even if it also entails processes that repair this damage. Indeed, a key reason why chronic inflammation is of key interest to behavioral scientists is because the damage it inflicts ultimately threatens the person's long-term health. In this paper, we show how newer findings on the role of IL-6 and CRP call the received view into question, and suggest that some states associated with moderately elevated levels of these molecules (in absence of other unambiguous inflammatory markers) may not be well characterized as low-grade inflammation.

3. Rethinking the role of IL-6

When inflammation is triggered, IL-6 is released into circulation (by neutrophils and macrophages, as well as resident cells at the site of infection or damage), partly induced by IL-1β and TNF-α. One major effect of IL-6 is to stimulate the production of CRP and other acute phase proteins (e.g., serum amyloid P component, serum amyloid A, fibrinogen, ferritin) in the liver and their release into the bloodstream. IL-6 similarly stimulates production of neutrophils in bone marrow, which are then attracted to the site of infection. It upregulates metabolism, partly by promoting lipolysis in the liver. It furthermore induces proteolysis in muscle, thereby making available amino acid building blocks for protein synthesis (Lochmiller and Deerenberg, 2000). And, as it crosses the blood-brain barrier, IL-6 induces changes in the body temperature set-point in the hypothalamus, leading to fever. For these reasons, IL-6 has long been thought to be a pro-inflammatory cytokine and, more generally, a reliable biomarker of inflammation.

The roles of IL-6 in the inflammatory response are varied. In addition to the initial effects just described, IL-6 suppresses neutrophil-attracting chemokines and enhances production of monocyte-attracting chemokines (Scheller et al., 2011). As such, IL-6 plays a crucial role in the transition from an initial neutrophil-mediated immune response to a macrophage-mediated response. IL-6 furthermore encourages differentiation of T-cells and B-cells, thereby leading immune responses to be increasingly targeted to infected cells (e.g., through cell-mediated attack via CD8+ T-cells) and cells exhibiting particular foreign antigen-specific profiles (via antibody-mediated responses via B-cells and CD4+ cells; Chalaris et al., 2011; Schaper and Rose-John, 2015; Scheller et al., 2011). IL-6 regulates the production of macrophage types and, under many circumstances, favors production of M2 types, which are involved in tissue repair, over production of M1 types, which are pro-inflammatory (Mauer et al., 2015). Finally, *in vitro* studies indicate that IL-6 inhibits release of IL-1β and TNF-α (Akira et al., 1990; Schindler et al., 1990), such that IL-6 elevation during inflammation may contribute to a negative feedback loop that ultimately contributes to dampen or terminate the response. These effects underscore the need to distinguish a cytokine's status as a biomarker of inflammation, given its participation in (and elevation during) inflammatory responses, and the specific roles in inflammation the cytokine plays, whether they be pro-inflammatory, anti-inflammatory, or repair-oriented. IL-6 plays all three kinds of roles, initially instigating certain tissue-damaging inflammatory reactions, but ultimately contributing to its resolution and the initiation of tissue repair (e.g., Fuster and Walsh, 2014).

3.1. Two pathways of IL-6 signaling

The past two decades have brought substantial progress toward understanding the molecular physiology of IL-6 (for reviews, see Scheller et al., 2011; Schaper and Rose-John, 2015). Notably, IL-6 signals through two distinct signaling pathways, the *classic signaling pathway* and the *trans-signaling pathway*. IL-6 in general exerts its effects by binding to a single receptor, IL-6R. The complex formed by IL-6 and IL-6R then binds to a specific signal-transducing membrane protein, gp130, instigating a signaling cascade that modulates cellular function (Scheller et al., 2011). In classic signaling, IL-6 binds to membrane-bound IL-6R. Membrane-bound IL-6R receptors are found in a limited number of cell types. Dense concentrations can be found in hepatocytes. Some epithelial cells (e.g., in the lungs) express them, as do some leukocytes (e.g., Rose-John et al., 2017). The dose response curve in this form of membrane-mediated signaling appears to be bell-shaped; hence, maximum cellular response is achieved at moderate levels of IL-6.

Under special conditions, IL-6R receptors cleave off from cell membranes, diffuse into plasma, and circulate in the bloodstream. These *soluble* receptors (sIL-6R) set the stage for IL-6 trans-signaling. The large majority of sIL-6R derives from cleavage, whereas a small proportion (about 10%) is synthesized by alternative splicing of the same messenger RNA that codes for IL-6R. Though the distribution of membrane-bound IL-6R is very limited in scope, gp130 is nearly ubiquitously found on cells. Once circulating IL-6 binds to circulating sIL6-R, the complex can bind to any tissue, instigate a signaling cascade, and, accordingly, affect cellular activity (Chalaris et al., 2011; Schaper and Rose-John, 2015; Scheller et al., 2011). Hence, whereas IL-6 classic signaling affects only certain tissues, IL-6 trans-signaling affects a much wider range of cell types.

A key question is, what are the special conditions under which sIL-6R cleaves off and circulates, thereby potentiating IL-6 trans-signaling? The answer appears to be, primarily, the conditions that give rise to an inflammatory cascade. Cleavage is triggered by pro-inflammatory cytokines such as IL-1β and TNF-α, bacterial toxins, and molecular cues of cell damage, largely mediated (to current knowledge) by the specialized metalloproteinase ADAM17, which is also responsible for shedding TNF- α into plasma (Scheller et al., 2011). Hence, during inflammatory episodes, IL-6 trans-signaling is powerfully upregulated; outside of these conditions, it operates at low levels and classic signaling predominates.

Within an inflammatory bout, classic and trans- pathways both play roles, albeit different ones. Through classic signaling in the liver, IL-6 upregulates the synthesis of acute phase proteins such as CRP, as well as lipolysis. Trans-signaling appears to mediate IL-6′s effect on sickness behavior and induction of fever in the brain (Burton et al., 2011). Locally, classic signaling stimulates the initial recruitment of neutrophils, which express membrane-bound IL-6R. Subsequently, however, neutrophils shed sIL-6R from the membrane, promoting the recruitment of monocytes and macrophages through trans-signaling. Hence, trans-signaling contributes to the resolution phase through monocyte and macrophage recruitment. The shift toward trans-signaling is exaggerated by the high levels of IL-6 released during an inflammatory response; the bell-shaped dose response curve of classic signaling means that, as circulating IL-6 reaches high concentrations, its effects through classic signaling pathways weaken. In addition, pro-inflammatory cytokines IL-1β and TNF-α modify the downstream effects of IL-6 signaling on the synthesis of acute phase proteins, promoting the expression of "class I" proteins such as CRP and complement factors, while suppressing that of "class II" proteins such as fibrinogen and α2-macroglobulin, which are involved in blood coagulation and tissue repair (Garbers et al., 2012; Samols et al., 2001).

In light of these contrasting roles, it is perhaps not surprising that studies of humans and non-human animals strongly imply, through direct experimental manipulation or strong correlational methods, that many deleterious health outcomes associated with

high levels of IL-6 in humans are mediated by IL-6 trans-signaling, not IL-6 classic signaling. Examples include heart dysfunction (e.g., Szabo-Fresnais et al., 2010; Velásquez et al., 2015), development and progression of various cancers (e.g., Brooks et al., 2016; Lo et al., 2011), degenerative effects on brain tissue (Campbell et al., 2014), Alzheimer's disease (Haddick et al., 2017), and periodontal disease (Hosokawa et al., 2014). We nonetheless stress a very important point: when an inflammatory state is absent, IL-6 can still function as a signaling molecule and affects cellular processes. During inflammatory states, trans- but not classic signaling is greatly upregulated. But even in absence of inflammation, IL-6 regulates multiple physiological processes; these effects occur mainly via classic signaling, though a certain degree of trans-signaling occurs in non-inflamed states, particularly in the central nervous system (see below). We now turn to discuss what IL-6 does when inflammation is absent.

3.2. IL-6 signaling in absence of infection or damage

3.2.1. Muscle use and IL-6 secretion

Another major development in our understanding of IL-6 concerns its release in skeletal muscle. IL-6 is secreted in large amounts by muscle tissue following intense exercise. Indeed, muscle use can result in a 100-fold increase in circulating levels of IL-6. Though this effect was initially ascribed to muscle damage, it has since become clear that exercise-induced IL-6 secretion occurs even in absence of damage. Perhaps a more powerful determinant of IL-6 production levels is the depletion of glycogen stored in muscle tissue (Pedersen and Febbraio, 2012). Pre-exercise depletion of glycogen in muscles results in a more robust IL-6 response, while carbohydrate ingestion during exercise reduces secretion of IL-6 from muscles (e.g., Steensberg et al., 2001; Nieman et al., 2003). Exercise-induced IL-6 secretion is not accompanied by elevated IL-1β and TNF-α; on the contrary, it stimulates release of the anti-inflammatory cytokine *interleukin 10* (IL-10) and a powerful inhibitor of IL-1 activity, the *interleukin 1 receptor antagonist* (IL-1ra; Gabay et al., 2001; Kasapis and Thompson, 2005; Petersen and Pedersen, 2006). Consistent with expectation, IL-6 has systemic effects mediated through classic signaling, notably in the liver. Acute phase proteins such as CRP are released—though in these instances "acute phase" is a misnomer, given the complete absence of acute inflammation. Furthermore, IL-6 has notable metabolic effects, as it stimulates lipolysis and release of energy sources into the bloodstream. At the same time, it stimulates insulin secretion and sensitivity (Scheller et al., 2011). It thereby promotes a shift from catabolic, glucagon-dependent pathways to anabolic, insulin-dependent pathways, which leads glucose to be absorbed by muscle and contributes to recovery (Mauer et al., 2015). During exercise, IL-6 prompts muscle to utilize fatty acids. Notably, regenerative processes in epithelial tissue (e.g., in the intestine) also seem to depend on classic IL-6 signaling (Chalaris et al., 2011; Garbers et al., 2012).

3.2.2. Production of IL-6 in adipose tissue

Adipocytes secrete IL-6 systemically, leading to increases in IL-6 levels in circulation. As adipocytes fill up with fatty acids, adipose tissue becomes increasingly infiltrated by macrophages. Both adipocytes and, to a greater extent, macrophages in this tissue secrete IL-6. Hence, adipocyte-triggered increases in circulatory IL-6 tend to be proportional to the total fat mass. This fact is widely recognized within the behavioral health literature, where it has generally been assumed that IL-6 production by adipose tissue reflects low-grade inflammation. As the literature clearly says, however, the effects of IL-6 can also be anti-inflammatory or repair-oriented. Whether its adipose-derived levels do or not reflect inflammation depends on the levels of other pro-inflammatory cytokines and whether IL-6′s actions mainly involve trans- or classic signaling.

The answer appears to be "both": though IL-6 secreted by adipose tissue sometimes reflects low-grade inflammation, it does not always do so. Adipose tissue does produce other pro-inflammatory cytokines as well, notably TNF-α. But under many conditions TNF- α, in contrast to IL-6, does not circulate and has only autocrine and paracrine effects. ADAM17, the enzyme that produces shedding, is suppressed by two other regulators, TIMP3 and *caveolin-1* (e.g., Dou et al., 2015). Suppression of ADAM17 also should lead sIL-6R levels to remain relatively low. Under these conditions, IL-6 signaling induced by production of adipocytes should occur mainly through the classic pathway, thereby leading to increases in circulating levels of acute phase proteins and affecting metabolism via lipolysis and insulin sensitivity. Indeed, transgenic mice with *deficits* in IL-6 signaling tend to experience insulin resistance, inflammation in the liver, and weight gain; on the contrary, the presence of IL-6 leads to increased insulin sensitivity, with a net *protective* effect against obesity (Scheller et al., 2011; Mauer et al., 2015). In line with this view, other studies indicate that IL-6 suppresses feeding in obese mice (Timper et al., 2017). The effect of IL-6 on food intake appears to be mediated by local trans-signaling in the central nervous system, as obese mice show elevated levels of soluble sIL-6R in the cerebrospinal fluid (Timper et al., 2017). This points to the possibility that, even in absence of inflammation, some actions of IL-6 in the central nervous system may be primarily mediated by trans-signaling.

When TNF-α is shed in fat tissue and circulates, often along with sIL-6R, an inflammatory state ensues. But then shedding of TNF-α and/or sIL-6R is responsible for insulin resistance and fat scarring, rather than IL-6 elevation *per se* (e.g., Fiorentino et al., 2010; Krogh-Madsen et al., 2006; Matsui et al., 2014; Mavilio et al., 2016). One question of interest concerns the conditions under which shedding of TNF-α and sIL-6R from fat tissue occurs. In elderly populations, total fat mass may be particularly associated with these pro-inflammatory biomarkers, an effect one research team attributed to age-related decline in caveolin-1 levels (Dou et al., 2017). Others have speculated that senescence increases the rate of internal danger signals (DAMPs) triggering inflammatory states, or that adipocyte death in aging fat tissue increases the rate of macrophage infiltration (Bai and Sun, 2015; Goldberg and Dixit 2015). Obesity, a condition in which fat cells become pathologically enlarged, may similarly promote inflammation (e.g., high sIL-6R levels; McFarlin et al., 2007). In obesity, adipose tissue is infiltrated by large numbers of macrophages, and macrophages that secrete IL-6 usually display the pro-inflammatory phenotype M1, a mechanism through which obesity can lead to chronic inflammation (Akira et al., 1990; Cua and Tato 2010; Lochmiller and Deerenberg, 2000; Mauer et al., 2015; Mohamed-Ali et al., 1997). Interestingly, IL-6 is mainly secreted by macrophages with a pro-inflammatory M1 phenotype, but stimulates a shift toward the anti- inflammatory M2 phenotype (Mauer et al., 2015). This suggests that IL-6 may play a homeostatic role in the regulation of macrophage populations in adipose tissue.

In younger populations, increases in fat mass across a wide range (excluding obesity) may produce increases in IL-6 levels but not high levels of circulating TNF-α or sIL-6R. Hence, for instance, one study compared identical twins whose BMI differed. The twin with the greater BMI experienced higher levels of circulating IL-6, but not TNF-α (Van Dongen et al., 2015). A large population study yielded a robust moderate association between BMI and IL-6 levels, but a very modest association between BMI and TNF-α levels (Himmerich et al., 2006). In many cases, then, elevated fat-derived IL-6 exerts effects largely through classical signaling, whereas—as noted above—most of the deleterious health outcomes associated with IL-6 are mediated by trans-signaling.

4. Rethinking the role of CRP

CRP is an acute phase protein produced in the liver and secreted into the bloodstream during an inflammatory episode, largely in response to IL-6 signaling (and, to a lesser extent, IL-1β and other pro-inflammatory cytokines). As IL-6 rises during acute inflammation, the concentration of CRP in plasma increases dramatically too, from less than 1 μg/mL to up to 1000 μg/mL in severe systemic infections or extensive burns. CRP levels begin to rise 4–6 h after the start of infection and peak about 1–2 days later (Schmit and Vincent, 2008). As noted above, the synthesis of CRP and other acute phase proteins contributes significantly to the energetic cost of inflammation. Like IL-6, CRP plays a variety of key roles during an inflammatory bout. It binds to damaged, necrotic, and microbial cells; promotes phagocytosis by neutrophils and macrophages; and activates the complement system, which itself helps maintain inflammation. Rising CRP concentrations furthermore activate neutrophils and monocytes, and promote the secretion of IL-6, IL-1β, and TNF-α (Black et al., 2004; Du Clos and Mold, 2004). Because of these effects, CRP has been classically regarded as a pro-inflammatory molecule. At the same, CRP has some *anti*-inflammatory effects: it stimulates release of anti-inflammatory agents such as IL-10 and IL-1ra and, while activating the complement system, it also recruits a number of complement inhibitors, possibly in a time-dependent manner (Mihlan et al., 2011). As a result, the net unfolding effect of CRP *in vivo* appears to be weakly anti-inflammatory (Eisenhardt et al., 2009; Pagano et al., 2012). And, as we discussed above, IL-6 classic signaling—through which IL-6 stimulates production of acute phase proteins such as CRP—can occur in complete absence of inflammation. On these occasions, CRP participates in wound healing, tissue repair, and clearance of damaged cells.

Over the past decade, many apparent inconsistencies concerning the physiological roles of CRP have been clarified thanks to the discovery that this protein exists in two isoforms with different functions, a *pentameric* isoform synthesized by the liver and a *monomeric* isoform that is activated by local cues of inflammation and tissue injury (Eisenhardt et al., 2009; Thiele et al., 2014; Trial et al., 2016).

4.1. Two CRP isoforms

When CRP is secreted by the liver, it consists of five identical subunits arranged in a ring. This pentameric isoform of CRP (pCRP) is a highly soluble molecule that diffuses in plasma and has a range of largely anti-inflammatory effects. pCRP is mainly involved in the resolution phase of inflammation, and induces the anti-inflammatory M2 phenotype in macrophages. While pCRP can activate the complement cascade, it also recruits complement inhibition factors that may function to limit indiscriminate tissue damage (Eisenhardt et al., 2009; Mihlan et al., 2011; Trial et al., 2016). When pentameric CRP comes into contact with cues of damage or ongoing inflammation (e.g., oxidized lipids from cell membranes), the five subunits dissociate irreversibly, giving rise to the momomeric isoform of CRP (mCRP). In contrast with the pCRP isoform, mCRP has a number of highly pro-inflammatory effects. It stimulates secretion of pro-inflammatory cytokines, induces the M1 phenotype in macrophages, and promotes the release of reactive oxygen species, which function to debilitate pathogens but also exact collateral damage on host tissue (Eisenhardt et al., 2009; Thiele et al., 2014; Trial et al., 2016). While mCRP activates the complement, it also blocks the final stages of the cascade in presence of certain inhibitory factors. This mechanism may permit a tightly controlled activation of the complement during the non-inflammatory removal of damaged cells (Mihlan et al., 2011). Importantly, mCRP is not soluble in the plasma and tends to remain localized in the inflamed tissue.

While pCRP has a range of physiological effects in its original form, it also effectively acts like a "sensor" of local inflammations. When cues of active inflammation are detected, the net effects of CRP radically change, as the dissociation of pCRP into mCRP promotes a positive feedback loop that further amplifies the local inflammatory state. In later stages of an inflammatory response, mCRP may actually contribute to resolve the inflammation by recruiting complement inhibitors and stimulating coagulation (Mihlan et al., 2011; Xu et al., 2015). However, pCRP—which accumulates with the transition from an innate to an acquired immune response—likely makes the largest contribution to the resolution phase, by inducing M2 macrophages and thereby promoting tissue repair and wound healing (Trial et al., 2016).

When IL-6 is secreted in absence of active inflammation, the majority of pCRP synthesized and secreted by the liver will remain in the pentameric form, as the monomeric form is produced only when local cues of damage or active inflammation are encountered. Under these circumstances, then, the functions of CRP will largely carry out in the arena of tissue maintenance and repair, and its net effects will be anti-inflammatory. Here we see parallel changes in modes of function of IL-6 and CRP during inflammatory and non-inflammatory episodes: during inflammatory bouts, IL-6 partly operates through trans-signaling and CRP appears in its monomeric form (mCRP); when inflammation is absent, IL-6 operates almost exclusively through classic signaling and CRP appears mainly in its pentameric form (pCRP).

As mentioned above, mCRP is not freely soluble in plasma, and tends to deposit on microparticles (vesicles formed by membrane lipids and other internal cell structures). As a result, the standard assays employed to measure plasma or salivary CRP in virtually all the behavioral and biomedical studies to date do not detect mCRP, and exclusively reflect levels of pCRP (Trial et al., 2016). Of course, extremely high concentrations of pCRP are likely to indicate an acute inflammation, despite pCRP *per se* not being pro-inflammatory. But moderate levels of circulating pCRP need not indicate the presence low-grade chronic inflammation, contrary to what has been widely assumed in the literature.

5. A Functional perspective

In the preceding sections, we provided an up-to-date summary of the many physiological actions of IL-6 and CRP, both during acute inflammation and in absence of an inflammatory reaction. The findings we reviewed are inconsistent with simple pro-inflammatory accounts in the prevailing behavioral literature. At the same time, these findings currently lack an alternative theoretical account. In an effort to address this lacuna, we now draw on concepts from life history theory and theoretical immunology to place the actions of IL-6 and CRP in a coherent functional perspective.

5.1. Somatic maintenance

All organisms harvest energy and other resources from the environment and convert them into fitness-enhancing activities (via effects on survival and reproduction). Selection favors organisms that efficiently capture energy and effectively allocate it to enhance fitness (i.e., the replication of one's genes across generations) within their particular ecological niche. Because energy, time, and resources are intrinsically limited, each individual lives within a finite energetic "budget"—itself earned through energy and time expenditures—and can never spend more than it has available. Allocation of a finite budget entails trade-offs and hence forces

decisions about the relative value of possible ways to spend. Increasing one's chances of survival by investing in a costly immune system reduces the amount of resources that can be channeled into reproduction; delaying reproduction to build a larger body and develop effective skills increases the risk of dying before ever reproducing; and so on. Trade-offs in the allocation of energy and resources are the subject matter of *life history theory* (LHT), a branch of theoretical biology (see Del Giudice et al., 2015; Roff, 2002).

From the perspective of LHT, a key phenotypic feature of organisms is their allocation strategy – the ways that they manage their "household budgets" and allocate it to specific fitness-enhancing activities. Selection favors allocation strategies that optimally invest effort into particular activities, that is, maximize fitness under the constraint of a limited budget. In fact, because optimal allocations depend on characteristics of an individual and its environment, an optimal allocation strategy consists of a menu of allocation specifications, which are contingent on those characteristics. Hence, for instance, newborns optimally allocate energy differently from adults; healthy individuals optimally allocate differently from those infected with disease; the best allocation strategy for individuals in stable circumstances differs from that of individuals whose future circumstances are highly unpredictable. Selection should favor allocation strategies that lead these features, and many more, to moderate allocation decisions.

One fundamental trade-off in the life history of an organism is that between *somatic effort* and *reproductive effort*. Reproductive effort includes mating, parenting, and all the activities that directly promote the replication of the individual's genes. Somatic effort is investment in the organism's body (including the brain and its repertoire of knowledge and skills), which enhances reproduction indirectly by increasing the individual's ability to forage, compete, and produce offspring. Within the broad domain of somatic effort one can further distinguish between *growth* and *maintenance*; allocations to growth build a larger or stronger body, whereas allocation to maintenance preserves the integrity and functionality of one's body through metabolic processes, tissue repair, and immune defense from pathogens. Somatic maintenance trades off against growth, first, because both require energy and molecular resources (e.g., amino acids for protein synthesis) and, second, because a larger body entails proportionally higher maintenance costs. In turn, somatic effort (which includes both growth and maintenance) trades off against reproduction. From a LHT perspective, selection "sees" and favors abstractly-defined resource allocation strategies. In real bodies, however, abstract allocations are carried out by physiological structures and systems. Selection on allocation strategies shapes these physiological systems to allocate resources in ways favored by selection. A LHT perspective hence leads us to seek to understand CRP and IL-6 in terms of how the systems in which they are embedded manage and direct resource allocations.

5.1.1. IL-6 and CRP as maintenance mechanisms

IL-6 and CRP participate in two kinds of activities, immunity (e.g., fighting and walling of the effects of pathogens) and tissue repair (e.g., disposal of dead or damaged cells by macrophages, formation of fibrous tissue). Both activities are components of somatic maintenance (McDade, 2003). Naturally, then, IL-6 and CRP participate in somatic maintenance. In addition, IL-6 appears to actively promote it, by stimulating the allocation of energetic resources and nutrients toward immunity and repair. As discussed above, IL-6 mobilizes energy through lipolysis and amino acids through proteolysis; these metabolic effects help sustain the remarkable costs of inflammation and tissue repair. In addition to directly mobilizing resources, Il-6 channels those resources toward maintenance by stimulating the synthesis of CRP and other acute phase proteins. More specific allocations to different aspects of maintenance (e.g., inflammation vs. tissue regeneration) are mediated by the interplay between the classic and trans-signaling pathways, and further modulated by the simultaneous presence of pro-inflammatory cytokines such as IL-1β. (As noted above, these cytokines stimulate fever, bias protein synthesis in the liver toward class I acute phase proteins, and more generally shift the actions of IL-6 in a pro-inflammatory direction.)

Production of IL-6 in adipose tissue may be fruitfully interpreted from this perspective. Energy stored in adipocytes is not immediately being used for growth or reproduction. It represents energy consumed exceeding immediate demands, which is then stored for future allocation. The more stored energy available to an organism, the larger the amount that can be allocated to ongoing maintenance functions, consistent with formal models of optimal resource allocation (Houston et al., 2007). IL-6 production in macrophages residing in adipose tissue, then, can be regarded as a state-dependent allocation mechanism: the greater the amount of fat stored, the greater the IL-6 production, the greater the metabolic tapping of fat (via IL-6 stimulated lipolysis) to sustain somatic maintenance effort. The fact that, in obese mice, IL-6 activity actually contributes to fat loss is evidence for this role.

Leptin is a hormone with marked structural and functional similarity to IL-6; indeed, leptin and IL-6 receptors are phylogenetically closely related, having derived from a common structure and then evolved to acquire overlapping but partly distinct roles (Fantuzzi and Faggioni, 2000; Zhang et al., 2005). Leptin is mainly secreted by adipocytes and functions as an endocrine indicator of energetic status. Perhaps its most widely recognized function is to suppress appetite. Yet leptin also plays a role in allocating energetic resources. Circulating levels of leptin modulate cytokine production and cell-mediated immunity, particularly with respect to T lymphocytes. As noted earlier, cell-mediated immunity is especially sensitive to malnutrition and starvation; this effect is partly mediated by dropping levels of leptin following food deprivation (Fantuzzi and Faggioni, 2000; McDade, 2003; Rauw, 2012). Leptin is secreted during inflammation, has anti-obesity effects, and contributes to wound healing. Indeed, the leptin receptor regulates the expression of some genes that are also targeted by IL-6 signaling, indicating a certain amount of cross-talk between the two molecules (Baumann et al., 1996; Zhang et al., 2005).

Like leptin, IL-6 too functions as an indicator of energetic status. Higher levels indicate that more energy is available and can be allocated to maintenance functions. At the same time, the two molecules may stimulate somewhat different aspects of somatic maintenance. Whereas leptin appears to be linked to the regulation of T lymphocytes, IL-6 activity may specifically lead to the proliferation and differentiation of macrophages, which are involved in both inflammation and tissue repair. In absence of inflammation, IL-6 may largely stimulate repair (see below). During an inflammatory response, energetic resources are mobilized to fuel an immune response. IL-6 levels at the time of inflammation may be calibrated to the organism's readiness to rapidly allocate significant amounts of energy to the process. Straub et al. (2010) suggested that the rapid elevation of IL-1β during inflammation works as an "energy appeal reaction" that calls for immediate energy allocation to the immune system. From a metabolic perspective, the interplay between IL-6 and IL-1β during the early phase of inflammation might be usefully understood as the interplay between a "readiness signal" provided by IL-6 and an "appeal signal" provided by IL-1β. If so, higher circulating IL-6 before inflammation occurs should predict a stronger and more rapid onset of the inflammatory response to infection.

From this perspective, IL-6 production in adipose tissue stems from mechanisms of *adaptive* metabolic allocation. This view contrasts with the prevailing idea that IL-6 production fundamentally reflects a low-grade inflammatory state, generally thought to reflect maladaptation (i.e., an effect that has not historically been

favored by natural selection). That said, adaptive mechanisms can become dysregulated under some abnormal conditions—specifi cally, in this case, when accumulation of fat depots exceeds the normal range in which adaptive IL-6 metabolic function evolved. As noted above, in conditions of obesity IL-6 production may be excessive. An abnormal number of macrophages may be recruited, resulting in hyperactivated repair processes and/or maladaptive states of chronic inflammation. We do not argue that obesity never leads to a low-grade inflammatory state—but we do stress that elevated IL-6 does not qualify as an unambiguous marker of an inflammatory state. Elevated IL-6 levels are compatible with alternative functional interpretations, including upregulated investment in tissue repair when energy availability is high.

Like IL-6, CRP participates in both pathogen defense and tissue repair during inflammation, as well as tissue repair and regeneration in absence of inflammation. In this framework, CRP may be appropriately understood as a "maintenance protein" with both immune and non-immune functions. The same might well be true of other acute phase proteins, particularly those in class II (e.g., fibrinogen). Fundamentally, then, elevated CRP levels indicate that an organism has increased its allocation of resources (energy, amino acids) to somatic maintenance. Depending on context, heightened maintenance effort may reflect the presence of acute inflammation, low-grade chronic inflammation, or simply a state of upregulated tissue repair and regeneration (for example, following intense exercise). These underlying states are partly differentiated by the amount of circulating CRP but, as discussed earlier, also by the relative proportion of monomeric vs. pentameric CRP and the concentration of pro-inflammatory cytokines such as IL-1β and TNF-α. In a number of large-sample studies, researchers took advantage of the fact that several alleles of the *CRP* gene generate higher levels of CRP, and compared rates of various diseases such as cancer, cardiovascular disease, arthritis, psoriasis, and diabetes in those with genetically higher levels of CRP with those who lacked the CRP-increasing alleles (*Mendelian randomization;* e.g., Allin et al., 2010; Brunner et al., 2008; Marott et al., 2010; Prins et al., 2016; Wium-Andersen et al., 2014). By treating genetic variants as instrumental variables, this design allows researchers to tease apart the causal and non-causal associations between biomarkers and health outcomes. Despite replicating the usual findings that circulating CRP is associated with higher disease rates, genetically influenced increases in CRP failed to predict increased risk for the same disorders. While Mendelian randomization studies have limitations and should be interpreted with some caution (Nitsch et al., 2006; VanderWeele et al., 2014), this evidence is consistent with the notion that pentameric CRP does not cause inflammatory tissue damage.

5.1.2. IL-6 and CRP in traditional populations

A challenge to the idea that elevated IL-6 and CRP indicate upregulated maintenance comes from a study of the Shuar, an indigenous Amazon population living in lowland Ecuador (Mcdade et al., 2012). In a sample of 52 Shuar adults, the authors found no evidence of moderate, stable CRP elevation in the range that is common in the United States and other industrialized countries. This finding is consistent with the hypothesis that chronic, low-grade CRP elevation (interpreted as an inflammation marker) is an evolutionarily novel and likely maladaptive pattern, stemming from lack of childhood exposure to pathogens in the artificially sanitized conditions of industrialized countries (McDade, 2012).

To be sure, a generalized absence of moderate IL-6/CRP elevation in traditional populations would present a stumbling block for our framework, though not a fatal one: for example, it could still be the case that higher IL-6 and CRP in industrialized countries do not *only* reflect chronic inflammation, but also non-inflammatory upregulation of repair mechanisms in response to other sources of tissue damage—such as environmental pollutants, drugs such as alcohol and tobacco, and other toxic chemicals (e.g., Danese and McEwen, 2012). So far, however, the remarkable finding by McDade et al. (2012) has not been replicated in other groups. A number of studies among non-industrialized populations—including Hazda hunter-gatherers from Tanzania, Tsimane horticulturalists from Bolivia, and horticulturalists in rural Ghana—have found IL-6 and CRP levels more in line with Western norms, with somewhat reduced (but not absent) prevalence of low-grade CRP elevation in Ghanian horticulturalists and the Hazda, and higher prevalence in the Tsimane (Blackwell et al., 2016; Koopman et al., 2012; Raichlen et al., 2017). Variation among these studies might be explained by a combination of environmental and genetic factors, in addition to the small size of most samples. Moreover, only the original study by McDade et al. (2012) measured CRP repeatedly over multiple weeks, and thus was able to distinguish with precision between temporary elevations due to acute inflammation from chronic low-grade elevations.

In conclusion, the evidence from traditional populations is not univocal and is still largely based on small samples. To the extent that they will be replicated in larger longitudinal studies, findings of moderate CRP elevation in populations with high pathogen exposure challenge the hypothesis that low-grade CRP elevation is necessarily an inflammation marker, and that it reflects a maladaptive mismatch between our evolved immune system and modern hygienic conditions.

5.2. Immune resistance vs. Tolerance

A general life history framework treats immunity and tissue repair as two overlapping aspects of somatic maintenance. It thereby provides useful insights into the overarching function of IL-6 and CRP. A complementary perspective consider how effective immunity against pathogens depends on the interplay between *resistance* and *tolerance* (Ayres and Schneider 2012; Medzhitov et al., 2012; Råberg et al., 2009; Rauw 2012; Sears et al., 2011).

Resistance and tolerance are two basic strategies an organism can adopt for dealing with pathogen attacks. (Avoiding contact with pathogens and thus preventing attacks before they occur through behavioral adaptations is a third strategy; see Medzhitov et al., 2012; Schaller, 2015.) Efforts at resistance have the straightforward aim of reducing the number of pathogens in the body ("pathogen limitation"). By contrast, tolerance mechanisms aim to reduce impairment and damage to the host without directly attacking pathogens and reducing their numbers ("damage limitation"). Resistance often requires immediate allocation of substantial amounts of energy to immunity (as in inflammation), which generally leads to reduced amount of energy available for other activities. Immune tolerance allows organisms to maintain functionality during infections, and avoids excessive collateral damage from the host's own defensive reactions (Råberg et al., 2009).

Tolerance mechanisms fall into three main classes: *efficiency*, *damage control*, and *pathogen manipulation* (Ayres and Schneider 2012; see also Medzhitov et al., 2012; Råberg et al., 2009). Efficiency mechanisms are designed to avoid overshooting and unnecessary responses to pathogens. They include negative feedback loops that regulate the intensity and duration of the immune response, as well as passive and active "ignorance" mechanisms that prevent responding (e.g., blocking threat detection). Damage control mechanisms prevent and repair tissue damage to the host, which may be inflicted by pathogens or by the host's own immune system. Damage can be prevented by: targeting the toxins produced by the pathogen rather than the pathogen itself (anti-toxin immunity); buffering the effects of dangerous substances released during infection (e.g., through production of antioxidants that

attenuate damage from reactive oxygen species, or increased production of red blood cells in presence of hemolytic toxins); and selecting less aggressive resistance mechanisms with lower potential for collateral tissue destruction (e.g., antimicrobial peptides instead of reactive species; recruitment of the complement through weaker activation pathways). The latter occurs frequently in sensitive, immune-privileged tissues such as the brain, eye chamber, and gonads. Because preventing harm is not always possible, repair mechanisms fix damage after it has occurred. The third class of tolerance is pathogen manipulation, and occurs when the host enacts coexistence strategies such as "blackmailing" the pathogen into a state of lowered virulence, or "bribing" the pathogen so as to limit its spread to certain organs or tissues (e.g., the intestine) and not others. Energy redistribution is sometimes listed as an additional class of tolerance mechanism (Ayres and Schneider 2012), but is probably best regarded as a functionally distinct kind of process—i.e., metabolic regulation—rather than a component of immunity *per se*.

Resistance and tolerance are by no means mutually exclusive. Most immune reactions reflect a combination of resistance and tolerance. Indeed, the same molecule or cell type may contribute to both functions in different phases of the response. Nonetheless, trade-offs between the two strategies exist. Some tolerance and resistance mechanisms are functionally incompatible with one another (e.g., effective tissue repair cannot occur during the acute phase of inflammation). Trade-offs also arise when energetic reserves are limited and cannot fuel both types of mechanisms. Most forms of tolerance and resistance are energetically costly, and require a steady supply of amino acids to sustain protein synthesis. As implied above, the benefits and costs of resistance and tolerance differ. Resistance potentially clears the pathogen and may avoid severe consequences that result from continued infection. But it risks collateral damage and cascades of physiological side effects that may become dangerous in and of themselves (e.g., compromised respiration, altered vascular function). Aggressive resistance mechanisms such as inflammation also necessitate substantial energetic commitments and are accompanied by adaptive mechanisms of sickness behavior; as a consequence, they can incapacitate the individual for days or weeks, resulting in nontrivial opportunity costs (e.g., inability to forage, missed mating opportunities). Greater investment in tolerance avoids or ameliorates many of these side effects. At the same time, infections may become more severe in absence of resistance efforts; moreover, tolerance mechanisms that buffer damage in the short term could lead to loss of tissue functionality in the long run (e.g., through scarring or fibrosis).

5.2.1. IL-6 and CRP as resistance and tolerance mechanisms

In the early phase of inflammation, IL-6 contributes to resistance by stimulating fever, recruiting neutrophils, prompting the synthesis of acute phase proteins, and promoting a positive feedback loop that amplifies the defensive response. Initially, IL-6 performs these functions through the classic pathway, but trans-signaling takes over as inflammatory cytokines rise and sIL-6R is cleaved off from cell membranes. At the same time, the profile of protein synthesis in the liver is biased toward resistance by the action of IL-1β and TNF-α, which promote the expression of class I acute phase proteins such as complement factors and CRP. Local inflammatory states cause the dissociation of pCRP into mCRP, which contributes to resistance by strongly activating the complement system (an aggressive mechanism with high collateral damage), inducing the M1 phenotype in macrophages, and stimulating the release of pro-inflammatory cytokines.

As inflammation proceeds toward resolution, both IL-6 and CRP switch function from resistance to tolerance. Sustained elevation of IL-6 exerts negative feedback on IL-1β and other pro-inflammatory cytokines, an efficiency mechanism that regulates the duration of the inflammatory bout. Similarly, mCRP begins to recruit complement inhibitors, another negative feedback loop that limits the initial phase of indiscriminate attack. IL-6 and CRP also make crucial contributions to damage control. IL-6 mediates the transition from neutrophil-mediated cell destruction to more targeted and less harmful forms of resistance (macrophages, B and T cells). As local inflammatory states subside and pCRP becomes more prevalent in tissues, it exerts anti-inflammatory actions, induces the M2 phenotype in macrophages, and participates in wound healing and tissue repair. Even after acute inflammation has resolved, IL-6 and CRP continue to exert tolerance functions by promoting repair of the damage inflicted by past infections. In addition, constant tissue repair likely helps contain the ever-present populations of microbes and potential pathogens that reside inside and outside the body—for example on the skin, in the digestive tract, and on genital mucosae.

5.3. Summary

To summarize, both IL-6 and CRP participate in processes of somatic maintenance—specifically, immunity and tissue repair. Furthermore, IL-6 promotes maintenance through its metabolic effects (e.g., stimulation of lipolysis). Similar to a related hormone, leptin, IL-6 levels reflect storage of energy in the form of deposited fat. The production of IL-6 in adipocytes, then, may be a mechanism whereby organisms increase allocation to ongoing somatic maintenance, contingent upon availability of stored energy. In total, elevated levels of IL-6 and/or CRP may reflect adaptive allocation of effort to somatic maintenance, even in absence of inflammation. Thought a state of chronic inflammation may underlie elevated levels, moderately elevated levels of IL-6 and CRP can exist in absence of an inflammatory state; they do not *define* an inflammatory state. Fig. 1 shows how various long- and short-term states of the organism can lead to different combinations IL-6, CRP, and inflammatory cytokines such as IL-1β and TNF-α.

Immunity itself involves two main strategies for dealing with pathogens, resistance and tolerance. Typically, immune responses to a pathogen collectively do both. Nonetheless, trade-offs exist. Each strategy has benefits and costs, which dictate state-contingent optimal allocation of effort to each. IL-6 and CRP participate in both kinds of functions (see Fig. 1). Early during an inflammatory response, both enhance efforts to resist pathogens. But both also play crucial roles in the resolution of inflammation, whereby they have important tolerance functions, hastening resolution via negative feedback processes and actively participating in tissue repair.

6. Implications for research

The expanded view of IL-6 and CRP we presented in this paper has important implications for understanding the causal processes that give rise to empirical findings, particularly in areas where these biomarkers have been interpreted by default as indicators of ongoing inflammation. In many such areas, existing findings may hide a considerable amount of heterogeneity. Individuals with moderately elevated IL-6 and/or CRP do not necessarily suffer from chronic low-grade inflammation; in an unknown proportion of cases, this profile may reflect increased investment in tissue repair and immune readiness in absence of ongoing inflammatory processes—a functional state with markedly different implications for theory and intervention. As illustrative examples, we briefly consider three conditions that have been ostensibly associated with inflammation via these biomarkers: low socioeconomic status, stress (both acute and chronic), and depression.

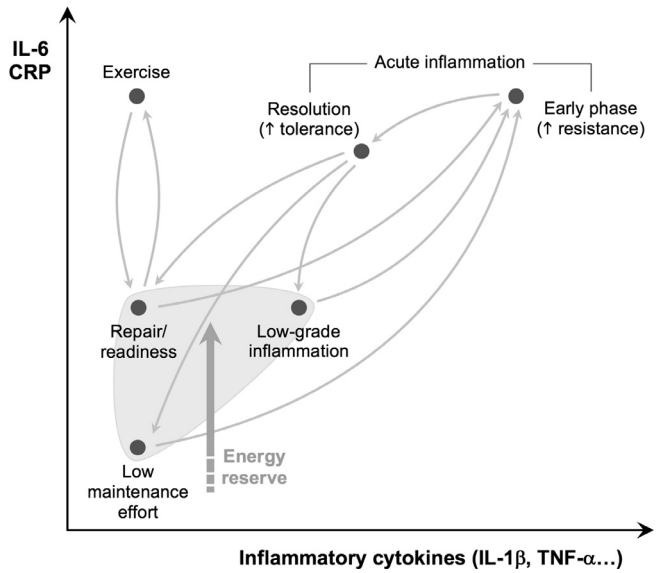

Fig. 1. Schematic illustration of how various states of the organism correspond to different combinations of IL-6/CRP (vertical axis) and inflammatory cytokines such as IL-1β (horizontal axis). Long-term (chronic) states are shown in the shaded area. Arrows represent transitions between states. Moderate levels of IL-6 and CRP in absence of elevated inflammatory cytokines may represent investment in tissue repair and immune readiness, conditional on sufficient energetic reserves. Note that the diagram is not exhaustive, and does not show all the possible states and transitions.

6.1. Example 1: Socioeconomic status

Socioeconomic status (SES) is an important predictor of health: low income and education are systematically associated with higher overall mortality and increased risk for disease (particularly cardiovascular and metabolic conditions) in adulthood and old age (Sommer et al., 2015; Stringhini et al., 2017). A growing literature has focused on chronic inflammation as a critical mediator of these effects. More specifically, low SES increases exposure to various sources of stress and adversity early in life, from unpredictability and disrupted caregiving to violence inside and outside the family. There is evidence that the resulting chronic stress—in combination with other lifestyle factors such as poor nutrition, drinking, and smoking—promotes the development of a "pro-inflammatory phenotype," which in turn contributes to increased rates of disease and mortality (Kuhlman et al., 2017; Miller et al., 2011). (Below we consider the role of cortisol and other stress-related hormones in more detail.)

In support of this model, studies have consistently found a negative correlation between SES and circulating levels of IL-6 and CRP (e.g., Friedman and Herd, 2010; Koster et al., 2006; Stringhini et al., 2013). The correlation between low SES in childhood and elevated CRP in adulthood was confirmed by a recent meta-analysis (Liu et al., 2017). The same analysis found evidence that this correlation is strongly mediated by adiposity (typically measured with the body mass index or BMI), which in developed countries is associated with lower SES. The mediating role of adiposity is consistent with the findings of a study carried out in the Philippines, where socioeconomic variables did not correlate with CRP levels (McDade et al., 2013) whereas BMI did (McDade et al., 2016a). The association between SES and inflammatory cytokines such as TNF-α has been investigated in a smaller number of studies. The available evidence is less consistent than in the case of IL-6 and CRP (e.g., Koster et al., 2006), which suggests that socioeconomic status may affect IL-6 and CRP levels through pathways that do not necessarily involve low-grade inflammation.

A plausible alternative hypothesis is that adverse socioeconomic conditions lead to chronic tissue damage—for example through increased exposure to toxic chemicals, poor nutrition (e.g., low antioxidant intake), lack of sleep, use of alcohol, tobacco, and other drugs, or the "wear and tear" caused by prolonged cortisol elevation (e.g., Danese and McEwen, 2012; Janicki-Deverts et al., 2009; Juster and McEwen, 2015). Especially in presence of abundant energetic resources (deposited fat), cues of chronic tissue damage may trigger the sustained activation of repair mechanisms through elevated IL-6 and CRP (see Fig. 1). Upregulated tissue repair may or may not be associated with inflammation; whether inflammatory cytokines such as IL-1β are also chronically elevated may depend on exposure to pathogens, early infections, and other environmental factors that specifically target the immune system. Hence, while we do not dispute that low SES can be associated with inflammation, it is possible that (a) investment in tissue repair contributes to explain the association between low SES and elevated IL-6 and CRP; and (b) in a certain proportion of low-SES individuals, elevated IL-6 and CRP reflect upregulated tissue repair in absence of chronic inflammation. In general, at least some of the effects of IL-6 and CRP in adverse socioeconomic conditions may turn out to be protective rather than harmful—an adaptive if costly response to widespread tissue damage. Note that, under this alternative hypothesis, it does not follow that higher IL-6 and CRP levels in absence of inflammation should correlate with *better* health. To the extent that IL-6/CRP release is triggered by cues of sustained tissue damage, the overall association should still go in the direction of worse health outcomes. However, one may predict that reducing IL-6 and CRP levels in those conditions (for example via pharmacological intervention) would further worsen health outcomes, rather than ameliorate them as the chronic inflammation hypothesis would predict.

While there are multiple potential pathways from low SES to elevated IL-6 and CRP, a life history perspective suggests that a similar pattern may also occur in the context of *high* SES. In a nutshell, safe and predictable environments characterized by low mortality are expected to favor "slow" life history strategies that delay reproductive effort and invest heavily in somatic effort, including upregulated maintenance and repair to preserve the long-term integrity of the organism (see Del Giudice et al., 2015). To the extent that growing up in favorable socioeconomic conditions entrains slower life history strategies, one can expect that at least some high-SES individuals will show moderate elevations of IL-6 and CRP. Mathematical models of evolutionary trade-offs also predict that organisms with longer expected lifespans should typically devote more resources to immunity, and invest comparatively more in immune tolerance compared with shorter-lived organisms (Miller et al., 2007). IL-6 can fulfill this role, by acting both as a tolerance mechanism and a readiness signal for the rapid allocation of energy to inflammation.

This hypothesis is admittedly speculative, but consistent with some recent findings that challenge the idea of a simple negative correlation between SES and IL-6/CRP. In two studies, the direction of the correlation was moderated by an interaction with personality factors: specifically, IL-6 and CRP were elevated in low-SES participants characterized by low conscientiousness, low emotional stability, and low levels of optimism and perceived control, but also—even if less strongly—in high-SES participants with high conscientiousness, emotional stability, optimism, and sense of control (Elliot and Chapman, 2016; Elliot et al., 2017). Since conscientiousness and perceived control are plausible psychological correlates of slower life history strategies (see Del Giudice et al., 2015), this pattern would seem consistent with our speculation. Another recent large-scale study found that CRP was elevated in people experiencing high stress and low positive affect, but also in those with low stress and high positive affect (Blevins et al., 2017). Nonetheless,

we stress that these findings are provisional and should be replicated before being accepted with confidence. Indeed, an earlier study found significant interactions between SES and personality in predicting IL-6 and CRP, but the effect of emotional stability was reversed (i.e., IL-6 and CRP were elevated in high-SES participants with low emotional stability; Millar et al., 2013). If consistently replicated, these results would point to an important source of heterogeneity in the functional pathways that determine individual levels of IL-6 and CRP. Since the putative bidirectional effects of SES are stronger at the low end of the socioeconomic scale, simple linear correlations between biomarker levels and SES are expected to return the usual negative pattern, thus failing to reveal the underlying heterogeneity. Doing so would require explicitly testing for interactions and/or nonlinear effects. The same applies to personality—for instance, the overall correlation of conscientiousness with IL-6 and CRP is negative across studies (Luchetti et al., 2014), but this seemingly straightforward pattern might hide an unknown amount of heterogeneity.

6.2. Example 2: Acute and chronic stress

6.2.1. Acute stress

In the typical response to acute stress, the sympathetic system becomes strongly activated and triggers a host of physiological changes, both directly through organ innervation and indirectly through secretion of catecholamines (epinephrine and norepinephrine) by the adrenal medulla. The rapid sympathetic response is followed by activation of the hypothalamic-pituitaryadrenal (HPA) axis, which culminates with the release of cortisol by the adrenal cortex. Cortisol levels peak 10–30 min after the start of a stressful event and mobilize energy by increasing blood glucose levels, while performing a complex array of metabolic and psychological functions. Many effects of cortisol show a biphasic trajectory, partly mediated by two types of receptors with different response timing: the early, high-affinity *mineralcorticoid receptor* (MR) and the later, low-affinity *glucocorticoid receptor* (GR). Cortisol initially enhances the effects of the sympathetic system but, later, downregulates sympathetic activity and contributes to terminate the stress response (see Del Giudice et al., 2011; Gunnar and Quevedo, 2007).

Traditionally, acute cortisol release into the bloodstream has been thought to have anti-inflammatory effects. Cortisol downregulates the expression of inflammatory cytokines such as IL-1β and other pro-inflammatory factors (Cain and Cidlowski, 2017; DeRijk et al., 1997); at the same time, it stimulates production of the anti-inflammatory cytokine IL-10 (Calcagni and Elenkov, 2006). In suppressing inflammation, IL-10 promotes a shift toward humoral immunity and away from cell-mediated immunity (Calcagni and Elenkov, 2006). Cortisol accelerates the resolution of the inflammatory response, and interferes with wound healing by inhibiting collagen synthesis, angiogenesis, and other processes (see Cain and Cidlowski,2017). Functionally, these effects of cortisol have been understood as adaptive reallocation of energetic and other resources: under challenging conditions that require energy mobilization enabled by cortisol, inflammation could take valuable resources away from efforts to meet the challenge, as well as induce reactions (e.g., sickness behavior) counterproductive to those efforts (e.g., Adamo, 2014).

More recently, this picture has been complicated by findings suggesting that cortisol may both enhance and suppress inflammation following acute stress, and do so in a time- and concentration-dependent manner (Cain and Cidlowski, 2017; Dhabhar, 2009). Specifically, the initial cortisol rise may upregulate inflammation and recruit lymphocytes through activation of the MR receptor (Muñoz-Durango et al., 2015), likely in tandem with the pro-inflammatory effects of norepinephrine. As time passes and cortisol concentration increases further, activation of the GR receptor begins to suppress inflammation, thus shifting the net effect of cortisol from pro- to anti-inflammatory. Indeed, meta-analyses show that acute stress is followed by release of pro-inflammatory cytokines IL-1β and TNF-α, but also anti-inflammatory IL-10. The rise of IL-6 is slower and reaches a peak after 90–120 min (Marsland et al., 2017; Segerstrom and Miller 2004; Steptoe et al, 2007). Overall, studies of acute stress fail to detect a significant increase in CRP within the first two hours. The likely reason is the slow time course of CRP synthesis and release: during infections, CRP levels begin to rise after 4–6 h and peak after 1–2 days (Schmit and Vincent, 2008). The same delayed time course has been observed after surgery, physical trauma, and intense physical activity (e.g., Di Napoli et al., 2012; Ispirlidis et al., 2008; Kasapis and Thompson, 2005; Nguyen-Vermillion et al., 2011).

The interplay between cortisol and IL-6 during acute stress is complex and still incompletely understood. IL-6 has an activating effect on the HPA axis and increases adrenal production of cortisol, thereby raising blood levels of cortisol in response to a stressor (see Marsland et al., 2017; Silverman et al., 2004; Zarkovic et al., 2008). IL-6 also upregulates glucocorticoid signaling (e.g., Zhang et al., 2005). Thus, pre-stressor levels of IL-6 may potentiate the cortisol response. In turn, cortisol tends to suppress IL-6 by inhibiting its production in macrophages, especially in response to infection (e.g., Garbers et al., 2012; Waage et al., 1990; see also Yeager et al., 2011). Consistent with expectation, a larger cortisol response following exposure to a laboratory stressor predicts a smaller increase in IL-6 (e.g., Carpenter et al., 2010; Kunz-Ebrecht et al., 2003). The slow IL-6 increase observed after acute stress may plausibly be driven by declining cortisol levels. Moreover, cortisol appears to lower blood levels of sIL-6R (see, e.g., Cullen et al., 2017), which shunts IL-6 activity away from the pro-inflammatory trans-signaling pathway; at the same time, it enhances sensitivity of the IL-6R receptor in the liver (Garbers et al., 2012), thus upregulating the production of acute phase proteins through classic signaling. These findings suggest that IL-6 plays two distinct roles in the immune response to acute stress. Initially, higher pre-existing levels of IL-6 may potentiate the HPA response, consistent with the idea that IL-6 functions as a signal of energetic readiness. As the stressor ends and cortisol begins to decline, IL-6 may rise to aid recovery through classic signaling pathways while exerting broadly anti-inflammatory effects. This dual role of IL-6 would be consistent with the recent hypothesis that a larger cortisol increase promotes a faster inflammatory response, but also a quicker resolution of inflammation and transition to recovery and repair (Cain and Cidlowski, 2017).

6.2.2. Chronic stress

When stress becomes chronic—with repeated, sustained exposures over a period of years—the resulting physiological patterns become more complex and harder to predict. The evidence indicates that chronic stress can lead to either upregulation or downregulation of HPA responsivity; in the former case, cortisol becomes chronically elevated, whereas in the latter cortisol levels become flat and unresponsive to stressors (McEwen, 2007, 2012). These patterns have been classically interpreted as outcomes of dysregulation, but from an evolutionary-developmental standpoint they may play a functional role in the coordination of behavior and physiology in the context of faster life history strategies (Del Giudice et al., 2011; Ellis et al., 2017). Most relevant for this paper, chronic stress and early trauma have been linked to elevated levels of various putative inflammatory biomarkers including TNF-α, IL-6, and CRP (e.g., Baumeister et al., 2016), as well as more aggressive inflammatory responses to infections (Kuhlman et al., 2017). These effects have been thought to reflect "glucocorticoid resistance," a particular kind of dysregulation whereby immune

cells (e.g., macrophages) become insensitive to the GR-mediated inhibitory effects of cortisol after prolonged overexposure (Kuhlman et al., 2017; Miller et al., 2009; Miller et al., 2011; Cohen et al., 2012). This hypothesis is implicitly predicated on the idea that chronic stress leads to HPA upregulation. Yet HPA downregulation is another frequent outcome and, in fact, may be more commonly associated with severe or traumatic stress in childhood (Ellis et al., 2017). In the alternative scenario of downregulated HPA activity, elevated levels of inflammatory cytokines may result not from glucocorticoid resistance but rather, more simply, from low circulating levels of cortisol.

Regardless of the specific mechanism, it is important to ask what is the functional significance of developing a pro-inflammatory phenotype in the context of early adversity and chronic stress. Most current models assume that upregulated inflammation is the maladaptive outcome of physiological dysregulation (Kuhlman et al., 2017). But other possibilities exist. First, some authors working within a LHT framework have proposed that increased investment in innate immunity (at the expense of acquired immunity) may be an adaptive response to cues of high mortality risk, as a correlate of faster life history strategies (McDade et al., 2016b; see also Miller et al., 2007). This hypothesis has received initial support (Georgiev et al., 2016), though it remains partly speculative. The crucial point is that patterns of immune activity that have typically been regarded as pathological or dysregulated may represent adaptive (or ancestrally adaptive) responses to environmental threats.

Second, individuals who engage in slower life history strategies may respond to periods of sustained stress and HPA activity with a compensatory investment in tissue repair, as a form of damage control against cortisol-induced wear and tear. In such cases, levels of inflammatory cytokines and IL-6 may not be elevated, owing to the suppressive effects of cortisol. But the production of CRP and other acute phase proteins (including the anti-inflammatory receptor antagonist IL-1ra, which interferes with IL-1β binding) could still be upregulated, as cortisol increases the sensitivity of classic signaling through IL-6R in the liver (Garbers et al., 2012). Indeed, in one study, individuals who were under prolonged stress but with no specific exposure to early adversity—i.e., familial caretakers of brain cancer patients—had nearly double the CRP levels of control participants, despite not having significantly higher levels of IL-6; they also had higher levels of IL-1ra (Miller et al., 2008). The authors interpreted this finding as being consistent with these individuals experiencing inflammation (the anti-inflammatory effect being a counter-response). A simpler, more plausible interpretation is that most caretakers in the study were *not* undergoing chronic inflammation but, rather, upregulated tissue repair in the face of sustained stress.

6.3. Example 3: Depression

The link between depression and immunity has become an important theme in biological psychiatry (e.g., Berk et al., 2013; Miller and Raison, 2016). A number of different hypotheses have been proposed to address the specific nature of this link. Some authors propose that chronic inflammation and dysregulated HPA functioning following early stress and adversity increase the risk for mental disorders, including depression (e.g., Kuhlman et al., 2017). Others note the analogies between depressive symptoms and aspects of sickness behavior such as inactivity, loss of motivation, and decreased appetite. In this perspective, depression in the context of inflammation contributes to the organism's response by helping conserve energy and prioritize resources for the immune system (e.g., Kinney and Tanaka, 2009). Indeed, there is evidence that inflammatory cytokines can induce or worsen depressive symptoms; also, illness in childhood may increase the risk of depression in adulthood, consistent with an etiological role of immune factors (Du Preez et al., 2016; Horowitz and Zunszain, 2015; Köhler et al., 2017). A more radical hypothesis is that depression is not just a behavioral correlate of inflammation but an integral component of immunity; on this view, even social stressors such as ostracism and status loss cause depression by first activating an inflammatory response, which then triggers the onset of depressive symptoms through cytokine signaling (Raison and Miller, 2013a). In modern environments, improved hygienic conditions and insufficient exposure to pathogens in childhood may exacerbate the tendency to develop low-grade inflammation and increase the risk of clinical depression—an instance of evolutionary mismatch (Raison and Miller, 2013a, 2013b; Miller and Raison, 2016).

The evidence on immune biomarkers in depression has been synthesized in a number of meta-analyses (Dowlati et al., 2010; Haapakoski et al., 2015; Howren et al., 2009; Köhler et al., 2017). Most consistently, IL-6 and CRP levels are elevated in depressed patients. These effects become substantially smaller when controlling for BMI, indicating that adiposity partly mediates the association. While an early meta-analysis found evidence of elevated IL-1β (Howren et al., 2009), the overall association has not been replicated in subsequent analyses (Köhler et al., 2017). There are indications that high-BMI patients show higher levels of IL-1β (Köhler et al., 2017). In general, depression is associated with higher levels of the antagonist receptor IL-1ra (Howren et al., 2009; Köhler et al., 2017). TNF-α shows evidence of higher levels in depression, but the overall effect is qualified by substantial heterogeneity across studies. First, the association is attenuated when controlling for BMI. Second, TNF-α is not significantly elevated in depression with *melancholic* features—weight loss, insomnia, loss of libido, and psychomotor agitation or retardation (Haapakoski et al., 2015; Köhler et al., 2017). In line with the meta-analytic evidence, a recent study found that *atypical* features in depression and bipolar disorder (e.g., hypersomnia, increased appetite, weight gain) were associated with elevated sIL-6R (indicating upregulated trans-signaling); melancholic features were not (Sowa-Kućma et al., 2018). Importantly, melancholic symptoms are associated with HPA hyperactivation and sustained cortisol elevation (Gold and Chrousos, 2002; Taylor and Fink, 2008), which tend to suppress inflammation.

Depressive disorders are extremely heterogeneous, and it is widely recognized that different subtypes of depression may require different functional explanations. For the purpose of this paper, it is important to note that low-grade inflammation does not seem to be a generalized feature of depression; in fact, patients with melancholic features—who tend to suffer from the most severe symptoms—may actually show an *anti*-inflammatory profile with normal or somewhat increased levels of CRP (as found by Lamers et al., 2013). Inflammation is likely restricted to a subgroup of patients, and appears to be especially common in association with atypical symptoms (e.g., Lamers et al., 2013; Rethorst et al., 2015). Importantly, atypical but not melancholic features correlate with higher BMI and obesity (Capuron et al., 2017), which—as noted above—robustly predict increased levels of IL-6, CRP, TNF-α, and IL-1β in depression. Furthermore, atypical symptoms tend to be associated with inflammation-related disease outcomes (e.g., metabolic syndrome; Lamers et al., 2016; Seppälä et al., 2012). Melancholic depression, despite being associated with higher IL-6 and CRP levels compared with controls, does not predict higher rates of metabolic syndrome (Seppälä et al., 2012; cf. Lamers et al., 2016, at 6-year follow-up only). In fact, genetic risk scores for severe melancholic depression seem to be associated with *lower* risk of adverse cardiac and metabolic symptoms (Wong et al., 2017).

In a widely cited study of treatment-resistant depression by Raison et al. (2013), patients with higher CRP levels at baseline

showed larger symptom improvements after administration of a TNF antagonist, supporting a role for inflammation in the etiology of depression. However, patients who responded to this treatment also had elevated baseline levels of TNF-α compared with non-responders (Raison et al., 2013). Thus, the study is consistent with the idea that only some depressed patients experience low-grade inflammation; moreover, the TNF-α elevation observed in responders suggests a predominance of atypical symptoms. (The study did not report symptom subtypes, or how many patients had high CRP but low TNF-α.) Of note, large-scale Mendelian randomization studies have found no evidence that increased CRP levels play a causal pathogenic role in depression and other psychiatric disorders; in fact, there is some evidence of a *protective* effect against schizophrenia (Prins et al., 2016; Wium-Andersen et al., 2014).

The functional approach we outlined in this paper suggests a speculative but not implausible possibility: that some depressed patients may show increased levels of IL-6 and CRP in absence of inflammation, as part of a generalized investment in somatic maintenance. Based on the evidence discussed above, this pattern is most likely to be found in patients with depressed mood but without significant levels of somatic symptoms (either melancholic or atypical). The existence of a sizable subgroup of patients with this profile would contribute to explain the meta-analytic finding of reliably elevated IL-6 and CRP in depression as a whole, despite the inconsistent and variable levels of TNF-α and IL-1β. This hypothesis is broadly consistent with the idea that the key biological function of depressive symptoms is to coordinate the reallocation of resources, away from reproduction and growth and toward tasks that promote survival and self-preservation (Andrews and Durisko, 2017; Andrews et al., 2015).

Whether low-grade inflammation in a subgroup of depressed patients reflects physiological dysregulation or a potentially adaptive response is still an open question. For example, Stieglitz et al. (2015) found that depressive symptoms in the Tsimane predicted higher levels of IL-6, CRP, and TNF-α (but not IL-1β), as well as stronger cytokine responses to immune stimulation. This pattern is similar to that observed in Western, industrialized countries, again challenging a simple mismatch account. The same study also found some evidence of specific symptom-biomarker associations (e.g., between IL-6, TNF-α, and irregular sleep) that might relate to the distinction between melancholic and atypical depression.

7. Summary and conclusion

In recent years, researchers have sought to integrate the behavioral, neurobiological, and immunological perspectives in a coherent, powerful way that speaks to how social contexts, lifestyles, and behavior exert long-term effects on physical and psychological health. These efforts have deservedly generated much excitement. A burgeoning empirical literature links current and developmental conditions (e.g., experiences of stress, obesity, hormonal exposures, infectious disease) with measured levels of cytokines and other components of the immune system. In turn, cytokine levels predict a wide range of health outcomes (e.g., heart disease, metabolic disorder, diabetes, pregnancy and birth outcomes, depression). This literature offers hope for understanding the mechanisms through which experience and behavior ultimately affect important aspects of health as well as the development of interventions that foster well-being (e.g., Miller et al., 2009).

Appropriate understanding of mechanisms revealed through associations with levels of cytokines and other biomarkers requires accurate appreciation of the processes that lead biomarker levels to rise and fall. In this regard, the current behavioral literature falls short. Elevated levels of IL-6 and CRP are near-uniformly interpreted to reflect an inflammatory state; when moderate, they purportedly represent a state of chronic, low-level inflammation. These interpretations ignore the consensus in immunology, where it is commonly accepted that IL-6 and CRP levels may be elevated even in the complete absence of an inflammatory state. Indeed, under these conditions, these molecules tend to exert net anti-inflammatory effects. A broader view of the role of IL-6 and CRP should prompt conceptual reexamination of key findings and ideas in the behavioral literatures. To this end, we outlined a functional framework for understanding the complex and seemingly contradictory actions of IL-6 and CRP. Specifically, we argued that IL-6 may generally function to dedicate energy and other limited resources (e.g., amino acids) to somatic maintenance, as well as play specific directive roles in this regard. Only in certain contexts does this entail an inflammatory response. Similarly, CRP can be framed as a maintenance protein, which routinely participates in tissue repair and is recruited with specific functions during inflammation.

We illustrated how a functional perspective may lead to alternative interpretations of specific empirical patterns, which at times contrast dramatically with prevailing models. Of course, full evaluation of these and other potential interpretations of the broad set of phenomena examined within the behavioral literature will require additional theoretical refinements, critical thought, and much empirical work. For one, IL-6 and CRP assays are insufficient to establish the existence of inflammatory states; assays of more unambiguous inflammatory biomarkers (e.g., IL-1β, TNF-α) are also necessary. Circulating levels of soluble IL-6 receptors (sIL-6R) could be informative as well, in that they may establish the extent to which IL-6 operates through generally pro-inflammatory trans-signaling (high sIL-6R levels) or through classic signaling (low sIL-6R levels). Nothing in our proposal diminishes the importance of the existing research involving IL-6 and CRP. We remain convinced as ever that this literature can powerfully inform our understanding of the development of health and well-being, and eventually contribute to the design of effective health-promoting interventions. To do so, however, theoretical explanation must be accurate. Our proposal to rethink IL-6 and CRP, then, is also a call to action: we urge scholars to critically evaluate interpretations of empirical patterns in light of the multiple processes in which these biomarkers are involved.

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