Review article

An index of the ratio of inflammatory to antiviral cell types mediates the effects of social adversity and age on chronic illness

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ABSTRACT

Background: It is assumed that both social stress and chronological age increase the risk of chronic illness, in part, through their effect on systemic inflammation. Unfortunately, observational studies usually employ single-marker measures of inflammation (e.g., Interleukin-6, C-reactive protein) that preclude strong tests for mediational effects.
Objective: The present study investigated the extent to which the effects of socioeconomic disadvantage and age on onset of chronic illness is mediated by dominance of the innate (inflammatory) over the acquired (antiviral) components of the immune system.
Methods: We assessed inflammation using the ratio of inflammatory to antiviral cell types (ITACT Ratio). This approach provided a stronger test of evolutionary arguments regarding the effect of social stress on chronic inflammation than is the case with cytokine measures, and afforded an opportunity to replicate findings obtained utilizing mRNA. We used structural equation modeling and longitudinal data from a sample of 100 middle-age African American women to perform our analyses.
Results: Dominance of inflammatory over antiviral cell activity was associated with each of the eight illnesses included in our chronic illness measure. Both socioeconomic disadvantage and age were also associated with inflammatory dominance. Pursuant to the central focus of the study, the effects of socioeconomic adversity and age on increased illness were mediated by our measure of inflammatory dominance. The indirect effect of these variables through inflammatory cell profile was significant, with neither socioeconomic disadvantage nor age showing a significant association with illness once the impact of inflammatory cell profile was taken into account.
Conclusions: First, the analysis provides preliminary validation of a new measure of inflammation that is calculated based on the ratio of inflammatory to antiviral white blood cells. Second, our results support the hypothesis that socioeconomic disadvantage and chronological age increase risk for chronic illness in part through their effect on inflammatory processes.

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1. Introduction

Although age-related chronic illnesses increase exponentially after age 50, some individuals demonstrate relatively early onset of

chronic illness whereas others remain relatively healthy well into their 90s (Finkel, 2005). The various chronic illnesses of old age tend to be highly correlated so that individuals who suffer early onset of one illness tend to develop others as well. This correlation of illnesses is a function of the fact that they share a common set of risk factors (Hayflick, 2007; Kennedy et al., 2014). Perhaps chief among these risk factors is chronic, systemic inflammation. Elevations in circulating markers of inflammation (e.g., C-reactive

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protein, interleukin-6, tumor necrosis factor alpha) have been associated with cardiovascular disorders, type II diabetes, osteoporosis, rheumatoid arthritis, Alzheimer's disease, and certain cancers (Maggio et al., 2006; Libby and Theroux, 2005). Such findings underscore the importance of identifying the causes of chronic, elevated inflammation.

In recent years, a large number of studies have established that exposure to social adversity (Cole, 2010, 2014) as well as simply chronological age (Franceschi and Campisi, 2014; Morrisette-Thomas et al., 2014) are robust predictors of increased inflammation. Much research has also linked social adversity and age to onset of chronic illness (Kennedy et al., 2014), and it is generally assumed that these factors foster chronic illness, at least in part, through their impact on inflammation. Surprisingly, however, few studies have investigated this mediation hypothesis.

Most observational studies are not well positioned to investigate this hypothesis as they employ a single marker, usually C-reactive protein or interleukin-6, to assess inflammation (Morrisette-Thomas et al., 2014). Thus, the associations between either adversity or age and inflammation, as well as the relation between inflammation and illness, are so modest as to preclude strong tests for indirect or mediational effects. The present study avoids this limitation by using a more comprehensive approach to assess inflammation.

The immune system entails two rather distinct programs, (1) an innate program that consists largely of pro-inflammatory genes that combat tissue damage, bacteria, and other extracellular pathogens, and (2) an acquired program comprised of antiviral genes which produce antibodies and target intracellular pathogens such as viruses. Using peripheral blood, we calculated a new measure of inflammation based on the ratio of inflammatory to antiviral cell types. Cole and colleagues (Cole, 2014; Irwin and Cole, 2011; Stavich and Cole, 2013) argue that adversity (threat, challenge, or danger) leads to increased expression of the inflammatory program, coupled with decreased expression of the antiviral program, as the organism prepares for possible attack, injury, and infection. Our cell-ratio measure might be considered an index of the extent to which the immune system's innate (inflammatory) program has come to dominate the acquired (largely antiviral) program. Using this index, we test the hypothesis that elevated systemic inflammation mediates the effect of both socioeconomic disadvantage (poverty, unemployment, low education) and chronological age on increases in chronic illness. We use structural equation modeling and longitudinal data from a sample of 100 middle-aged African American women to perform our analyses.

1.1. Social adversity, inflammation, and illness

Over the years, a multitude of studies have reported a link between exposure to social adversity and onset of chronic illness, and recently research has established a similar association between adversity and inflammation. Findings suggest that social adversity is associated with increased inflammation and that this relation holds even after controlling for health risk behaviors such as smoking, excess drinking, bad diet, lack of exercise, BMI, among others. Steven Cole and his colleagues have provided what is perhaps the most compelling explanation for this association (Cole, 2010, 2014; Cole et al., 2012). Specifically, the Cole team note that the immune system comprises two rather distinct programs: proinflammatory cytokine genes that combat tissue damage, bacteria, and other extracellular pathogens, and antiviral genes that produce antibodies and target intracellular pathogens such as viruses. They argue that adversity (threat or danger) leads to increased expression of the inflammatory program, coupled with decreased expression of the antiviral program, as the organism

prepares for possible attack and injury. Cole (2014) labels this pattern of gene expression the *conserved transcriptional response to adversity* (CTRA). Support for this idea comes from studies reporting a link between various types of social adversity (loneliness, low SES, bereavement, PTSD) and the CTRA transcription pattern in blood leukocytes (Stavich and Cole, 2013; Cole, 2014). Presumably, this pattern of gene expression evolved to help adapt molecular physiology to the types of sporadic and transient threats that characterized our ancestral environments (Cole, 2014). In contemporary society, in contrast, purely symbolic or anticipated threats undermine health by fostering chronic activation of the inflammatory program and risk for inflammation-related diseases such as CHD, diabetes, arthritis, neurodegeneration, and cancer while simultaneously down-regulating the antiviral program and resistance to viral infections (Cole, 2013, 2014).

The CTRA hypothesis implies that the effect of socioeconomic disadvantage on chronic illness should be mediated, at least to some extent, by a physiological pattern characterized by increased activation of the inflammatory program combined with decreased activation of the antiviral program. We test this idea in the present study. Further, to evaluate the generality of their argument, we use a different approach to assessing the dominance of the inflammatory over the antiviral program. Specifically, rather than use mRNA as Cole and colleagues have done in most of their past research (Cole, 2014), we estimate the relative proportion of various types of peripheral leukocytes.

Some leukocytes, such as monocytes and natural killer cells, mediate innate immune responses and express genes that promote the cascade of cytokines involved in the inflammatory process, whereas B cells, CD4 T-helper cells, and CD8 T-helper cells are involved in adaptive immune responses and express genes involving antibodies and antiviral activities (Abbas et al., 2015; Parmely, 2006). In addition to influencing gene expression in these various white blood cells, adversity has been shown to influence the number and proportion of these different cell types (Dhabhar, 2014; Powell et al., 2013). Thus, the body has two avenues whereby it can influence the production of proteins associated with either the inflammatory or antiviral immune system. It can either: (1) increase or decrease the *number* of cells associated with a particular immune response, or (2) increase or decrease mRNA *expression* within the cells associated with a particular immune response. Dominance of the inflammatory over the antiviral system in response to adversity might be achieved, for example, by increasing the number and expression of monocytes while decreasing the number and expression of B cells. Cole and colleagues have generally assessed one of these avenues — inflammatory gene expression relative to antiviral gene expression (although Powell et al., 2013, and Cole et al., 2015, also provide some initial assessments of cell numbers). We extend their work by focusing upon the second avenue for activating or inactivating an immune response — changes in the relative proportion of inflammatory versus antiviral leucocytes using genome-wide DNA methylation profiles (Houseman et al., 2012). Specifically, we assess the ratio of monocytes and natural killer cells versus B cells, CD4 T-helper cells and CD8 T-helper cells.

1.2. Age, inflammation, and illness

It is common knowledge that age is related to chronic illness. In recent years, numerous studies have established that age is also associated with increased inflammation (Franceschi and Campisi, 2014; Kennedy et al., 2014). Indeed, the link between age and inflammation is so marked that it is often dubbed "inflammaging" (Franceschi and Campisi, 2014; Morrisette-Thomas et al., 2014). This pattern of associations indicates the importance of controlling