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suPAR: A newer biomarker of systemic chronic inflammation

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Exposure to adverse life experience associates with increased morbidity and mortality from a range of diseases in later life (Cohen et al., 2012). Growing evidence suggests that systemic inflammation may contribute to these relationships, with early childhood adversity and stressful life experiences in adulthood associating positively with circulating levels of C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α (Cohen et al., 2012; Baumeister et al., 2016). In a recent paper in Brain, Behavior and Immunity (BBI), Bourassa et al. (2021) contribute to an emerging literature examining the association of psychosocial risk factors with a nascent marker of inflammation, soluble urokinase Plasminogen Activator Receptor (suPAR), thought to provide a more stable index of systemic chronic inflammation than more widely used biomarkers.

suPAR is the soluble form of a receptor (uPAR) found on the membrane of many cell subtypes, including monocytes, macrophages, T lymphocytes, and vascular endothelial cells (Thunø et al., 2009). The soluble receptor is cleaved from the surface of immunologically activated cells and can be detected in peripheral circulation. As such, it is thought to provide an index of total immune activation (Thunø et al., 2009). Physiologically, suPAR plays a role in immune cell signaling, adhesion, chemotaxis and proliferation (Thunø et al., 2009). Circulating levels increase in response to infections and inflammatory conditions, including autoimmune diseases, cardiovascular disease (CVD), diabetes and cancer (Thunø et al., 2009; Hodges et al., 2015; Backes et al., 2012). Higher suPAR levels predict poorer prognosis across conditions (Backes et al., 2012), accelerated biological aging (Rasmussen et al., 2021), and mortality both in clinical and healthy populations (Eugen-Olsen et al., 2010). In sum, suPAR is recognized as a nonspecific marker of systemic chronic inflammation that is common to many inflammatory diseases and may serve as a marker of health risk in the general population.

Many characteristics make suPAR a good candidate as a biomarker of chronic inflammation. Circulating levels of suPAR are stable over relatively long periods, are not subject to diurnal variation, increase with age, and show smaller responses to acute immune stimulation (e.g., injection of endotoxin) than more established biomarkers (Thunø et al., 2009; Andersen et al., 2008). Among the general population, plasma suPAR predicts incident CVD, diabetes, and cancer, as well as mortality independently of CRP, IL-6 and TNF-α (Thunø et al., 2009; Eugen-Olsen et al., 2010; Lyngbæk et al., 2013). Interestingly, suPAR relates differently to metrics of cardiometabolic disease risk than the more established biomarkers. For example, suPAR associates more strongly with preclinical measures of endothelial dysfunction and atherosclerosis than CRP, whereas CRP relates more strongly with adiposity, dyslipidemia and higher blood pressure than suPAR (Lyngbæk et al., 2013). These observations have led to the conclusion that suPAR may tap a different pathophysiological process than the traditional biomarkers, and that the biomarkers should be considered in combination as a measure of inflammatory burden in the prediction of health risk (Lyngbæk et al., 2013).

Recent attention has begun to establish a positive association of psychosocial risk factors with suPAR levels. To date, much of this literature, including the new study published by Bourassa et al. (2021), has examined data collected in the Dunedin Longitudinal study. Prior findings show a positive association between exposure to adverse childhood experiences assessed prospectively across the first 15 years of life and elevated suPAR at age 38 years (Rasmussen et al., 2019). In the new analysis, Bourassa and colleagues replicate this association with suPAR assessed at age 45 years and also show a positive relationship between adult life event stress recalled across the prior six years and suPAR at ages 38 and 45 years. Associations of childhood adversity and adulthood life stressors with suPAR were partially independent and retained in analyses that adjusted for sex, smoking, body mass index, and anti-inflammatory medication use. Interestingly, the strongest positive associations of life event stress with suPAR were observed among individuals who experienced more childhood adversity, lower socioeconomic conditions in childhood, and less self-control as children. These moderators were examined in separate statistical models, making it impossible to determine how they overlap in the prediction of risk. However, results suggest that some individuals, by virtue of their childhood exposures and dispositional characteristics, are more vulnerable to heightened immune activation in response to life stress in adulthood.

Multiple mechanisms may link exposure to stress to levels of systemic immune activation. Recent attention has focused on the possibility that childhood exposures may program biological stress regulatory systems, such as the hypothalamic pituitary adrenal axis, and thus contribute to stress responsivity across the lifespan and a phenotype prone to systemic inflammation (sensitization model) (Miller et al.,

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2011). The presented findings are consistent with this possible pathway. The findings also support an additive model, with childhood experiences predicting exposure to life stress in adulthood and the cumulative impact of lifetime exposure predicting midlife suPAR (cumulative model). Finally, the findings suggest that childhood adversity also contributes independently of adult exposures to the prediction of midlife inflammation (biological embedding model). Here, it is possible that childhood adversity predicts poorer lifelong health habits, psychological function or exposure to environmental stressors beyond those assessed in the study (e.g., crowding, unemployment, crime). Further research is warranted to examine these pathways and individual difference factors that may relate to health risk or resilience.

Contrary to expectations, but consistent with prior findings from this sample, Bourassa et al. (2021) did not observe strong associations of recent life event stress or adverse childhood experiences with CRP or IL-6 measured at age 45. Reasons for stronger associations with suPAR than the other biomarkers are unclear. However, the authors and others propose that suPAR provides a more stable biomarker of systemic chronic inflammation than CRP or IL-6, and is less subject to the influence of acute infection and environmental exposures (Thunø et al., 2009). Further research is warranted to support these assertions and demonstrate that suPAR is more stable and less reactive than CRP, which is also not subject to time-of-day variation (Meier-Ewert et al., 2001) and does not respond to acute exposures, such as psychological challenge (Marsland et al., 2017). Considering evidence that these inflammatory biomarkers may tap different underlying pathophysiologic processes, another way to consider the contributions of these different markers may be to examine them together as a measure of systemic inflammation in the prediction of health risk. For example, Rasmussen et al. (2020) recently showed the strongest associations between childhood adversity and systemic inflammation when combining CPR, IL-6 and suPAR.

In sum, suPAR is an exciting new biomarker that may provide a more stable measure of systemic chronic inflammation and supplement more traditional markers of inflammation in the prediction of health risk.

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