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Commentary

Identification of Immune Activation Profiles That May Predict Morbidity During Antiretroviral Therapy Treated HIV Infection

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Chronic elevation in markers of immune activation is a hallmark of HIV infection, even when viral replication has been suppressed by antiretroviral therapy (ART) (Lederman et al., 2013). The Strategies for the Management of Antiretroviral Therapy (SMART) study demonstrated that plasma levels of interleukin-6 (IL-6), C-reactive protein, and D-dimer are independent predictors of mortality in HIV infection, including deaths related to cardiovascular disease (CVD) (Kuller et al., 2008; Emery et al., 2008). The predictive value of markers of immune activation and inflammation has been confirmed in several studies (Psomas et al., 2016; Hunt et al., 2014; Kalayjian et al., 2010). Potential mechanisms have also been identified that may contribute to increased activation of both the innate and the adaptive immune systems in chronic HIV infection, including: copathogens, microbial translocation, pro-inflammatory lipids, low level viral replication, and the immune system's response to cytopenia (Lederman et al., 2013).

In their manuscript in *EBioMedicine*, Psomas and colleagues used a combination of 68 markers of immune activation and inflammation and two independent hierarchical clustering analyses to identify 5 donor groups from among 120 HIV-infected virologic responders (Psomas et al., 2016). These donor groups were characterized using combinations of activation markers among CD4+ T cells, CD8+ T cells (CD38, HLA-DR, CD279, CD57), B cells (serum levels of IgG, IgA, IgM) natural killer cells (HLA-DR, CD69), monocytes (soluble CD14 and sCD163), and markers of inflammation and coagulation. The authors propose to use these donor groups to establish relationships between HIV-infected individuals displaying certain activation phenotypes and clinical indices that are related to morbidity and mortality. For example, the "inflammatory group," which was identified by increased levels of inflammatory markers including tumor necrosis factor alpha receptor I (TNFR-I), was associated with markers of metabolic syndrome. This group was enriched for donors with hyperinsulinemia (insulinemia >24.9 mIU/L, odds ratio [OR] 12.17%, $p = 0.011$), high tryglycerides (>2.85 mM, OR 4.18, $p = 0.038$) and lipodystorphy (OR 4.87, $p = 0.015$). Several studies have demonstrated that markers of inflammation, including levels of TNFR-I and II, are predictive of morbidity and mortality in persons infected with HIV (Hunt et al., 2014; Kalayjian et al., 2010; Tenorio et al., 2014) and chronic inflammation is a likely contributor to the development of metabolic syndrome and CVD risk. The authors suggest that the characterization of these donor profiles may identify differences in the causes of chronic immune activation among these groups, provide linkages to associated disease states, and enable clinicians to tailer treatment strategies specific for members of these groups.

While identification of distinct immune activation profiles among HIV-infected individuals receiving ART may provide tools for improving patient care, further assessment of the predictive value of these profiles, and their feasibility in diverse clinical settings, is warranted. First, the participants in this study were 95% Caucasian, and differences among racial and ethnic backgrounds, as well as lifestyle choices including diet and exercise, may contribute to several comorbidities. A panel containing 68 biomarkers, and the interpretation of the subsequent results, may not be feasible in all infectious disease clinics, particularly those providing care in resource limited settings. The authors claim that they can identify these donor groups using a single flow cytometry panel that includes 8 markers; while this could widen the potential utility of the authors' identification strategy, it will still need to be validated in diverse clinical settings. Also, it is not clear to what degree these panels offer a significant advance in the ability of a clinician to predict morbidity or progression of comorbid disease states when compared to indices that are measured as part of routine care, or when compared to other individual biomarkers that have been linked previously to disease outcomes (Kuller et al., 2008; Emery et al., 2008; Psomas et al., 2016; Hunt et al., 2014; Kalayjian et al., 2010; Tenorio et al., 2014). The association between increased levels of TNFR-I and the prevalence of metabolic syndrome is not entirely surprising, as inflammation plays a key role in modulation of lipid levels, including decreased levels of high density lipoprotein (HDL), increased levels of low density lipoprotein (LDL), and decreased cholesterol efflux (Tall and Yvan-Charvet, 2015). The use of standard clinical measurements may provide insights into risk for comorbidities in ART-treated HIV+ individuals, however, measurement of traditional lipid panels (LDL, HDL, and triglycerides) (Munger et al., 2015) and risk calculators such as the

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American College of Cardiology/American Heart Association pooled-risk equations or the Framingham Risk Score may underestimate CVD risk in this population (Longenecker et al., 2016). The profiles identified by Psomas et al. may provide incremental benefit in the identification of HIV+ individuals who may be at risk for CVD events or may help identify patients who could benefit from lifestyle modifications or pharmaceutical lipid lowering intervention, when results from standard lipid panels may not indicate treatment (Longenecker et al., 2016).

While many potential contributors to immune activation in ART-treated HIV infection may activate similar intracellular signaling pathways (p38 and NFKB, as examples), likely resulting in expression of similar gene products (IL-6 and TNFα), the authors do provide interesting relationships among several previously underappreciated markers. Of note, the authors describe relationships between natural killer cell activation and markers of endothelial cell activation. Exploring relationships among markers that cluster together in these donor groups, may provide mechanistic insights to the development of morbidity in ART-treated HIV infection. While the overall generalizability of these results may not be readily applied in clinical settings, they do provide directions for future investigation which may uncover targets for therapeutic intervention.

Disclosure

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