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Commentary

A complex system of chemokines may hold the key to optimal CD4+ T-cell recovery after antiretroviral therapy

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Widely validated research has established that various co-morbidities, including cardiovascular disease, malignancies, liver/renal disease, and neurocognitive decline, appear earlier and with greater frequency in people with HIV (PWH) on antiretroviral therapy (ART) compared to HIV-negative individuals with otherwise similar risk factors. Moreover, higher levels of inflammatory biomarkers and persistently low CD4+ T-cell counts have been associated with these co-morbidities and with early mortality, despite virologic suppression attributable to ART [1]. Strategies to intensify or modify ART have not been successful in reducing inflammation or improving CD4+ T-cell counts [2].

Chemokines play an important role in the immune system, including regulation of leukocyte maturation and traffic, and positioning of immune cells [3]. Certain chemokines and their receptors are involved in HIV pathogenesis as well as immune recovery after ART. Circulating levels of these chemokines and chemokine receptors have been specifically associated with CD4+ T-cell recovery among ART-treated PWH via both viral replication-dependent and independent mechanisms. In particular, Ahuja et al. demonstrated a relationship between CCR5/CCL3L1 genetic risk groups and CD4+ T-cell recovery that was independent of virologic suppression and HLA alleles [4]. Restrepo et al. also found an association between CXCL12/CCR2 genotypes and CD4+ T-cell recovery [5]. Although recent studies have attempted to identify candidate genes associated with CD4 response to ART, the findings have not been consistent, often due to inadequate sample size, limited SNP coverage, and varying phenotype definitions across differing populations [6].

In this issue of *EBioMedicine*, Yeregui et al. have conducted a targeted analysis of baseline predictors for immune non-response (INR) and immune response (IR) in patients who started ART with a CD4+ T-cell count below 200 cells/μL compared to patients starting treatment with a count >200 cells/μL [7]. They found that baseline MCP-1 (i.e., CCL2) and SDF-1 (i.e., CXCL12) levels accounted for 9% and 4% of the variance of the baseline and 48-week post ART CD4+ T-cell counts, respectively. They also found that CXCL12 variant rs1801157 was associated with CD4+ T-cell recovery. Additionally, genetic variants in CX3CR1, CCR2 and CCR5 genes were associated with immune response in a haplotype association analysis, although the CCR2 and CCR5 SNPs had a strong linkage disequilibrium. This demonstrates a clear genetic association between chemokines and immune decline and immune response.

Since CD4+ T-cell recovery on ART is a key predictor for various co-morbidities and early mortality independent of virologic suppression, the predictors of CD4 recovery on ART could provide insight into inter-individual variability in immune response and long-term outcomes for PWH (predictive analytics) as well as identify novel therapeutic targets (precision medicine). The chemokines and genetic variants identified by Yeregui et al. demonstrated specific predictors of CD4 recovery at the protein and genetic level, which could encourage discovery of additional protein and genetic predictors of immune response after ART [7]. Other categories of molecular signatures such as transcriptomic and metabolomic markers may also predict CD4 recovery and provide additional functional insights of inter-individual variability. A previous study of CD4+ T-cell recovery during ART for PWH identified a gene expression signature that accurately predicted CD4 recovery for 24 participants [8]. Transcriptional profiling of blood cells may also allow us to characterize, at a molecular level, how genetic factors influence CD4 recovery and immune function. With this information, therapeutic strategies could be designed that more effectively impact outcomes beyond those developed based upon genetic data alone.

The metabolome is a global collection of small molecules produced by cells during metabolism, providing a direct functional readout of cellular activity and physiologic status. High-resolution metabolomics assays measure thousands of metabolites simultaneously, without requiring *a priori* knowledge of their chemical profiles. Recent advances have enabled metabolome-wide association studies (MWAS) to become a powerful method to investigate complex biomedical processes including HIV infection. Using a multi-level approach, transcriptomic and metabolomic data may

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complement protein and genetic predictors in illuminating complex biological processes linked particular clinical states of CD4 recovery [9]. This knowledge can inform interventions designed to prevent or treat poor CD4 recovery and reduce the subsequent associated morbidity and mortality.

While Yeregui et al. demonstrated promising results in this longitudinal study, the diversity of genetic variants predicting CD4 recovery will need to be investigated in PWH with non-European ancestries to confirm the genetic effects of the chemokines. Current genetic and genomic findings are overwhelmingly driven by European ancestry that disproportionally represents the majority of the global population at risk for HIV infection and insufficient CD4 recovery. Recent studies have demonstrated the benefits of including diverse ancestries in discovering novel genetic loci associated with diseases [10] and improving the variance explained across ethnic groups.

This current study illustrated the synergistic effects of multiple chemokines and receptors, a proof of concept of integrative multisystem study of immune response. Improved understanding of the molecular mechanisms underlying the immune response after ART may lead to more effective predictive and therapeutic strategies to manage individuals with HIV.

Author contributions

Dr. Sun and Dr. Marconi contributed to the writing and review of this manuscript. They have both read and approved the final text.

Declaration of Competing Interests

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