Inflammation and innate immune activation in chronic HIV infection

Presently, there is no effective therapeutic HIV vaccine or a protective vaccine against de novo infection, and antiretroviral therapy is the only effective treatment for the many people currently infected with HIV. Current antiretroviral regimens, while effective at controlling HIV viremia, do not reduce inflammation and innate immune activation increased in chronically infected HIV+ individuals, who suffer increased prevalence of non-AIDS co-morbidities with an inflammatory aetiology. An understanding of the causes, and development of robust biomarkers, for innate immune activation is needed to improve health outcomes for the estimated 35 million HIV+ individuals.

Despite extensive efforts, and new technologies for determining effective neutralising antibody targets, a vaccine that is effective in protecting against acquisition of HIV has not been developed and is unlikely in the short to medium term. HIV ‘cure’ research is still in its infancy and considerable progress needs to be achieved in order to understand the immunological requirements to achieve a functional cure. At present, life-long treatment using antiretroviral therapy remains the only effective strategy for treating HIV infection in the estimated 35 million people currently living with HIV.

Combination antiretroviral therapy (cART) has proven extremely effective at preventing progression to AIDS in the majority of individuals receiving it; however, HIV+ individuals have a decreased life expectancy compared to their uninfected peers and an increased prevalence of co-morbidities with an inflammatory aetiology such as cardiovascular disease, osteoporosis and HIV-associated neurocognitive disorders. Management of HIV-related co-morbidities in cART-treated, chronically infected individuals is one of the most immediate and significant challenges in HIV medicine.

Many investigators, including ourselves, have measured plasma markers of inflammation and innate immune activation in HIV+ individuals, and shown via the use of cross sectional studies that such markers remain elevated after effective HIV virological suppression with cART (reviewed by Hearps et al.). While it is important to carefully age-match the cohorts given that age is a major factor determining the level of chronic inflammation/immune activation, life-style factors such as smoking and obesity are major confounders in these studies. The causes of innate immune activation and inflammation in patients who achieve virological suppression with cART remain to be fully elucidated and debate continues as to the relative importance of factors such as residual HIV replication, damage to the gastrointestinal tract leading to increased circulating bacterial products, and reactivation of latent viruses such as cytomegalovirus or endogenous retroviruses. The elevation of several markers of inflammation in virologically suppressed patients in these studies suggests that factors other than HIV viremia significantly contribute to inflammation/immune activation. Studies of inflammation and immune activation in chronic HIV disease have measured a variety of plasma markers such as the acute phase reactants (e.g. high sensitivity CRP), oxidation products of metabolites secreted by IFN-activated macrophages (neopterin) and pro-inflammatory cytokines (IL-6, TNF) or chemokines (IP-10: CXCL10). Assumptions are often made as to the cell types or tissues responsible for secreting these markers. It is reasonable to assume that neopterin is principally derived from IFN-activated macrophages and that acute phase reactants are derived from hepatocytes...
activated by IL6. For other markers (e.g. IP-10) it is not clear to what extent activation of endothelial cells, monocytes or other cell types is responsible. The challenge remains to determine which markers are the most robust measures in the setting of chronic HIV infection, to what extent the information gained by their measurement overlaps and which individual markers reflect the response of the innate immune system to the factors presumed to cause inflammation in HIV patients, listed above.

We have taken the approach of measuring cellular markers of innate immune activation, in particular those of monocyte phenotype and function, since activated monocytes are directly involved in the aetiology of many HIV-related co-morbidities such as atherosclerosis. We have shown that HIV infection is associated with alterations in the proportions of monocyte subsets, their phagocytic ability, surface receptor expression and telomere lengths and results in monocytes, particularly the intermediate subset of monocytes, which have increased responses to innate immune stimuli. We are currently determining the relationship between plasma markers of inflammation and changes to monocyte phenotype and function to determine which markers may be useful in predicting monocyte-dependent disease processes. A complementary approach that is likely to be useful in mapping the pathways between inflammatory stimuli and innate immune activation in chronic HIV disease is to compare gene signatures in monocytes isolated from HIV+ individuals to those of monocytes activated by specific ligands. In one study, monocytes were shown to have a gene signature more similar to IFNα-activated monocytes than LPS-activated monocytes suggesting that chronic endotoxemia, which we see elevated in HIV+ individuals, is not the dominant factor activating monocytes in chronically infected individuals. In contrast, others have shown a monocyte signature consistent with bacterial product activation via TLR2. Clearly, more work needs to be done in this area to understand the factors leading to monocyte activation in HIV+ individuals.

Large-scale prospective and retrospective longitudinal studies are required to both determine whether effective virologic suppression eventually decreases inflammation to age-adjusted, healthy levels and to determine how HIV-related inflammation contributes to elevated risk of inflammatory co-morbidities. These studies will inform the need for adjunctive therapies to reduce inflammation-related comorbidities in HIV+ patients receiving antiretroviral therapy.

References

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Biographies

Anna Hearps is a clinical research scientist and Research Fellow at the Burnet Institute, Melbourne. Her research interests are in understanding how HIV infection and normal human ageing impact innate immunity, especially monocyte function.

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