Draining HIV reservoirs

Highly active retroviral therapies (HAART) suppress circulating HIV levels below the limits of detection and restore immune function. The early promise of such therapies, that they might eliminate HIV infection from the body within a few years treatment, has been tempered because the virus is able to persist silently in infected CD4+ cells in patients undergoing HAART. Eradication of HIV within the body therefore requires the difficult task of purging of such latently infected cells: Lehrman et al (2005) present proof that this is a feasible concept by using histone deacetylase 1 inhibitor (HDAC1) valporic acid to overcome the latency of integrated HIV genomes in resting CD4+ cells.

Infection of CD4+ cells with HIV leads to activation and up-regulation of cell surface proteins that further facilitate HIV entry, usually culminating in cell death through apoptosis. However, some activated cells survive and return to their resting state with HIV integrated into their genome and remain as a reservoir capable of HIV replication, and commonly persist even after intensive HAART.

Valproic acid is a well known anticonvulsant that is licensed to treat epileptic seizures. Its target HDAC1 mediates chromatin remodeling and viral expression, resulting in HIV production ex vivo in resting CD4+ T cells of aviraemic HAART-treated patients, but without upregulating cell surface markers that increase susceptibility to de-novo HIV infection. Lehrman et al (2005) studied four patients in which HIV infection was well controlled by HAART, and who were pre-administered enfuvirtide, a fusion-entry inhibitor, prior to starting valoporic acid in order to prevent the spread of the virus once resting CD4+ cells were activated. The results of the study showed that 16-18 weeks after the start of valporic acid the amount of infectious HIV in latent cells declined substantially in three of the four patients studied. The only side-effect attributed to valporic acid was zidovudine-related anaemia, explained by increased bioavailability of HAART-derived zidovudine in the presence of valporic acid.

Group leader David Margolis has been keen to stress that this was a small study to provide "proof of concept", and that no immune activation was noted in patients, perhaps due to effective containment by HAART and efuvirtide. Additionally, the side-effect of increased zidovudine bioavailability needs to be addressed. Other groups have previously reported similar success with interleukin-2, but HIV quickly re-surfaced after treatment was halted. It must also be established that depletion of the latent pools does not impact on patient health.

Caveats aside, this new therapeutic provides an additional approach to tackling HIV and other persistent infections – valporic acid, in addition to an anti-herpetic reagent, has also been shown capable of inducing apoptosis in B-cell lymphoma cells associated with human herpesvirus 8, in vitro. It provides welcome further support to the notion that long-term careful management might eventually allow eradication of chronic viral infections.

REFERENCES