HIV Persistence during Therapy
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Interview of Sarah Palmer

Sarah Palmer is the Deputy Director, Centre for Virus Research, Westmead Millennium Institute for Medical Research and Associate Professor, Faculty of Medicine, University of Sydney, Sydney, Australia.

Her research group applies innovative techniques which provide new insights into HIV disease pathogenesis.

Quantitatively, what is the exact size of the HIV reservoir?

Currently, no universal measure is available to determine the exact number of cells containing replication-competent HIV or the actual size of the latent HIV reservoir. The minimal estimate of the frequency of latently infected cells is 1 replication-competent provirus per 1 million resting memory CD4+ T cells. However, as recently described by Ho and colleagues, the number of replication-competent proviruses in these cells is underestimated. Therefore, there is a critical need for an assay which accurately measures the exact size of the latent HIV reservoir. Looking ahead, to determine the effectiveness of curative strategies, our field will need to develop such an assay which is sensitive, efficient, less costly, and adoptable in local settings.

What is the role, if any, played by defective proviruses?

The detection of defective proviruses by PCR-based assays leads to the overestimation of the latent reservoir, as these defective proviruses are unable to produce replication-competent virus. Defective proviruses represent a large proportion of HIV DNA integrants, and their measurement could potentially mask the successful clearance of the latently infected cells by curative strategies. However, the production of viral proteins from some defective proviruses may contribute to the persistent immune activation found in HIV-infected individuals on effective therapy.

How is this reservoir maintained?

The major contributors to the cellular HIV reservoir during effective therapy are memory CD4+ T cells. These antigen-experienced cells provide long-lived cellular immunity. As long as new HIV infections are prevented by effective therapy, the decay of the HIV reservoir is determined by the biology of these memory T cells containing HIV proviruses. This includes maintenance of the HIV reservoir by self-renewal, antigenic response and homeostatic proliferation.

Is there any role left for ongoing viral replication in some tissue compartments to maintain this reservoir?

Several studies have provided evidence that viral replication is not a major cause of HIV persistence in memory T cells sorted from the peripheral blood, GALT and lymp node. But, in specific tissue sites, residual replication may be contributing to HIV persistence. For example, this may be the case with lymph node follicles, where tissue fibrosis caused by HIV infection alters the local anatomical architecture and prevents drug penetration,

Several approaches to get HIV remission in patients have been a failure (HDAC inhibitors, Boston patients, Mississippi child…). What have we learned from them to design future trials?

First of all I would not say these approaches have been entirely failures for we have learned some important lessons from these treatments. In the case of HDAC inhibitors, these compounds caused an increase of cell-associated HIV RNA indicating that they reactivate the virus. Hopefully the treatment with targeted immunotherapy and more potent HDAC inhibitors will achieve better results. The treatment of the Boston Patients and the Mississippi Child, also provided proof of concept that a reduction in the viral reservoir will cause a delay in viral rebound when antiretroviral therapy is stopped. These cases also underscore that we must apply even more sensitive assays to assure that all replication-competent virus has been eliminated. We also do not have an understanding of the possible presence of viral reservoirs in tissues such as the spleen and/or liver, a gap in our knowledge which needs to be addressed.

What is currently your area of research?

My group's principal areas of research interest focus on molecular and medical virology and the application of innovative techniques and assays which provide new insights into disease pathogenesis and treatment, especially for HIV. Our current research focuses on understanding the genetic characteristics and dynamics of persistent HIV across a range of tissues and cells to guide and assess treatment interventions designed to reduce persistent HIV reservoirs and inform HIV eradication strategies.