Regulation of human immunodeficiency virus type-1 (HIV-1) infection and latency under low oxygen tension

Gabriel Williams*, Chris Sanborn*, Khalid A. Timani and Johnny J. He
Department of Microbiology, Immunology and Genetics, UNT Health Science Center,
Fort Worth TX, 76107

The human immunodeficiency virus type 1 (HIV-1) is not efficiently contained by the host immune response. Despite combination retroviral therapy being potent and life-prolonging, it is not curative and fails to eradicate integrated copies of HIV-1 genome since treatment interruption inevitably results in a rapid viral activation and rebound of plasma viremia. Therefore, an increased understanding of factors that regulate HIV-1 replication and reactivation from latent reservoirs is needed to inform the development of new strategies to control/eradicate HIV-1. The roles of physiological factors in controlling HIV-1 are not fully understood. Among these factors is hypoxia (low oxygen tension). Levels of hypoxia differ among different cells/tissues, e.g. CD4+ T cells, the principal target of HIV-1 replication and latency, exist in a hypoxic environment in lymphoid tissues (1% O2) whilst circulating CD4+ T cells encounter variable oxygen tension as they traffic around the body (13% O2 in arterial blood). Therefore, it is highly possible that viruses have evolved certain strategies to replicate or persist in their host under varied oxygen concentrations. Nevertheless, most of the in vitro experiments to study HIV-1 replication and infection were performed under the normal oxygen condition (21% O2). Thus, in the present study, we investigated effects of hypoxia on HIV-1 replication and latency using acutely and chronically HIV-1 infected cells. Several techniques were used including cells proliferation assay, reverse-transcriptase assay and Western blotting analysis. Our results showed that exposure of HIV-1 infected T lymphocyte cell line Jurkat to 1% O2 up to 72 hr led to inhibited HIV-1 replication. Chronically infected HIV-1 cell lines (ACH2 and J1.1) that were treated with TNF-α for 48 hr, followed by exposure to hypoxia for 24 hr showed an initial increased HIV-1 replication, then decreased after 72 hr. In contrast, ACH2 and J1.1 cultured under normoxia appeared to have a slow but steadily increased HIV-1 replication over the period of 72 hr. Unexpectedly, we found a greater increase in ACH2 and J1.1 proliferation under hypoxia compared to their normoxia counterpart, which may explain the increase in the HIV-1 replication at early time points. Our data further showed that treatment of HIV-1 infected cells with hypoxia-mimicking drugs (DFO or DMOG), which stabilize hypoxia senescing protein, HIF1-α, caused an inhibition of HIV-1 replication suggesting that HIF-1α may act as a repressor for HIV-1. Taken together, the level of oxygen in the cells environment could alter the HIV-1 replication and silencing which may play important role in developing latency.
Regulation of HIV-1 infection and latency by low oxygen tension

**Working Model**

- Hypoxia → HIV-1 Transcription and Silencing
- Periphery: ~13% O₂, NF-κB activators
- Lymph node: ~1% O₂, HIF-1 repressors?
- Promotes latency?

**CD4 T cells**

**Microenvironment**