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Title: INVESTIGATION OF REDOX SIGNALLING DURING HIV INFECTION

ABSTRACT

Redox signaling plays a crucial role in the pathogenesis of Human Immunodeficiency Virus type-1 (HIV-1). Majority of HIV redox research relies on measuring redox stress using invasive technologies, which are unreliable and do not inform the contributions of sub-cellular compartments. A major technological leap emerges from the development of genetically encoded redox sensitive green fluorescent proteins (roGFPs), which provide sensitive and compartment specific insights into redox homeostasis. Here, we exploited a roGFP based specific bioprobe of glutathione redox potential (E_{GSH}; Grx1-roGFP2) and measured subcellular changes in E_{GSH} during various phases of HIV-1 infection using U1 monocytic cells (latently infected U937 cells with HIV-1). We show that while U937 and U1 cells demonstrate significantly reduced cytosolic and mitochondrial E_{GSH} (~ -310 mV), active viral replication induces substantial oxidative stress (E_{GSH} > -240 mV). Furthermore, exposure to a physiologically-relevant oxidant, hydrogen peroxide (H_2O_2) induces significant deviations in sub-cellular E_{GSH} between U937 and U1, which distinctly modulates susceptibility to apoptosis. Using Grx1-roGFP2, we demonstrate that

a marginal increase of about ~25 mV in E_{GSH} is sufficient to switch HIV-1 from latency to reactivation, raising the possibility of purging HIV-1 by redox modulators without triggering detrimental changes in cellular physiology. Importantly, we show that bioactive lipids synthesized by clinical drug resistant isolates of Mycobacterium tuberculosis (*Mtb*) reactivate HIV 1 through modulation of intracellular E_{GSH}. Finally, the expression analysis of U1 and patient Peripheral Blood Mononuclear Cells (PBMCs) demonstrated a major recalibration of cellular redox homeostatic pathways during persistence and active replication of HIV.

KEY WORDS: HIV-1, MONOCYTES, GLUTATHIONE POTENTIAL, Grx1-roGFP2 AND LATENCY