CELL CYCLE
2016, VOL. 15, NO. 18, 2389–2390
http://dx.doi.org/10.1080/15384101.2016.1211448

Taylor & Francis
Taylor & Francis Group

CELL CYCLE NEWS & VIEWS

HIV Vpr controls CNS metabolism

Stacey Boyd, Yao Akpamagbo, and Fatah Kashanchi

Laboratory of Molecular Virology, George Mason University, Manassas, VA, USA

ARTICLE HISTORY Received 9 June 2016; Accepted 22 June 2016

KEYWORDS HAD; HAND; HIV-1; Vpr

The *vpr* gene is conserved among human and simian immunodeficiency viruses and encodes the regulatory viral protein R (Vpr), a small basic protein (14 kDa) of 96 amino acids.[1] The significance of Vpr has been initially shown in macaque rhesus monkeys that were infected with a *vpr*-mutated SIVmac, and exhibited a decrease in virus replication and a delay in disease development progression. Also, in the absence of Vpr, HIV-1 replicates less efficiently in macrophages, a cell type that represents an important viral reservoir by harboring the virus over long periods of time. Due to its specific incorporation into the viral particle by interaction with the Pr55Gag-derived p6 protein, Vpr is readily present upon entry of the virus into the cell, which speaks in favor for enrollment during early steps of viral replication. Furthermore, Vpr also affects the nuclear import of the viral DNA within the pre-integration complex (PIC), the cell cycle progression, and regulation of apoptosis, as well as the transactivation of the HIV-1 LTR as well as host cell genes.[2]

Individuals infected with HIV have conditions of fluctuating degrees of impairment of cognition and associated functioning and can develop HIV-associated neurocognitive disorders (HAND). Invasion and replication of HIV in the brain parenchyma is accomplished by brain perivascular macrophages, endogenous microglia, and some astrocytes that are infected and can initiate the neuropathogenesis of HAND. Immune activation of resident glia and neuroinflammation are associated with this infection and neuronal injury. The general occurrence of HAND and related diseases continue to be at high levels even with the extensive use of antiretroviral therapy (ART) that has radically reduced the occurrence of the severest form of HAND, HIV-associated dementia (HAD). The persistence of this high risk for HAND in individuals experiencing effective control of systemic HIV viral load is incompletely explained, and suggested factors include effects of aging on brain vulnerability, persistence of HIV replication in brain macrophages, evolution of highly neurovirulent CNS HIV strains, and even long-term CNS toxicity of ART.[3] Prevention and treatment of HAND requires strategies aimed at suppressing CNS HIV replication is critical in treatment of systemic and CNS inflammation, especially in aging and substance-abusing HIV populations.

The features linked with increasing the inflammatory setting within the CNS and HIV replication are what drive the pathogenesis of HAND. Neuronal damage associated with HAND can be augmented by subordinate effects of aging, movement of activated monocytes, systemic immune activation and drug abuse and can continue in spite of the effective systemic control of HIV replication by ART. Active complementary neuroprotectants are substances that can overturn systemic immune activation and associated inflammation both systemically and within the CNS.[4] Drugs that aim toward these cellular pathways could quickly ease testing and application of possible complementary neuroprotective approaches against HAND.

It has previously been shown that some CNS related viruses, including CMV, can control metabolism (i.e., Glutamine) and regulate viral replication. For instance, production and TCA cycle biosynthetic intermediates are present in infected cells, which allow glucose to be diverted for use in synthetic processes.[5] The authors further showed this by the rescuing of ATP synthesis and viral growth when stoichiometrically equal amounts of the citric acid cycle intermediates α-ketoglutarate, oxaloacetic acid, and pyruvate were added individually to glutamine-free medium.

In a recent article by Datta et al., the authors show for the first time that a human retroviral infection, namely HIV-1, leads to increase in glutamate production mediated by Vpr and glutaminase.[6] Using a SILAC-based proteomics study, these authors have previously shown that HIV-1 Vpr overexpression in macrophages induced changes at the protein level in many of the enzymes involved in cellular metabolism. This is consistent with the role of Vpr, which has been found in CNS of infected individuals and its association with HAD. HAD has been linked to macrophage toxin production including glutamate, and increased glutamate levels are also seen in the plasma, and cerebrospinal fluid (CSF) of HIV-1 infected patients.[7]

These colleagues have developed a state-of-the-art mass spectrometry-based Isotope-assisted metabolomics targeting 13C-metabolic flux profiling of glucose to measure de novo synthesis and release of glutamate upon activation of the glycolytic-TCA pathways to evaluate the role of HIV-1 Vpr in

CONTACT Fatah Kashanchi fkashanc@gmu.edu

News & Views to: Datta PK, et al. Glutamate metabolism in HIV-1 infected macrophages: Role of HIV-1 Vpr. Cell Cycle 2016; 15(17):2288-98; PMID: 27245560; http://dx.doi.org/10.1080/15384101.2016.1190054

orchestrating changes in macrophage glutamate metabolism. Selected metabolites, namely G6P, F6P, citrate, α-KG, fumarate, malic acid, glutamic acid and glutamine were used for flux profiling. They observed a significant decrease in levels of α-KG and malate in Vpr transduced macrophages. Interestingly, they observed a significant increase in levels of α-KG and glutamine in the extracellular media of macrophages transduced with Vpr on day 7 in comparison to the Ad-Null transduced macrophages, which correlated with a significant increase in 13C6-glucose uptake on day 3 and 7. Their collective observations show that Vpr most likely inhibits fumarase activity. Fumarate is a competitive inhibitor of α-KG or 2-oxoglutarate-dependent 10-11 translocation enzymes (TETs) for DNA demethylation and many JmjC-type of histone demethylases. Also, α-KG a key intermediate in glutamate metabolism is known to stabilize reactive oxygen species (ROS) homeostasis in cells and thereby mitigate oxidative stress-mediated damage to proteins, lipids and DNA. This further enforces the notion that maintenance of ROS homeostasis in infected HIV-1 macrophages can promote long-term survival and persistence.

The regulation of glutamine metabolism further suggests its significance in ROS pathway as well as not wanting the glucose to be metabolized for energy in the citric acid cycle but instead maintaining it potentially for synthetic purposes such as fatty acid synthesis. This would also fit the role of glutamine as a major anaplerotic substrate regulated in cancers cells. Future experiments using inhibitors of the TCA pathway as well as the ROS will better answer these significant questions in reducing HAND in patients undergoing retroviral treatment regimens.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

[1] Steffy K, et al. Genetic regulation of human immunodeficiency virus. Microbiol Rev 1991; 55(2):193-205; PMID:1886517

[2] Guenzel CA, Hérate C, Benichou S. HIV-1 Vpr—a still "enigmatic multitasker". Front Microbiol 2014; 5:127; PMID:24744753; http://dx.doi.org/10.3389/fmicb.2014.00127

[3] Heaton RK, Clifford DB, Franklin DR, WOods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy. Neurology 2010; 75(23):2087-96; PMID:21135382; http://dx.doi.org/10.1212/WNL.0b013e318200d727

[4] Grovit-Ferbas K, Harris-White ME. Thinking about HIV: the intersection of virus, neuroinflammation and cognitive dysfunction. Immunol Res 2010; 48(1-3):40-58; PMID:20725864; http://dx.doi.org/10.1007/s12026-010-8166-x

[5] Chambers JW, Maguire TG, Alwine JC. Glutamine metabolism is essential for human cytomegalovirus infection. J Virol 2010; 84 (4):1867-73; PMID:19939921; http://dx.doi.org/10.1128/JVI.02123-09

[6] Datta P, et al. Glutamate metabolism in HIV-1 infected macrophages: Role of HIV-1 Vpr. Cell Cycle 2016; 15(17):2288-98; PMID: 27245560; http://dx.doi.org/10.1080/15384101.2016.1190054

[7] Erdman N, Tian C, Huang Y, Zhao J, Herek S, Curthoys N, Zhang J. In vitro glutaminase regulation and mechanisms of glutamate generation in HIV-1-infected macrophage. J Neurochem 2009; 109: 551-61; PMID:19222703; http://dx.doi.org/10.1111/j.1471-4159.2009.05989.x