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HUMAN IMMUNODEFICIENCY VIRUS-1 TAT MEDIATED ELICITATION OF NEUROTOXICITY AND NEUROAIDS

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Abstract- Human immunodeficiency virus-1 (HIV-1) Tat induces the replication of HIV by alleviating the transcription of viral genes. Tat is released from HIV infected cells and it modifies the functions of uninfected cells. HIV infected cells enter the brain through BBB. In the brain, Tat induces neuronal damage and leads to neuroAIDS. Oxidative stress is believed to play an important role for causing HIV-dementia. NeuroAIDS is more common in aged HIV positive adults and drug abusers.

Keywords- HIV-1, Tat (transactivator of transcription), reverse transcription, apoptosis, neuropathogenesis, HAD, HAND, BBB, neuroAIDS, Tat, NMDAR

Introduction

HIV-1 is the retrovirus which has affected almost 34 million people all around the globe. HIV-1 is prevalent more in low and middle income countries and it is also spreading in children [1]. HIV-1 can be classified into three major groups- M, N, O and subgroups- A to K [2]. The HIV genome, has three structural genes (gag, pol, env), two regulatory genes (tat and rev) and four auxiliary genes (nef, vpu, vpr, and vif) [3]. Nearly 35% of the people infected with HIV are suffering from HIV-1 associated dementia (HAD) and it is more serious in drug abusers. Upon the administration of Highly Active Antiretroviral Therapy (HAART) on HIV positive patients, their life span increases but they might have more chances of having neurological disorders as HAART is effective in reducing the viral replication but it is unable to destroy the viral reservoirs in the brain [4,5]. In the condition of HAD, infected macrophages and monocytes enter the Central Nervous System (CNS) and spread leading to neuronal damage neuronal damage in brain cells [6]. Post-mortem studies on brain tissues have shown, that all the disorders occur due to the increase in levels of proinflammatory cytokines like tumor necrosis factor-α (TNF-α) and interleukin (IL-1β), PAF, excitatory amino acids mainly glutamate, soluble viral proteins and chemokines. The *in vivo* and *in vitro* studies have suggested that there is involvement of these factors as mediators of neuro-degeneration. HIV mainly affects the macrophages/microglial cells during the initial stage of viral replication in CNS. A small fraction of astro-cytes are also affected but the virus entry and replication in these cells is not possible. The role of these infected astrocytes is not well understood. Till now there is no proof stating that the neurons are affected by HIV but the neuronal damage is surely caused by the indirect mechanisms like neurotoxins released by HIV infected cells. One of the main neurotoxin which acts as the transactivator re-leased by the infected cells is HIV Tat which plays a crucial role in development of HAD [7,8]. Another HIV protein Nef is also known to have a role in the growth and development of virus cells by protect-ing the infected cells from apoptotic signals in the brain [9].

Oxidative Stress and its Connection to Dementia

Oxidative stress is the alteration and change which occurs due to the reactive oxygen species (ROS). Oxidative stress occurs due to the imbalance between the anti-oxidant and pro-oxidant molecules [10]. The ROS are highly reactive and toxic molecules, such as peroxyl radical, hydrogen peroxide, hydroxyl radical, super oxide anion and peroxynitrite. The half-lives of ROS molecules vary from nanoseconds for the hydroxyl radicals to few seconds for peroxyl radicals and nitric oxide. It has been observed that protein oxidation is seen more in the brains of HIV infected patients suffering from mild or severe dementia compared to non-dementia patients. Oxidative stress and activation of cytokine receptors leads to the elevation in the levels of sphingomyelin and ceramide which are significant mediators for causing neuronal apoptosis. Therefore, oxidative stress may be much higher in HIV associated dementia patients compared to non-dementia patients.

Oxidative Stress and Antioxidants

To counteract the hazardous effects of ROS, there are antioxidant molecules, like glutathione reductase, glutathione peroxidase, glutathione transferase, S-methyl transferase, superoxide dismutase, and catalase. Small, non-protein cellular anti-oxidants such as vitamin C, vitamin E, glutathione, carotenoids, flavonoids, uric acid and thioredoxin provide protection against ROS molecules. Glutathione (GSH) is the main antioxidant molecule which plays a crucial role in maintaining the balance in redox reactions. The biosynthesis of Glutathione is decreased by Tat, which may affect many cellular functions. In human monocytes derived lymphocytes and macrophages, GSH hinders the viral replication *in vitro*. In HIV patients the antioxidant levels are altered, so they suffer from oxidative stress which leads to dementia [11].

Tat, the Transcriptional Transactivator Gene

Tat is a multifunctional transcriptional transactivator protein of 101 amino acids encoded by the *tat* gene which consists of two exons: 1

and 2 [12]. Tat gene promotes replication by more than two times compared to normal replication rate. Tat protein over takes the host RNA polymerase II elongation machinery by interacting with positive transcription elongation factor, P-TEFb. It attaches mainly with cyclin T1 subunit of P-TEFb along with the T-loop of the Cdk9 subunit. Tat induces significant conformational changes in P-TEFb which leads to stimulation of HIV mRNA elongation [13] [Fig-1]. Tat protein is released by HIV infected cells in to the extracellular space, cerebrospinal fluid and sera. Tat binds to the RNA base-paired stem loop structure called transactivation response region (TAR) [14]. Studies have reported the presence of Tat in brains of HAD patients by Western and southern blot analyses [15]. In HIV-1 infected patients, neurons are not affected much but still notable neuronal loss and dysfunction occurs. Astrocytes secrete Tat, which provides the protection from cellular injury. So Tat protein is over-expressed in people suffering from HIV.

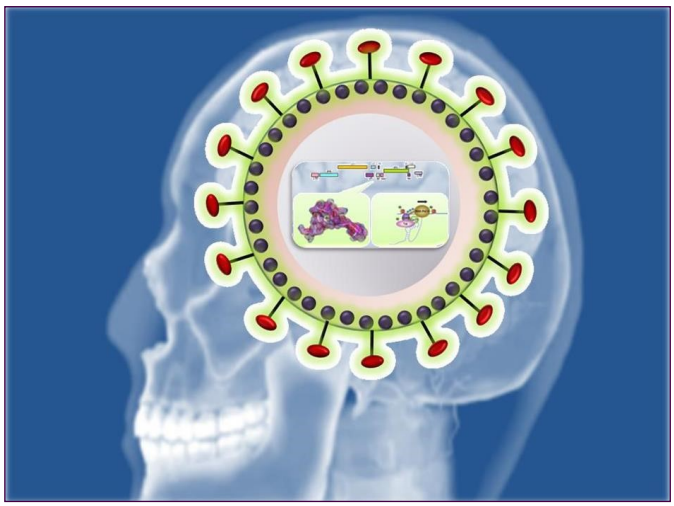

Fig. 1- Displaying HIV-1 in human brain. Tat gene in HIV genome encodes for Tat protein which follows a complex mechanism and interferes with the host factor leading to neurological disorders.

HIV Entry into the Brain through BBB

It is still not clear whether the detected Tat is secreted by the infected cells present in CNS which includes macrophages, microglia and astrocytes or it is particularly transported to the brain beyond the Blood brain barrier (BBB) from the sera. BBB is the separation between the circulating blood and the brain for the protection of the brain from infection and toxicity. The integrity of BBB is lost when infected monocytes/macrophages enter the BBB during immune surveillance [16,17]. These infected macrophages in turn secrete various toxins and chemotactic agents which recruit more cells which leads to increased infection in the brain. This happens due to the altered expression of adherens junction (AJ) and tight junction (TJ) proteins in BBB. All the different types of CNS cells like oligodendrocytes, macrophage, astrocytes, neurons, and microglia can be certainly infected by HIV-1 as they have receptors and co-receptors for HIV-1 entry but only microglia and macrophages are mostly infected [18].

Tat Induced Dementia

Tat causes the apoptosis in neurons. Tat promotes N-Methyl-D-aspartate (NMDA), Lipoprotein Receptor related Protein (LRP), and postsynaptic density protein-95 (PSD-95) receptors and form a macromolecular complex which cause neuronal disorders [19-22]. Tat modulates NMDA only in the presence of zinc. Tat induces p53 and p73 proteins which are transcription factors in neuroAIDS and cause apoptosis of neuronal cells [23]. Studies suggests that HIV-1 clade B and C Tat proteins have differential roles in the neuropathogenesis of HAD [7].

Role of Tat in Neurotoxicity

Tat activates neuronal nitric oxide synthase (nNOS) by associating it with NMDAR through PSD-95. nNOS is activated by calcium flux through the NMDAR leading to NO production which is necessary for the apoptosis of neurons [24]. It has been studied that NO toxicity starts by interacting with cytochrome C in the mitochondria which results in the production of ONOO- which damages the DNA and mitochondrial membrane. This production leads to mitochondrial dysfunction and swelling, along with release of cytochrome C and calcium. It is shown experimentally that NO triggers the p38 MAPK pathway which leads to cell death. In vitro Tat treatment of mouse neurons showed the activation of both the JNK MAPK and p38 pathways, although, only p38 MAPK pathway was requisite for Tat induced toxicity. However Tat induced caspase 3 activation was greatly reduced by blockage of JNK MAPK pathway but still neuronal viability did not change specifying that neither the caspase activity nor the JNK pathway is required for Tat induced toxicity [8].

Indirect Neurotoxicity of Tat

In CNS, the microglias are the primary cells which are attacked by HIV [25,26]. Tat activates microglia that leads to release of various inflammatory mediators like chemokines and cytokines, reactive nitrogen and oxygen molecules which brings other inflammatory cells to the brain [27-29]. TNF-α enforces the glutamate secretion from astrocytes and prevents them to further uptake the glutamate. This promotes the build-up of glutamate in the proximity of neurons, NMDA receptors gets hyper activated, increased influx of calcium, and ultimately leads to cell death. HIV-1 gp120 protein has been reported to hinder the ability of astrocytes to transport the glutamate leading to the defect that prevents the transcription of excitatory amino acid transporter -2 (EAAT2), glutamate transporter gene [30,31]. Astrocytes are activated by Tat, which promotes the expression of inducible nitric oxide synthase (iNOS). This results in excessive formation of nitrous oxide (NO) that reacts with superoxide anion (O2-) and forms neurotoxic peroxynitrite (ONOO-) in HIV infected macrophages. Tat gene induces Tat protein and TNF-α which induces the production of quinolinic acid (QUIN) that activates NMDA receptor.

Tat and the Drugs Abuse

Psychoactive drugs (like cocaine, morphine and methamphetamine) abusers are reported to have more critical disease conditions compared to non-drugs abusers [32]. Psychoactive drugs alter the integrity of BBB and acts as cofactors for HIV-infection which leads to influx of infected monocytes/macrophages into the brain [33]. According to recent studies opiate drugs elevate the production of inflammatory cytokines by astrocytes intensify the neuronal degeneration in opiate abusers [34-40].

Conclusions

HIV infects CNS cells of human brain and causes neuroAIDS. From the last 30 years, many different strategies and methods have been applied for combat against neuroAIDS. The infection caused by HIV -1 associated neuroAIDS is long-lasting and many areas of the

brain are affected. NeuroAIDS is more prevalent in aged HIV positive adults and associated drug abusers and in these patients virus replication occurs at a faster pace. HAART is effective in reducing the viral replication but it is unable to destroy the viral reservoirs in the brain. Inspite of HAART, 50% of HIV-1 positive adults are suffering from HAD. Glutamate and its receptors play a crucial role in the apoptosis of neurons during neuroAIDS. Therefore, targeting the glutamate transport pathway may be promising for the treatment of HAD. A novel, infallible and improved drug strategy like nanotherapeutics could be used to treat Tat mediated neuroAIDS. In addition Oligopeptide based vaccines can also be a promising solution against neuroAIDS.

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Conflicts of Interest: None declared.

References

[1] Sundaravaradan V., Saxena S.K., Ramakrishnan R., Yedavalli V.R., Harris D.T. & Ahmad N. (2006) *Proceedings of the National Academy of Sciences, USA*, 103(31), 11701-11706.

[2] Saxena S.K., Tiwari S. & Nair M.P. (2012) *Science*, 337(6096), 798.

[3] Saxena S.K., Shrivastava G., Tiwari S., Swamy M.A. & Nair M.P. (2012) *Future Virology*, 7(6), 609-620.

[4] Saiyed Z.M., Gandhi N., Agudelo M., Napuri J., Samikkannu T., Reddy P.V., Khatavkar P., Yndart A., Saxena S.K. & Nair M.P. (2011) *Neurochemistry International*, 58(6), 656-664.

[5] Mocchetti I. (2012) *Journal of Neurovirology*, 18(6), 443-444.

[6] Avgeropoulos N.G., Burris G.W., Ohlandt G.W., Wesselingh S.L., Markham R.B. & Tyor W.R. (1998) *Journal of NeuroA-IDS*, 2(1), 1-20.

[7] Samikkannu T., Rao K.V., Gandhi N., Saxena S.K. & Nair M.P. (2010) *Journal of Neurovirology*, 16(4), 255 -263.

[8] King J.E., Eugenin E.A., Buckner C.M. & Berman J.W. (2006) Microbes and Infection, 8(5), 1347-1357.

[9] Saxena S.K., Shrivastava G., Tiwari S. & Nair M.P. (2012) *Future Virology*, 7(2), 117-120.

[10] Mollace V., Nottet H.S., Clayette P., Turco M.C., Muscoli C., Salvemini D. & Perno C.F. (2001) *Trends in Neuroscience*, 24 (7), 411-416.

[11] Pocernich C.B., Sultana R., Abdul H.M., Nath A. & Butterfield D.A. (2005) *Brain Research Reviews*, 50(1), 14-26.

[12] Tiwari S., Nair P.N. & Saxena S.K. (2012) *American Journal of Infectious Diseases*, 8(2), 79-91.

[13] Tahirov T.H., Babayeva N.D., Varzavand K., Cooper J.J., Sedore S.C. & Price D.H. (2010) *Nature*, 465(7299), 747-751.

[14] Hetzer C., Dormeyer W., Schnölzer M. & Ott M. (2005) *Microbes and Infection*, 7(13), 1364-1369.

[15] Zou W., Kim B.O., Zhou B.Y., Liu Y., Messing A. & He J.J. (2007) *American Journal of Pathology*, 171(6), 1923-1935.

[16] Gandhi N., Saiyed Z.M., Napuri J., Samikkannu T., Reddy P.V., Agudelo M., Khatavkar P., Saxena S.K. & Nair M.P. (2010) *Journal of Neurovirology*, 16(4), 294-305.

[17] Banks W.A., Ercal N. & Price T.O. (2006) *Current HIV Research*, 4(3), 259-266.

[18] Saxena S.K., Tiwari S. & Nair P.N. (2013) *Current Perspectives in HIV Infection, InTech, Europe*, 109-124.

[19] Merino J.J., Montes M.L., Blanco A., Bustos M.J., Oreja-Guevara C., Bayon C., Cuadrado A., Lubrini G., Cambron I., Munoz A., Cebolla S., Gutierrez-Fernandez M., Bernardino J.I., Arribas J.R. & Fiala M. (2011) *Reviews Neurology*, 52(2), 101-111.

[20] Eugenin E.A., King J.E., Nath A., Calderon T.M., Zukin R.S., Bennett M.V. & Berman J.W. (2007) *Proceedings of the National Academy of Sciences, USA*, 104(9), 3438-3443.

[21] Irish B.P., Khan Z.K., Jain P., Nonnemacher M.R., Pirrone V., Rahman S., Rajagopalan N., Suchitra J.B., Mostoller K. & Wigdahl B. (2009) *American Journal of Infectious Diseases*, 5(3), 231-258.

[22] King J.E., Eugenin E.A., Hazleton J.E., Morgello S. & Berman J.W. (2010) *American Journal of Pathology*, 176(6), 2819-2830.

[23] Mukerjee R., Deshmane S.L., Fan S., Del Valle L., White M.K., Khalili K., Amini S. & Sawaya B.E. (2008) *Cell Cycle*, 7(17), 2682-2690.

[24] Eugenin E.A., King J.E., Hazleton J.E., Major E.O., Bennett M.V., Zukin R.S. & Berman J.W. (2011) *Neurotoxicity Research*, 19(1), 138-148.

[25] Kilareski E.M., Shah S., Nonnemacher M.R. & Wigdahl B. (2009) *Retrovirology*, 6, 118.

[26] D'Aversa T.G., Eugenin E.A. & Berman J.W. (2005) *Journal of Neuroscience Research*, 81(3), 436-446.

[27] Gandhi N., Saiyed Z., Thangavel S., Rodriguez J., Rao K.V. & Nair M.P. (2009) *AIDS Research and Human Retroviruses*, 25 (7), 691-699.

[28] Mishra M., Taneja M., Malik S., Khalique H. & Seth P. (2010) *Journal of Neurovirology*, 16(5), 355-367.

[29] Cao S., Wu C., Yang Y., Sniderhan L.F., Maggirwar S.B., Dewhurst S. & Lu Y (2011) *Journal of Neuroinflammation*, 8, 48.

[30] Aksenov M.Y., Aksenova M.V., Mactutus C.F. & Booze R.M. (2010) *Neuroscience Letters*, 475(3), 174-178.

[31] Podhaizer E.M., Zou S., Fitting S., Samano K.L., El-Hage N., Knapp P.E. & Hauser K.F. (2012) *Journal of Neuroimmune Pharmacology*, 7(4), 877-891.

[32] Dutta R., Krishnan A., Meng J., Das S., Ma J., Banerjee S., Wang J., Charboneau R., Prakash O., Barke R.A. & Roy S. (2012) *Journal of Neuroscience*, 32(29), 9917-9930.

[33] Turchan-Cholewo J., Dimayua F.O., Gupta S., Keller J.N., Knapp P.E., Hauser K.F. & Bruce-Keller A.J. (2009) *Journal of Neurochemistry*, 108(1), 202-215.

[34] Yuan Y., Arnatt C.K., El-Hage N., Dever S.M., Jacob J.C., Selley D.E., Hauser K.F., Zhang Y. (2013) *Medchemcomm*, 4(5), 847-851.

[35] Pilakka-Kanthikeel S., Atluri V.S., Sagar V., Saxena S.K. & Nair M. (2013) *PLoS One*, 8(4), e62241.

[36] Tiwari S., Nair M.P. & Saxena S.K. (2013) *Future Virology*, 8(2), 121-127.

[37] Reddy P.V., Pilakka-Kanthikeel S., Saxena S.K., Saiyed Z. &

Nair M.P. (2012) *AIDS Research and Treatment*, 2012, 953678.

[38] Hauser K.F., Fitting S., Dever S.M., Podhaizer E.M. & Knapp P.E. (2012) *Current HIV Research*, 10(5), 435-452.

[39] Shapshak P., Duncan R., Nath A., Turchan J., Pandjassarame K., Rodriguez H., Duran E.M., Ziegler F., Amaro E., Lewis A., Rodriguez A., Minagar A., Davis W., Seth R., Elkomy F.F., Chiappelli F. & Kazic T. (2006) *Frontiers in Bioscience*, 11, 1774-1793.

[40] Fitting S., Xu R., Bull C., Buch S.K., El-Hage N., Nath A., Knapp P.E. & Hauser K.F. (2010) *American Journal of Pathology*, 177 (3), 1397-1410.