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# ROLE OF SIRTUIN1 IN VIRAL DISEASES

**Syam P K Jeepipalli**

Skill Development Cell (Food Processing), Central University of Karnataka, Kadaganchi, Gulberga, Karnataka, India-585367.

**ABSTRACT** The obligate intracellular parasites (viruses) depend on host for the synthesis of viral progeny. They control host cells metabolism for energy and propagate by capturing the control over host cell genome. Infected viruses are regulating the expression of certain proteins for their hassle free proliferation. Sirtuins are transcriptional regulators and metabolic sensors in the viral infected cells. SIRT1 is acting as friend and foe to different groups of viruses. SIRT1 is a positive regulator for HIV-1, hepatitis B virus and negative regulator for neurotropic viruses. In this review the role of sirtuin1 in viral diseases discussed which a versatile pharmacological target.

**Summary:**Regulated control of sirtuin1 could enhance of arrest of virus life cycle in different viral diseases.

**KEYWORDS :** Virus, Metabolism, Sirtuin, Sirtinol, Tat

## INTRODUCTION

Virus is an obligate intracellular parasite was causative agent for many epidemics. The persisted virus could pass from one infected organism to another through the general ways of oral–fecal, airborne, blood-borne (including viruses that are spread by bloodsucking arthropods), sexual, and congenital. Viruses depend on host-cell metabolism for energy, production of viral components and genomes, as well as for organization of cellular compartments of replication, maturation and dissemination. For the uninterrupted viral multiplication, histone deacetylases are playing a pivotal role in different disease pathologies.

Sirtuins are class III histone deacetylases. Silent mating type information regulation 2 homolog 1 (SIRT1) is a NAD+ dependent protein deacetylase localized in nucleus (Nogueiras et al 2012). SIRT1 protein plays an important role in inflammation and apoptosis. Pharmacological inhibition of SIRT1 increasing the production of infectious virions (Li et al 2014). Knockdown of SIRT1 increasing the DNA and RNA virus titres through its enzymatic activity (Koyuncu et al 2014). Many viral diseases are aggravating via SIRT1 mediation and offering a cue for potential pharmacological target for viral infections. Here we reviewed in detailed about SIRT1 contribution for different viral diseases propagation.

### Role in retrovirus life cycle

Viral transactivator (Tat) is potential activator of HIV viral transcription. SIRT1 is a novel cofactor necessary for efficient Tat-mediated transactivation of the HIV promoter (Pagans et al 2005). Tat protein blocking the SIRT1 that deacetylate the p65 subunit of NFκB and hyperactivates the expression of NFκB-responsive genes (Kwon et al 2008). This disturbs the activation of T cell genes. In the HIV-1 infected kidney patients, increased expression of SIRT1 negatively regulating the expression of HIV-1 proviral genes and inactivating the NFκB p65 and long terminal repeat promoter activity (Pinzone et al 2013; Wang et al 2020).

Human T cell leukemia virus 1 (HTLV-1) is the first recognized oncogenic retrovirus. SIRT1 inhibitor sirtinol is directing the viral infected cells to apoptosis. In the HTLV-1 infected T cells sirtinol decreasing the SIRT1, phospho-SIRT1 levels and inducing apoptosis. Induction of apoptosis was also observed in the SIRT1 knockdown T cells on HTLV-1 infection (Kozako et al 2012).

### Role in respiratory virus's life cycle

Dysregulated inflammatory profile plays important role in COVID19 pathogenesis. COVID-19 patients had a higher inflammatory cytokines and p53 expression with decreased sirtuin1 expression (Bordoni et al 2021) further impacting the cell survival, B cell signalling and antibody production. Melatonin antiviral activities are associated with activation of SIRT1 in dengue virus infection and COVID19. Melatonin upregulating K63 polyubiquitination of the mitochondrial antiviral-signalling protein by increasing SIRT1 levels, thereby boosting the COVID19 mediated induction of type 1 interferons (Morchang et al 2021; DiNicolantonio,McCarty and Barroso-Aranda, 2021). Respiratory syncytial virus (RSV) is affecting the lower respiratory tract of children. RSV is worsening mitochondrial membrane potential, oxygen consumption rate and abrupt the adoptive immune response activation in SIRT1 deficient bone marrow derived dendritic cells (Elesela et al 2020). SIRT1 activators (Resveratrol and Metformin) are inhibiting the expression of matrix metalloproteinase 9 (MMP9) and promoting the respiratory function in the human nasal epithelial cells (Suzuki et al 2018; Fukuda et al 2020). Inhibiting the SIRT1 decreasing the lung pathology in the respiratory syncytial virus infected mice (Owczarczyk et al 2015).

### Role in hepatitis virus's life cycle

Multiple sclerosis is causing inflammation and neuronal loss in the central neural system. In the hepatitis virus (MHV-A59) induced multiple sclerosis mice, SIRT1 activation is preventing the neuronal loss in optic neuritis (Khan et al 2014). Increasing the SIRT1 levels playing a pivotal role for proliferation, migration and invasion of hepatitis B virus induced hepatocellular carcinoma (Wang, Cheng and Chen, 2020). SIRT1 is a potential target for miR-141 for the inhibition of autophagy mediated hepatitis B virus (Yang et al 2017). In the hepatitis B virus transgenic mice, nicotinamide suppressing the serum levels viral DNA, surface (HBsAg), envelop antigens (HBeAg) and viral DNA in the liver by decreasing the expression of AP-1, C/EBPα and PPARα transcription factors (Li et al 2016).

### Role in human papilioma virus life cycle

Cervical cancer is the fourth leading cancer in the women causing by sexually (skin to skin) acquired human papilioma virus. Viral oncogene HPV16 E7 is inducing SIRT1 levels in the primary human keratinocytes similar to those observed in human cervical cancer cells. HPV E7 protein is attenuating pro-apoptosis functions of p53 via SIRT1 upregulation (Jiang and Milner, 2002).

### Role in herpesvirus life cycle

Human herpes virus 8 or KHSV is causing Kaposi's sarcoma highly angiogenic and causing lesions on skin and visceral organs. Kaposi's sarcoma-associated herpesvirus (KSHV) is an oncogenic □2 herpes virus. Herpes virus had a long latency soon after primary infection. Pharmacological up-regulation of SIRT1 is reducing the reactivation of these neurotropic viruses. Inhibiting the SIRT1 in the latent KSHV infected PEL cell line BCBL-1, expressing the lytic genes and facilitating the viral replication cycle to complete. Evidently, SIRT1 is directing the KSHV to a long latency (He and Gao, 2014). SIRT1 antagonists were enhancing both human cytomegalovirus and influenza viral production, on the contrary, SIRT1 activators restricting both viruses (Koyuncu et al 2014).

### Role in Enterovirus life cycle

Enterovirus replicate in the intestine but can also spread to the blood and some internal organs. Enterovirus 71 (EV71) possess single stranded positive RNA as the genetic material. EV71 is activating SIRT1 production and enhancing its entry into the cytoplasm. SIRT1 interact with 5' UPR of EV71 RNA, binds with internal ribosomal entry site and respectively inhibiting transcription and translation (Han et al 2016).

## CONCLUSION

The positive regulatory events of SIRT1 are focusing area to invest more research for controlling the virus multiplication. The negative

regulatory events of SIRT1 are well observed in the antagonist study and inhibitor study could also need to focus on their impact on other tissue if used as pharmacological targets to control the virus spread in the human body.

**Conflict of Interest**

The author has no competing interest.

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