Pharmacology & Therapeutics xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Diverse roles of HDAC6 in viral infection: Implications for antiviral therapy

Linlin Zhang [a], Angela Ogden [b], Ritu Aneja [b], Jun Zhou [a,c,*]

[a] State Key Laboratory of Medicinal Chemical Biology, College of Life Sciences, Nankai University, Tianjin 300071, China
[b] Department of Biology, Georgia State University, Atlanta, GA 30303, USA
[c] Institute of Biomedical Sciences, College of Life Sciences, Key Laboratory of Animal Resistance of Shandong Province, Key Laboratory of Molecular and Nano Probes of the Ministry of Education, Shandong Normal University, Jinan 250014, China

ARTICLE INFO

Keywords:
HDAC6
Viral infection
Viral pathogenesis
Antiviral therapy

ABSTRACT

Histone deacetylase 6 (HDAC6), a cytoplasmic enzyme important for many biological processes, has recently emerged as a critical regulator of viral infection. HDAC6 exerts this function either directly, via orchestrating various stages of the viral life cycle, or indirectly via modulating cytokine production by host cells. The broad influence of HDAC6 on viral pathogenesis suggests that this protein may represent an antiviral target. However, the feasibility of targeting HDAC6 and the optimal strategy by which this could be accomplished cannot simply be concluded from individual studies. The primary challenge in developing HDAC6-targeted therapies is to understand how its antiviral effect can be selectively harnessed. As a springboard for future investigations, in this review we recapitulate recent findings on the diverse roles of HDAC6 in viral infection and discuss its alluring potential as a novel antiviral target.

Contents

1. Introduction

Histone deacetylase 6 (HDAC6) is a member of the HDAC family that contains two functional catalytic domains and a ubiquitin-binding domain. Unlike most other HDACs, HDAC6 is predominantly localized in the cytoplasm and deacetylates non-histone proteins, such as α-tubulin, Hsp90, and cortactin (Hubbert et al., 2002; Kovacs et al., 2005; Zhang et al., 2007). By its deacetylase and ubiquitin-binding activities and interaction with partner proteins, HDAC6 plays an important role in a variety of biological processes, including cell migration, cell–cell interaction, autophagy, and ciliary homeostasis. Recent evidence suggests that HDAC6 is also an important regulator of viral infection, through both deacetylase-dependent and -independent mechanisms. A more detailed understanding of the intricate involvement of HDAC6 in the viral life cycle might reveal unique opportunities for antiviral therapy. Towards this end, in this review we summarize recent studies about the integral role played by HDAC6 during viral infection and its varied mechanisms of action. We begin from the perspective of the

Abbreviations: CBP, cAMP response element-binding protein (CREB) binding protein; HCV, hepatitis C virus; HDAC6, histone deacetylase 6; HIV, human immunodeficiency virus; IAV, influenza A virus; IFN, interferon; IRF3, IFN regulatory factor 3; KSHV, Kaposi's sarcoma-associated herpesvirus; NF-κB, nuclear factor κB; PKCα, protein kinase C alpha; RIG-I, retinoic-acid-inducible gene-I; SeV, Sendai virus; Tat, transactivator of transcription; Vif, viral infectivity factor.

* Corresponding author at: State Key Laboratory of Medicinal Chemical Biology, College of Life Sciences, Nankai University, Tianjin 300071, China. Tel.: +86 22 2350 4946; fax: +86 22 2350 4946.
E-mail address: junzhou@nankai.edu.cn (J. Zhou).

http://dx.doi.org/10.1016/j.pharmthera.2016.04.005
0163-7258/

host and discuss the impact of HDAC6 on the interferon (IFN) response, and then we shift perspective to that of the virus itself and delineate the wide-ranging effects of HDAC6 on various stages of the viral life cycle.

2. From the perspective of the host: effect of HDAC6 on host IFN response

Central to combating viral infections are type I IFNs (Perry et al., 2005; Haller et al., 2006; Stetson & Medzhitov, 2006), especially IFN-β, which is produced by many cell types as a key component of the innate immune response to viral infection (Nagarajan, 2011; Sin et al., 2012). Expression of the gene encoding IFN-β is modulated by the transcription factors IFN regulatory factor 3 (IRF3) and nuclear factor κB (NF-κB) (Hiscott, 2007; Severa & Fitzgerald, 2007). Early studies suggest that phosphorylation and nuclear translocation of IRF3 are the only regulated steps of IRF3 transcriptional activity (Yoneyama et al., 2002; Panne et al., 2007); however, subsequent research reveals that acetylation is also involved (Nusinzon & Horvath, 2006), suggesting a possible role for HDACs in modulating IFN-β levels. When cells are infected with Sendai virus (SeV) or treated with double-stranded RNA (dsRNA), the expression of IFN-β is induced by the binding of IRF3 and NF-κB to its promoter. Interestingly, Nusinzon and Horvath demonstrate that HDAC inhibitors suppress the production of IFN-β by decreasing the transcriptional activity of IRF3 but not NF-κB (Nusinzon & Horvath, 2006). By RNA interference, the authors further show that it is HDAC6 that functions as a coactivator for IFN-β induction. HDAC6-silenced cells exhibit diminished IFN-β production and accordingly increased viral replication (Nusinzon & Horvath, 2006). Though this study does not pinpoint the exact mechanism through which HDAC6 regulates IFN-β expression, it provides the first evidence that HDAC6 is a key regulator of innate response against viral infection.

Further mechanistic studies by Zhu et al. suggest a relationship between protein kinase C alpha (PKCα), HDAC6, and β-catenin in the regulation of IRF3 transcriptional activity and IFN-β production (Zhu et al., 2011) (Fig. 1). Following SeV infection, PKCα is activated by autophosphorylation, permitting it to recruit and phosphorylate HDAC6. Thereafter, activated HDAC6 causes deacetylation and nuclear translocation of β-catenin. Finally, β-catenin functions as a coactivator for IRF3-mediated transcription in the nucleus (Yang et al., 2010; Zhu et al., 2011) (Fig. 1). It is worthwhile to note that this study, for the first time, reveals the upstream and downstream components and signaling pathways involved in HDAC6-modulated IFN-β production. Subsequently, Chattopadhyay et al. reveal that HDAC6-mediated deacetylation of β-catenin is a prerequisite for the interaction between IRF3 and its coactivator cAMP response element-binding protein (CREB) binding protein (CBP), which is bridged by β-catenin (Chattopadhyay et al., 2013) (Fig. 1). The authors also show that HDAC6-knockout mice are more susceptible to SeV infection (Chattopadhyay et al., 2013). Intriguingly, a recent study by Choi et al. further demonstrates that HDAC6 regulates RNA virus infection at the very beginning, the sensing step, in a deacetylase-dependent manner (Choi et al., 2016). HDAC6 transiently interacts with the viral sensor, retinoic-acid-inducible gene-I (RIG-I), and specially deacetylates lysine 909 of RIG-I in response to RNA viral infection, which is essential to RIG-I viral RNA-sensing activity and the activation of downstream signaling pathway (Choi et al., 2016). HDAC6-knockout mice are sensitive to lethal RNA viral infection and show decreased

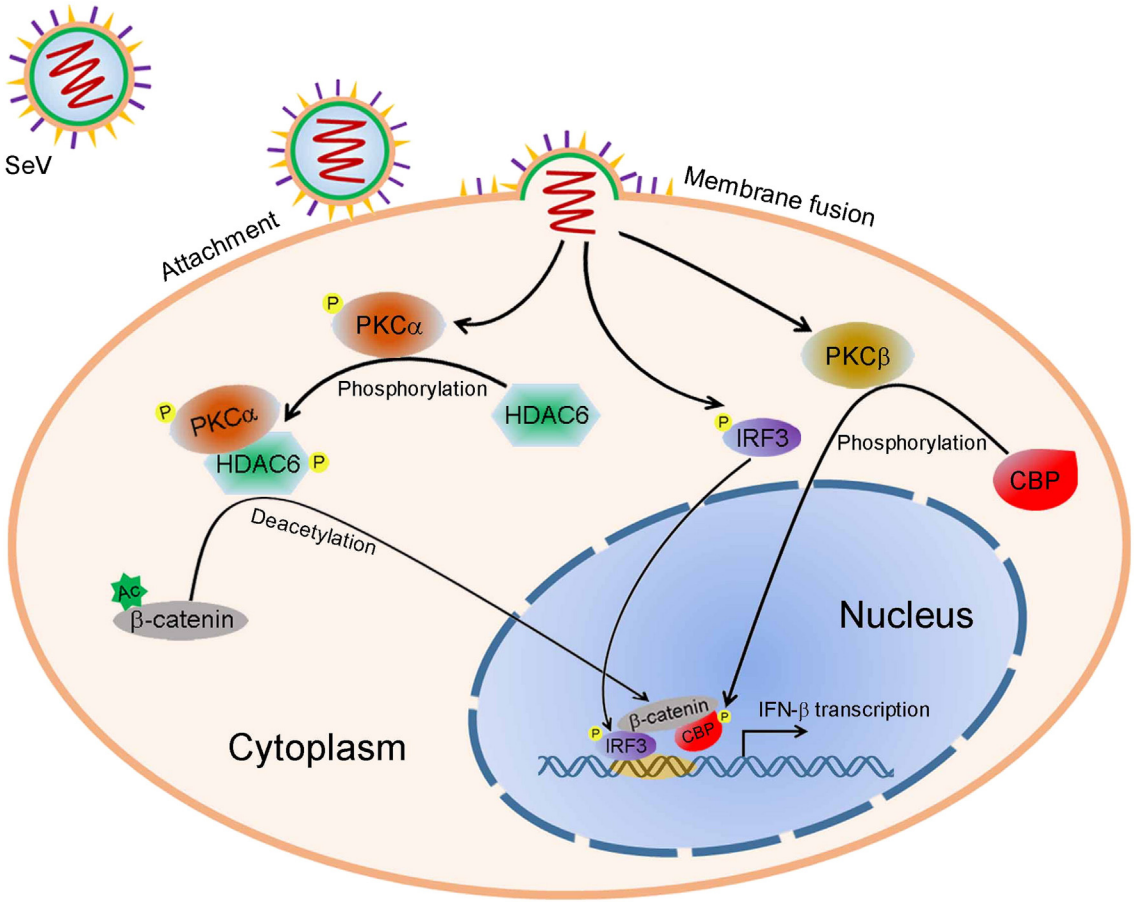

Fig. 1. HDAC6 inhibits SeV infection by upregulating IFN-β expression. SeV infection causes the self-phosphorylation and activation of PKCα. Activated PKCα then recruits and phosphorylates HDAC6. Phosphorylated HDAC6 in turn deacetylates β-catenin and induces its translocation to the nucleus, where it functions as a coactivator for IRF3-mediated transcription. CBP, another coactivator, is phosphorylated by PKCβ. The interaction between IRF3 and CBP is bridged by β-catenin. The formed stable initiation complex induces IFN-β transcription.

Please cite this article as: Zhang, L., et al., Diverse roles of HDAC6 in viral infection: Implications for antiviral therapy, *Pharmacology & Therapeutics* (2016), http://dx.doi.org/10.1016/j.pharmthera.2016.04.005