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Persistent human Borna disease virus infection modifies the acetylome of human oligodendroglia cells towards higher energy and transporter levels

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ABSTRACT

Background: Borna disease virus (BDV) is a neurotropic RNA virus persistently infecting mammalian hosts including humans. Lysine acetylation (Kac) is a key protein post-translational modification (PTM). The unexpectedly broad regulatory scope of Kac let us to profile the entire acetylome upon BDV infection.
Methods: The acetylome was profiled through stable isotope labeling for cell culture (SILAC)-based quantitative proteomics. The quantifiable proteome was annotated using bioinformatics.
Results: We identified and quantified 791 Kac sites in 473 Kac proteins in human BDV Hu-H1-infected and non-infected oligodendroglial (OL) cells. Bioinformatic analysis revealed that BDV infection alters the acetylation of metabolic proteins, membrane-associated proteins and transmembrane transporter activity, and affects the acetylation of several lysine acetyltransferases (KAT).
Conclusions: Upon BDV persistence the OL acetylome is manipulated towards higher energy and transporter levels necessary for shuttling BDV proteins to and from nuclear replication sites.
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Introduction

Borna disease virus (BDVs) is the main genus of the family *Bornaviridae and* persistently infects a wide variety of mammalian host species. In contrast to all other members of the order *Mononegavirales*, its non-segmented, negative- and single-stranded (NNS) RNA genome replicates in the nucleus of infected cells (de la Torre, 1994; Ludwig et al., 1988; Schneemann et al., 1995). BDVs-infection may induce a large spectrum of neuropsychiatric pathologies ranging from immune-mediated neurological disease to non-inflammatory behavioral alterations (Hornig et al., 2003; Ludwig and Bode, 2000; Zhang et al., 2014). According to many disease patterns notably reminiscent of symptoms observed in certain human neuropsychiatric disorders (Hornig et al., 2001), infection in human psychiatric illness has been studied since three decades, but the findings remain controversial (Bode and Ludwig, 2003; Bode et al., 1995; Hornig et al., 2012; Iwata et al., 1998; Rott et al., 1985; Zhang et al., 2013). Notwithstanding, a few human BDV strains have been isolated through co-cultivation of freshly isolated white blood cells from German psychiatric inpatients with a human fetal oligodendroglial cell line (OL cells) (Bode et al., 1996). Genetic analysis has validated both the identity of the BDV RNA in the original samples and the corresponding isolates as well as their authenticity as human viruses, as these human strains differ genetically from the laboratory reference strain V and another lab strain termed C6BV by a few distinct mutations (de la Torre et al., 1996). Moreover, our group has found that the human BDV strain Hu-H1 inhibits proliferation and promotes apoptosis of OL cells in vitro, while laboratory strain V displays the opposite effects (Li et al., 2013).

Post-translational modifications (PTMs) regulate the functional and physical properties of proteins in response to changes in external conditions or internal states. Acetylation and phosphorylation are supposed to be ancient conserved PTMs which occur ubiquitously

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across all domains of life (Beltrao et al., 2013) and have shown to be intertwiningly related on a long timescale in evolution (Sabo et al., 2008; van Noort et al., 2012). BDV is an evolutionarily very old virus with a suggested co-evolution of more than 40 million years in primate ancestor hosts up to humans (Horie et al., 2010). Whether and to which extent an ancient neurotropic virus like BDV is able to manipulate ancient PTMs of its host cells should improve our understanding of how BDV impacts on neuropathogenesis.

Lysine acetylation (Kac) is a reversible PTM, initially discovered on histones about four decades ago on account of their high abundance

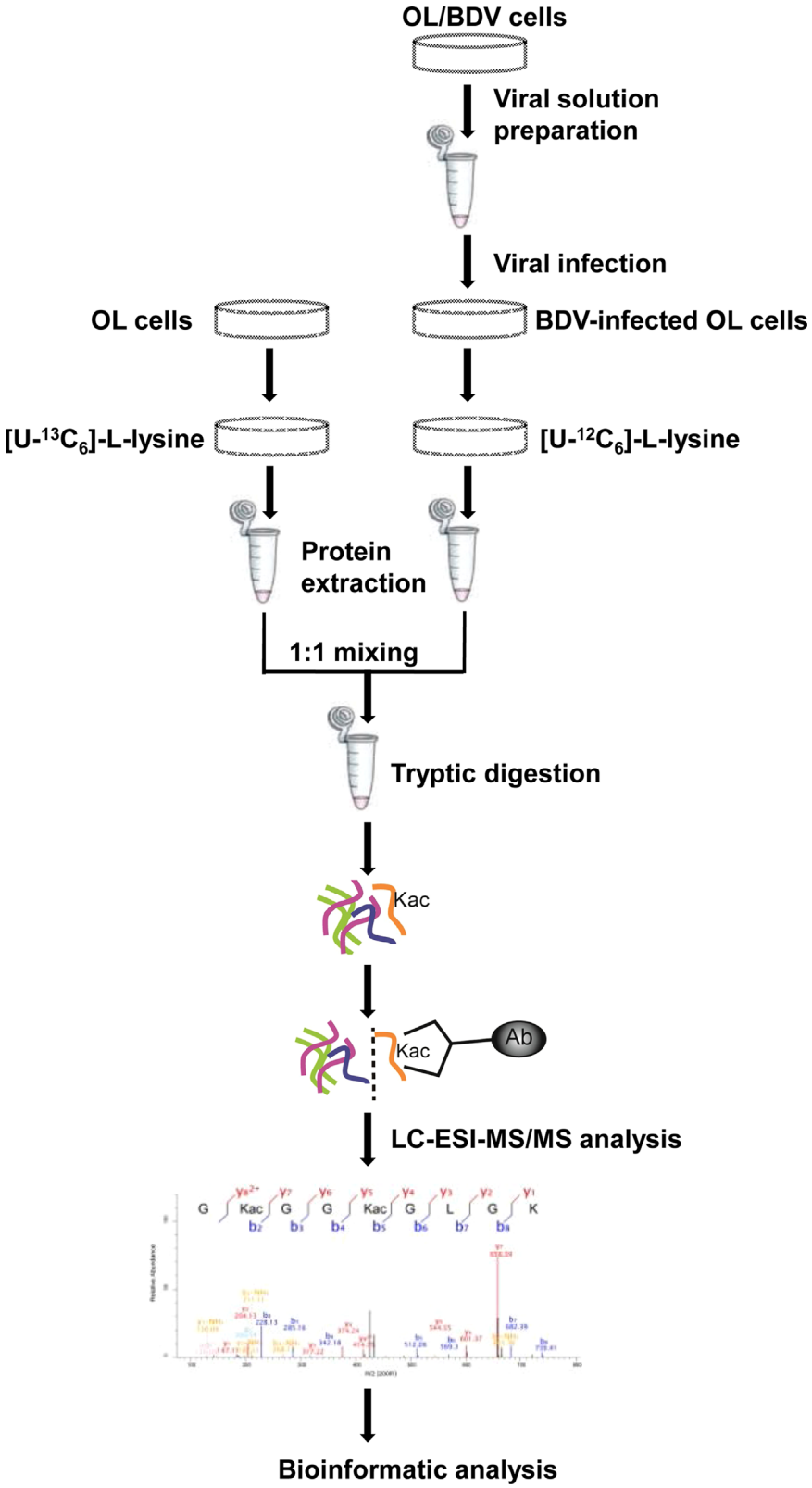

Fig. 1. Experimental Workflow Whole-cell extracts were prepared from BDV-infected and non-infected control OL cells. Immunoprecipitation coupled with SILAC-based quantitative proteomics was used to comparatively analyze the two groups followed by bioinformatical analysis.

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