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Review article

Astrocyte elevated gene-1 (AEG-1) and the A(E)Ging HIV/AIDS-HAND☆

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ABSTRACT

Recent attempts to analyze human immunodeficiency virus (HIV)-1-induced gene expression changes in astrocytes uncovered a multifunctional oncogene, astrocyte elevated gene-1 (AEG-1). Our previous studies revealed that AEG-1 regulates reactive astrocytes proliferation, migration and inflammation, hallmarks of aging and CNS injury. Moreover, the involvement of AEG-1 in neurodegenerative disorders, such as Huntington's disease and migraine, and its induction in the aged brain suggest a plausible role in regulating overall CNS homeostasis and aging. Therefore, it is important to investigate AEG-1 specifically in aging-associated cognitive decline. In this study, we decipher the common mechanistic links in cancer, aging and HIV-1-associated neurocognitive disorders that likely contribute to AEG-1-based regulation of astrocyte responses and function. Despite AEG-1 incorporation into HIV-1 virions and its induction by HIV-1, tumor necrosis factor-α and interleukin-1β, the specific role(s) of AEG-1 in astrocyte-driven HIV-1 neuropathogenesis are incompletely defined. We propose that AEG-1 plays a central role in a multitude of cellular stress responses involving mitochondria, endoplasmic reticulum and the nucleolus. It is thus important to further investigate AEG-1-based cellular and molecular regulation in order to successfully develop better therapeutic approaches that target AEG-1 to combat cancer, HIV-1 and aging.

Contents

Abbreviations: Aβ, amyloid beta; AEG-1, astrocyte elevated gene-1; AD, Alzheimer's disease; AIDS, acquired immune deficiency syndrome; ARE, antioxidant responsive element; ART, antiretroviral therapy; BBB, blood brain barrier; BCCIP, breast cancer 2 early onset and cyclin-dependent kinase inhibitor 1A interacting protein; BiP, binding immunoglobulin protein; CBP, cAMP response element-binding protein-binding protein; CD, cluster of differentiation; CHOP, CCAAT/enhancer binding protein homologous protein; EAAT, excitatory amino acid transporter; ER, endoplasmic reticulum; exNLS, extended nuclear localization signal; Gag, group-specific antigen; GFAP, glial fibrillary acidic protein; gp, glycoprotein; H_2O_2, hydrogen peroxide; HCC, hepatocellular carcinoma; HAD, HIV-associated dementia; HAND, HIV-associated neurocognitive disorders; HIV-1, human immunodeficiency virus-1; HIVE, HIV encephalitis; HD, Huntington's disease; HO-1, heme oxygenase-1; IKKβ, IκB kinase β; IL, interleukin; LYRIC, lysine-rich carcinoembryonic antigen-related cell adhesion molecule 1 co-isolated; MDR1, multi-drug resistance gene 1; MTDH, metadherin; NF-κB, nuclear factor-κB; NLS, nuclear localization signal; Nrf-2, nuclear factor erythroid-2 related factor-2; NRTI, nucleoside reverse transcriptase inhibitors; PLZF, promyelocytic leukemia zinc finger protein; ROS, reactive oxygen species; Rrs1, regulator of ribosome synthesis 1; SND1, staphylococcal nuclease and tudor domain containing 1; STAT3, signal transducer and activator of transcription 3; Tat, trans-activator of transcription; TLR, toll-like receptors; TMD, transmembrane domain; TNF, tumor necrosis factor; Ubn-1, ubinuclein-1; UPR, unfolded protein response; YY1, yin yang protein 1.

☆ HAND: HIV-associated neurocognitive disorders.

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1. Introduction

With the introduction of antiretroviral therapy (ART), the perspectives on aging in human immunodeficiency virus (HIV)-1-infected people have been evolving. A new paradigm encompassing premature and/or accelerated aging has been recognized in the HIV+ population. The increased life expectancy of HIV patients allows a greater time span for comorbidities that include neurological outcomes, termed HIV-associated neurocognitive disorders (HAND). HAND is characterized by altered immunological and molecular changes in the brain such as pro-inflammatory signaling, oxidative stress pathways and cytotoxic neuroglial crosstalk. These conditions are exacerbated in the context of aging and may play an important role in influencing not just HIV-1 CNS disease pathogenesis, but also other comorbidities, thereby affecting patient quality of life and survival. Similar to the HIV-1-induced neurocognitive deficits, aging alone also leads to degenerative capacities in the brain. Therefore, understanding the mechanistic interplay among HIV-1 CNS infection, comorbidities and aging is highly warranted.

HIV-1 infection increases the risk of developing certain types of cancer, including Kaposi's sarcoma, non-Hodgkin's lymphoma, cervical and anal cancers, compared to the risk of the general population (de Sanjose et al., 2008; Lederman et al., 2013; Robbins et al., 2015). However, the relationship between HIV-1 infection, oncogenic predisposition and aging has not been well studied. A widely applied tool for elucidating complex disease processes is initiating 'hypothesis generating studies'. To these ends, gene expression changes were analyzed using HIV-1-infected astrocytes to identify mechanistic targets to combat HIV-1 disease. Astrocyte elevated gene (AEG)-1 was one such protein associated with responses to HIV-1 infection, and later suggested as a prognostic marker in several cancers (Ke et al., 2013; Li et al., 2008, 2014a; Liu and Yang, 2013; Song et al., 2010; Sun et al., 2011; Tokunaga et al., 2014; Xia et al., 2014; Zhou et al., 2012). Our new data presented herein suggest a novel link of human brain AEG-1 levels in the context of age.

AEG-1 expression was detected at a basal level in naïve astrocytes and was significantly induced by HAND-relevant activation. Interleukin (IL)-1β and tumor necrosis factor (TNF)-α are known astrocyte activators (John et al., 2005), which were also proposed as inducers of AEG-1 in addition to HIV-1 (Kang et al., 2005). These observations identify AEG-1 as an inflammatory responsive gene in astrocytes, as opposed to being solely an HIV-1-inducible transcript. Our prior studies established that AEG-1 binds to the key orchestrator of inflammation, nuclear factor (NF)-κB, and facilitates NF-κB nuclear localization (Vartak-Sharma et al., 2014).

Detection of AEG-1 in the prefrontal cortex or frontal white matter regions provides physiological evidence for AEG-1 expression in the cognitive areas of the human brain, implying the need for functional studies to gauge the importance of AEG-1 in health and disease. In this review, we explore novel mechanistic links between the diverse AEG-1 roles in the context of aging and HAND. Further, we discuss several important pathways coupling AEG-1 to the aging HAND, including, but not limited to, inflammation, mitochondrial dysfunction, excitotoxicity and endoplasmic reticulum (ER), nucleolar and oxidative stress. As an astrocyte inflammatory gene relevant to HIV-1 CNS disease, we illustrate that AEG-1 is also associated with the aging brain. We present novel data regarding AEG-1 in aging human brains and its cellular redistribution in astrocytes under oxidative stress. Yet, despite the volume of information and perspectives we have summarized and discussed, we barely begin to answer some key questions: (1) What are the cellular functions of AEG-1 in human astrocytes at homeostasis? (2) How is AEG-1 expression induced in human astrocytes? (3) What are the implications of AEG-1 modulation in the aging brain? (4) Through what specific mechanism(s) does AEG-1 modulate astrocyte functions? (5) What is the disease relevance of AEG-1 in the CNS under multifactorial challenges? We propose that, AEG-1 regulation of multiple mechanisms related to neurodegeneration *via* astrocyte function is a key finding that can be utilized in developing therapeutic targets for CNS disorders including the aging HAND.

2. AEG-1: historical perspectives

AEG-1 was originally described in 2002 as an HIV-1 neuropathology-associated gene whose expression is significantly elevated upon HIV-1 or TNF-α exposure (Su et al., 2002). Basic local alignment search tool analysis of AEG-1 gene indicated that AEG-1 has a unique gene structure, which does not resemble any other gene and is evolutionarily conserved among mammals and higher vertebrates. AEG-1 genomic environment is a known hot spot for genetic alterations in many cancers (Hu et al., 2009a; Wan and Kang, 2013) and in other CNS pathologies such as migraine (Anttila et al., 2010; Anttila et al., 2011). AEG-1 is recognized as a pleiotropic protein localizing in various intracellular locations, including

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