Autophagy and apoptotic genes implicated in Alzheimer’s disease are modulated following infection of neuronal cells with Chlamydia pneumoniae

Denah M. Appelt  
*Philadelphia College of Osteopathic Medicine, DenahA@pcom.edu*

Ian Kohler  
*Philadelphia College of Osteopathic Medicine*

Annette K. Slutter  
*Philadelphia College of Osteopathic Medicine, AnnetteKS5@gmail.com*

Juliana Zoga  
*Philadelphia College of Osteopathic Medicine, JulianaZo@pcom.edu*

Susan T. Hingley  
*Philadelphia College of Osteopathic Medicine, susanh@pcom.edu*

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Autophagy and apoptotic genes implicated in Alzheimer’s disease are modulated following infection of neuronal cells with Chlamydia pneumoniae

Denah Appelt, Ian Kohler, Annette Slutter, Juliana Zoga, Susan Hingley, Brian Balin

Philadelphia College of Osteopathic Medicine, Center for Chronic Disorders of Aging, Philadelphia, PA, USA

Abstract

Background: The focus of the current studies was to determine the relationship between the molecular mechanisms interconnecting autophagy and apoptosis following Chlamydia pneumoniae infection in neuronal cells. Dysfunctions in autophagy and apoptosis have been implicated in the neuropathogenesis associated with Alzheimer’s disease (AD). Autophagy in AD pathogenesis has been shown to play a role in amyloid processing through the endosomal-lysosomal system. Apoptosis may contribute to the neuronal cell loss observed in AD; however, there is limited evidence of the apoptotic process participating in terminal completion. Although Aβ-42 has been shown to induce apoptosis in neurons and may be an early factor in AD, our previous investigations demonstrated that neurons infected with Chlamydia pneumoniae are resistant to apoptosis, and that Aβ-42 is induced following this infection. Thus, these studies address infection as an initiator/trigger or inhibitor for the presence of autophagy and apoptosis observed in Alzheimer’s disease.

Methods: SKN-MC neuronal cells obtained from ATCC, were infected with ATCC’s A-39 strain of Chlamydia pneumoniae at an MOI of 24 for 24, 48, and 72hrs and were analyzed using Real-time PCR arrays from SABiosciences specific for autophagy and apoptosis genetic markers.

Results: Transient gene associations with apoptosis such as BAX, BDNF, TP53, TRPV1 were down regulated by 72hrs post-infection. Genes involved with the regulation of apoptosis such as FAS, NOTCH1, CASP8, CASP9, and BCL2L11 were up-regulated within 72hrs post infection. WT-1 genes involved with regulation of autophagy and apoptosis, BNP1 was significantly up-regulated within 48-72hrs post-infection. Off the gene linking apoptosis to lysosomes, FAM170a was up-regulated throughout 24-72hrs post-infection.

Conclusions: Modulation of apoptosis and autophagy genes occur in neuronal cells at 24, 48, and 72hrs post-infection with Chlamydia pneumoniae. These genetic changes lead to dysregulation in those basic cellular processes, dysfunction in those processes has been shown to contribute to the neuropathology of late-onset Alzheimer’s disease. This work will allow future studies to further focus on the apoptotic and autophagic pathways to better understand how a pathogen such as Chlamydia pneumoniae plays a role in the development of late-onset Alzheimer’s disease.

Introduction

Neurodegeneration has been well-documented in the CNS of Alzheimer individuals and a continuum of deterioration has been identified within the AD brain. Strong evidence suggests that dysregulation of the autophagy and apoptotic pathways are contributing factors in the pathogenesis of Alzheimer’s disease. Our laboratory has focused on exploring the role of infection with C. pneumoniae as a causative agent in late-onset AD. In separate studies, polyclonal sera reactive directed C. pneumoniae DNA in 60-80% of promoter specific AD brain samples [1], but only 51%-55% of promoter specific AD brain samples from age-matched, non-AD, control individuals. Furthermore, a mouse model has been developed in which mice infected with C. pneumoniae demonstrate defects in the brain areas typically affected in AD [2]. Recently, we have demonstrated that C. pneumoniae is capable of inhibiting apoptosis in neuronal cells through the inhibition of the infected neuronal cell [3]. Other laboratories have demonstrated that chlamydia-infected breast cells were resistant to apoptosis stimuli such as TNFβ. For the mitochondria, norepinephrine and UV-light [4]. C. pneumoniae has been shown to induce pre-apoptotic cytopathic effects, such as apoptosis and caspase activation, as well as the anti-apoptotic micro-environmental protein Bcl-2 and the anti-caspase protein c-FLIP [5].

In somatic tissues, cells activate the autophagy pathways, either as a result of, or before, initiating apoptosis. Induction of the autophagic process may lead to modulation of the apoptotic process. Autophagy is associated with the endosomal-lysosomal system, in which contents of an autophagosome are degraded as a product of autolysosome formation with the lysosomal [6]. An increase in the number of autophagic vacuoles (AV) was identified in neurons of AD brains implicating autophagy as a pathological process in AD [7]. The endosomal pathway is linked to the lysosomal pathway because endosomal contents fuse with late endosomes or lysosomes. Neurons from the AD brain have been shown to exhibit enlarged endosomal contents. This is significant in AD because enlarged endosomal contents play a role in mitochondrial dysfunction and the initiation of programmed cell death. The lysosomal pathway is involved with autophagy and apoptosis. When induced by autophagy, these processes occur in a cell body and cell nucleus. When induced by apoptosis, cell death occurs. From the above, these pathways appear to be abnormal in Alzheimer infected neuronal cells. These studies are an attempt to identify the defects in the regulation genes associated with autophagy and apoptosis in neuronal cells observed in AD following an infection by C. pneumoniae.

Material and Methods

The SKN-MC (ATCC) human neuroblastoma cell line were infected with ATCC A-39 strain of Chlamydia pneumoniae at an MOI of 8 for 24, 48, and 72 hrs. Cells were immunostained with FITC- anti-chlamydia antibody (Invitrogen) for verification of the infection. The Human Autophagy RT2 Profiler PCR Arrays from SABiosciences resulted in the expression of a gene set involved in autophagy and apoptosis. All data was derived from experiments performed in triplicates.

Conclusions

Modulation of genes associated with the autophagic and apoptotic pathways is observed in neuronal cells at 24, 48, and 72hrs in the presence of C. pneumoniae. These genetic changes lead to dysregulation in the basic cellular processes of apoptosis and autophagy, respectively. Dysfunction in these processes has been shown to contribute to the development of late-onset Alzheimer’s disease. This work will allow future studies to further focus on the analysis of genes involved in the apoptotic and autophagic pathways to better understand how a pathogen such as C. pneumoniae plays a role in the development of AD.

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