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Transcriptomic gene-network analysis of exposure to silver nanoparticle reveals potentially neurodegenerative progression in mouse brain neural cells

Ho-Chen Lin, Chin-Lin Huang, Yuh-Jeen Huang, I-Lun Hsiao, Chung-Wei Yang, Chun-Yu Chuang *

Department of Biomedical Engineering and Environmental Sciences, National Tsing Hua University, 101, Section 2, Kuang-Fu Road, Hsinchu 30013, Taiwan

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ABSTRACT

Silver nanoparticles (AgNPs) are commonly used in daily living products. AgNPs can induce inflammatory response in neuronal cells, and potentially develop neurological disorders. The gene networks in response to AgNPs-induced neurodegenerative progression have not been clarified in various brain neural cells. This study found that 3–5 nm AgNPs were detectable to enter the nuclei of mouse neuronal cells after 24-h of exposure. The differentially expressed genes in mouse brain neural cells exposure to AgNPs were further identified using Phalanx Mouse OneArray® chip, and permitted to explore the gene network pathway regulating in neurodegenerative progression according to Cytoscape analysis. In focal adhesion pathway of ALT astrocytes, AgNPs induced the gene expression of RasGRF1 and reduced its downstream BCL2 gene for apoptosis. In cytosolic DNA sensing pathway of microglial BV2 cells, AgNPs reduced the gene expression of TREX1 and decreased IRF7 to release pro-inflammatory cytokines for inflammation and cellular activation. In MAPK pathway of neuronal N2a cells, AgNPs elevated GADD45α gene expression, and attenuated its downstream PTPRR gene to interfere with neuron growth and differentiation. Moreover, AgNPs induced beta amyloid deposition in N2a cells, and decreased PSEN1 and PSEN2, which may disrupt calcium homeostasis and presynaptic dysfunction for Alzheimer's disease development. These findings suggested that AgNPs exposure reveals the potency to induce the progression of neurodegenerative disorder.

1. Introduction

Silver nanoparticles (AgNPs) have antimicrobial characteristics commonly used in cosmetics, clothes, food containers, wound dressing and biomedical devices. The widespread AgNPs use increases AgNPs release to environment and enhances the risk of human exposure (Ribeiro et al., 2014). AgNPs are toxic to mammalian cells, e.g., liver, vascular system, lung, reproductive organs skin and brain (Ahamed et al., 2010). Both of AgNPs and Ag ion present cytotoxicity in vivo (Beer et al., 2012) and in vitro (Bilberg et al., 2012) studies, and lead to ultrastructural changes in synapses of the brain (Skalska et al., 2015). AgNPs (50–60 nm) can easily enter and accumulate in the mouse brain inducing neurotoxicity to alter cognitive functions and motor sensory (Sharma and Sharma, 2012). Moreover, AgNPs increase the protein expression of heme oxygenase 1 (HO-1) and enhance reactive oxygen species (ROS) generation to directly interfere with calcium responses and cause neuronal oxidative damage in primary mixed neural cells (Haase et al., 2012). Mice administered 25 nm of AgNPs produce neurotoxicity by generating free radical-induced oxidative stress and apoptosis in the frontal cortex, caudate and hippocampus (Rahman et al., 2009).

Alzheimer's disease (AD) is a progressive neurodegenerative disease presenting memory and learning dysfunction due to neuron death and synaptic degeneration (Arendt, 2009). The aggregated amyloid β(Aβ)40/Aβ42 peptides are primary constituent of the plaques as the pathological hallmark in brain of AD patients (Ballard et al., 2011; Golde et al., 2000). Both Aβ40 and Aβ42 induce apoptotic cell death in cultured rat neuronal cells (Estus et al., 1997; Gschwind and Huber, 1995). The Aβ peptides generate from β-amyloid precursor protein (APP) were enzymatically cut by β- and γ-secretases (Wiltfang et al., 2007). Howlett and Richardson (2009) indicated that the accumulation of Aβ plaques was found in early age of APP transgenic mice.

Astrocytes, neuronal cells and microglial cells are main components of the brain. Astrocytes preserve neural environments buffering neurotransmitters and ions (Lian and Stringer, 2004). Microglia is the resident macrophage-like cell of the spinal cord and brain to release some cytokines and mediate neuroinflammatory processes (Wang et al., 2011). Neurons are specific cells to transmit information, and communicate with other nerve cells through chemical and electrical signals in the nervous system (Weiss et al., 2009). In the previous study, we have reported that 3–5 nm of AgNPs can enter mouse neuronal cells to induce pro-inflammatory cytokine production, and alter gene expressions related to Aβ deposition to induce AD progression (Huang et al., 2015). However, the potential gene network pathway of various brain neural cells in

* Corresponding author.
E-mail address: cychuang@mx.nthu.edu.tw (C.-Y. Chuang).

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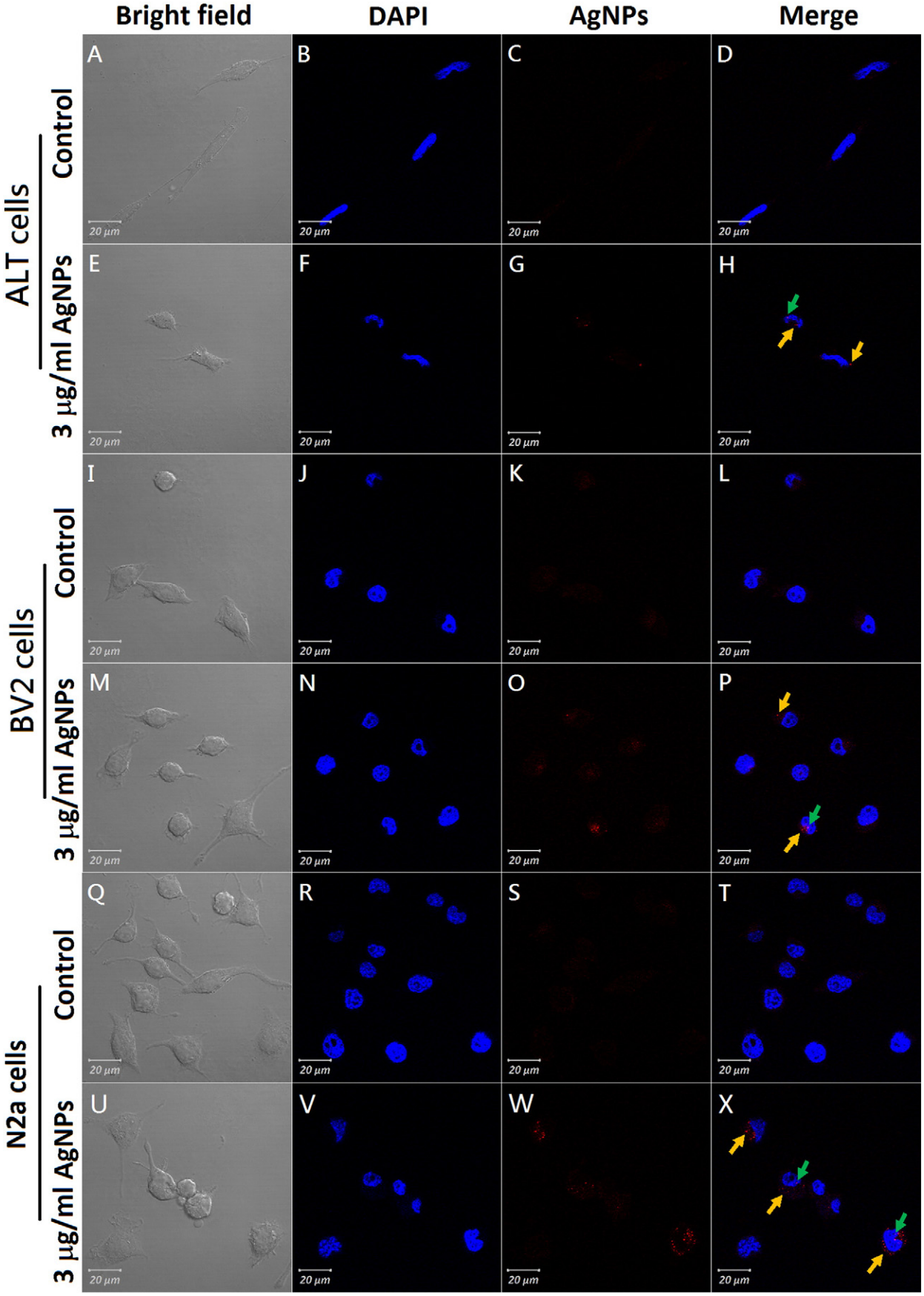
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