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The apoptotic perspective of autism

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ABSTRACT

Autism is a severe neurodevelopmental disorder characterized by impairments in social interaction, deficits in verbal and non-verbal communication, and repetitive behavior and restricted interests. The normal brain development during fetal brain development and the first year of life is critical to the behaviors and cognitions in adulthood. Programmed cell death (apoptosis) is an important mechanism that determines the size and shape of the brain and regulates the proper wiring of developing neuronal networks. Pathological activation of apoptotic death pathways under pathological conditions may lead to neuroanatomic abnormalities and possibly to developmental disabilities. It has been demonstrated a possible association between neural cell death and autism. Here, the abnormal apoptosis found in autism from postmortem and animal studies was reviewed and the possible mechanism was discussed.

1. Introduction

Autism is a common neurodevelopmental disorder. Typically diagnosed before three years old, autistic children usually present with significant language delays, social and communication impairments, as well as abnormal repetitive and restrictive behaviors (Nazeer and Ghaziuddin, 2012). Although the pathogenesis of autism is not understood, emerging evidence points to apoptotic mechanisms being involved in this disorder. Programmed cell death, also termed as "apoptosis", is an essential part of normal development, particularly in the nervous system. Spatial, temporal, or quantitative errors in the stimuli that initiate programmed cell death, or errors within the programmed cell death pathway itself, can result in an abnormal number of neurons and pathological neural development. The apoptosis mechanism in the central nervous system has been suggested to include three signaling pathways, which are the mitochondrial, death receptor and inflammatory pathways (Jarskog et al., 2005). Excesses and deficits in neuronal numbers have been observed not only in typical neurodegenerative disorders such as Alzheimer's and Huntington's diseases but also in several neurodevelopmental disorders, including schizophrenia and autism (Jarskog et al., 2005; Margolis et al., 1994).

So far, there is relatively few of the neuropathology specific to autism has been detected because of a limited amount of brain tissue available for the neuropathologic study of autism (Silver and Rapin, 2012). However, earlier studies have shown that abnormalities occur in many areas of the autistic brain, including decreased Purkinje cell counts in the cerebellar hemispheres and vermis, loss of granular cells, and Purkinje cell atrophy (Bauman and Kemper, 1985, 2005; Kemper and Bauman, 2002; Ritvo et al., 1986). One study of postmortem brain tissues from autistic patients demonstrate an active and ongoing neuroinflammatory process in the cerebral cortex and white matter characterized by astroglial and neuroglial activation (Vargas et al., 2005). Magnetic resonance imaging (MRI) studies of total brain volume demonstrate that young children with autism have 5–10% abnormal enlargement in brain volumes, compared to those of normal controls (Amaral et al., 2008). Reduced corpus callosum volume and increased amygdala volume have also been reported in subjects with autism (Egaas et al., 1995; Piven et al., 1997; Schumann et al., 2004; Sparks et al., 2002). In addition, multiple brain regions exhibit aberrant structural organization in children and adolescents with autism in the structure MRI studies (Stigler et al., 2011; Uddin et al., 2011).

Abbreviations: Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; GFP, green fluorescent protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-γ; IL, interleukin; MAPK, mitogen-activated protein kinases; MCP, macrophage chemoattractant protein; MRI, magnetic resonance imaging; PBMCs, peripheral blood mononuclear cells; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; TNF-α, tumor necrosis factor alpha.

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These pathological changes could involve altered apoptosis. In this review, we focus on discussion of abnormal apoptosis findings in autism from postmortem and animal studies.

2. Apoptosis-related proteins in autism

2.1. Bcl-2

Several studies implicate B-cell lymphoma 2 (Bcl-2) involvement in neuropsychiatric disorders, including schizophrenia (Jarskog et al., 2000, 2005), bipolar disorder, major depression, and lissencephaly (Hong et al., 2000). The study to examine the potential role of apoptosis in autism firstly measured levels of the anti-apoptotic regulatory protein Bcl-2 in postmortem brain tissue. Quantification of Bcl-2 showed a significant 34–51% reduction in autistic cerebellum compared with controls by western blotting (Fatemi et al., 2001a,b). The same group also investigated the levels of Bcl-2 in several important brain tissues of autistic subjects and compared with age-, sex-, and postmortem-interval-matched normal control subjects. In the autistic group, mean Bcl-2 values were reduced by 32% in parietal cortex, albeit nonsignificantly when compared to controls (Fatemi and Halt, 2001). The levels of Bcl-2 decreased by 38% and 36% in autistic superior frontal and cerebellar cortices, respectively when compared to control tissues (Araghi-Niknam and Fatemi, 2003). Bcl-2 is a membrane-bound protein with a neuroprotective role in the central nervous system. Bcl-2 has been shown to inhibit apoptosis and enhance the survival of neurons (Sasaki et al., 2006). Recently, Sheikh et al. (2010a,b) also found that the Bcl-2 expression was significantly reduced in the frontal cerebral cortex and cerebellum of autistic subjects. Lymphoblast cell lines have been suggested to be a valuable tool for identifying genes associated with autism and provide an alternative approach for understanding the biology and genetics of autism (Baron et al., 2006; Wei et al., 2011). By examining Bcl-2 protein expression in the lymphoblasts of autistic subjects and compare the results with age-matched normal controls, Malik et al. identified that Bcl-2 protein expression is also significantly decreased in lymphoblasts of autistic subjects (Malik et al., 2011).

2.2. Cathepsin D

Cathepsin D is a predominant lysosomal aspartic acid protease abundantly expressed in the brain and hydrolyzes select peptide bonds of target proteins with high specificity. Cathepsin D initiates apoptosis through caspase-8 and has been shown to play an important role in regulation of cellular apoptosis. It was shown that cathepsin D protein expression was notably higher in the pyramidal and granule cells of the hippocampus, in the neurons of the cerebellum, and in the frontal cortices of autistic subjects as compared with the age-matched control subjects (Sheikh et al., 2010a). And cathepsin D mRNA and protein expression were also significantly increased in autistic lymphoblasts (Malik et al., 2011).

Several studies have shown that cathepsin D may be involved in inflammation. Fusek et al. (2007) reported that procathepsin D initiated secretion of cytokines. Erdmann et al. (2008) found that inflammatory cytokines, including TNF-α and IFN-γ, increased extracellular procathepsin D in primary endothelial cell cultures. Recently, several studies have demonstrated that several inflammatory cytokines such as TGF-β1, MCP-1, IL-6, IL-8, IL-10, GM-CSF, TNF-α and IFN-γ were increased in autistic brains and lymphoblasts (Li et al., 2009; Malik et al., 2011; Vargas et al., 2005). In addition, studies have also demonstrated that apoptosis can be initiated by activation of a group of inflammatory cytokines (Grunnet et al., 2009; Wright et al., 1999), and cathepsin D protease mediates apoptosis induced by cytokines TNF-α and IFN-γ (Deiss et al., 1996). Based on these findings, we reason that the increased apoptosis and cathepsin D expression in the autistic brain could be induced by elevated levels of cytokines, and cathepsin D may be involved in the mediation of apoptosis induced by the cytokines.

2.3. P53

The tumor suppressor and transcription factor p53 is a key modulator of cellular stress responses. Activation of p53 can trigger apoptosis in many cell types including neurons (Culmsee and Mattson, 2005). P53 mediates apoptosis through a linear pathway involving bax transactivation and translocation, cytochrome c release from mitochondria and caspase activation. P53-mediated apoptosis can be blocked by Bcl-2 family members regulating mitochondrial function and by caspase inhibitors (Shen and White, 2001). One research group has demonstrated that the levels of p53 were increased by 130%, 67.5% and 38% in autistic parietal cortex, superior frontal and cerebellar cortices respectively when compared to control tissues. In addition, it has been shown that the Bcl-2/P53 ratio has a 64% reduction in autistic brain as compared to controls in the same brain areas (Araghi-Niknam and Fatemi, 2003; Fatemi and Halt, 2001). With immunohistochemistry studies, (Sheikh et al., 2010b). detected an increased p53 expression in the Purkinje cells and granule cells in the cerebella of autistic brains in comparison with the age-matched controls. However, no obvious differences in p53 expression were seen in the frontal cortices of autistic subjects and control subjects.

2.4. Caspase

Caspases are cysteinyl aspartate-specific proteases that play a critical role in the regulatory and execution phases of apoptosis. Similar to classic neurodegenerative disorders such as Alzheimer's and Parkinson's diseases where high caspase-3 levels are found in postmortem brain tissue (Hartmann et al., 2000; Masliah et al., 1998), Sheikh et al. (2010a) found that the expression of caspase-3 was increased in the cerebellum of autistic subjects. However, caspase-3 levels were essentially unchanged and actually trended toward a slight decrease in schizophrenia temporal cortex (Jarskog et al., 2004). Furthermore, it has been reported that Saudi autistic patients have a remarkable lower plasma caspase-3 compared to age and gender matching controls (El-Ansary et al., 2011). Recent studies suggest that peripheral blood mononuclear cells (PBMCs) may represent a useful tool to investigate systemic neurochemical changes in neurodegenerative disease (Buttarelli et al., 2006). The work by Siniscalco et al. (2012) showed an up-regulation and activation of several caspases in PBMCs from autistic subjects. The mRNA levels for caspase-1, -2, -4, -5 were also found to be significantly increased in autistic children as compared to healthy subjects. In addition, protein levels of caspase-3, -7, -12 were shown to be increased in autistic patients (Siniscalco et al., 2012). However, the findings in the peripheral blood of autistic patients may not correlate with that in the central nervous system.

Propionic acid has often been reported to induce a number of behavioral changes, neuroinflammation responses and oxidative stress similar to those observed in humans with autism (MacFabe et al., 2008). It was showed that the level of caspase-3 was elevated in propionic acid-treated rat and the elevation of caspase-3 proved the pro-apoptotic and neurotoxic effect of propionic acid to rat pups (El-Ansary et al., 2012). A similar increase in caspase-3 has been reported in developing rat brains as neurotoxic effects of thimerosal, an environmental factor involved in the etiology of autism (Olczak et al., 2010). In addition, sodium valproate administered to neonatal mice causes cognitive and motor deficits similar to those observed in humans with autism. The number of TUNEL-positive cells was significantly increased in sodium