Q1 Please cite this article in press as: Kovacs GG et al. Linking pathways in the developing and aging brain with neurodegeneration. Neuroscience (2014), http://dx.doi.org/10.1016/j.neuroscience.2014.03.045

Neuroscience xxx (2014) xxx–xxx

NEUROSCIENCE FOREFRONT REVIEW

Q1 LINKING PATHWAYS IN THE DEVELOPING AND AGING BRAIN WITH NEURODEGENERATION

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Abstract—The molecular and cellular mechanisms, which coordinate the critical stages of brain development to reach a normal structural organization with appropriate networks, are progressively being elucidated. Experimental and clinical studies provide evidence of the occurrence of developmental alterations induced by genetic or environmental factors leading to the formation of aberrant networks associated with learning disabilities. Moreover, evidence is accumulating that suggests that also late-onset neurological disorders, even Alzheimer's disease, might be considered disorders of aberrant neural development with pathological changes that are set up at early stages of development before the appearance of the symptoms. Thus, evaluating proteins and pathways that are important in age-related neurodegeneration in the developing brain together with the characterization of mechanisms important during brain development with relevance to brain aging are of crucial importance. In the present review we focus on (1) aspects of neurogenesis with relevance to aging; (2) neurodegenerative disease (NDD)-associated proteins/pathways in the developing brain; and (3) further pathways of the developing or neurodegenerating brains that show commonalities. Elucidation of complex pathogenetic routes characterizing the earliest stage of the detrimental processes that result in pathological aging represents an essential first step toward a therapeutic intervention which is able to reverse these pathological processes and prevent the onset of the disease. Based on the shared features between pathways, we Q3 conclude that prevention of NDDs of the elderly might begin during the fetal and childhood life by providing the mothers and their children a healthy environment for the fetal and childhood development. © 2014 Published by Elsevier Ltd. on behalf of IBRO.

Key words: brain, human, development, neurodegeneration, neurodegenerative disease-associated proteins, developmental pathways.

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Q4 *Abbreviations:* Aβ, amyloid-β; AD, Alzheimer's disease; ALP, autophagy–lysosome pathway; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ApoER2, apolipoprotein E receptor 2; APP, Aβ precursor protein; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; CDK5, cyclin-dependent kinase 5; DAB1, disabled-1; DR6, death receptor-6; DS, Down syndrome; FCD, focal cortical dysplasia; GSK3β, glycogen synthase kinase 3β; IGF-1, insulin-like growth factor 1; IIS, insulin/IGF-1 signaling pathway; LTP, long-term potentiation; MCD, malformation of cortical development; mTOR, mammalian target of rapamycin; NDDs, neurodegenerative diseases; NGF, nerve growth factor; NMDA, *N*-methyl-D-aspartate; NSC, neural stem cell; PD, Parkinson's disease; PrP^C, cellular prion protein; PS, presenilins; sAPP, soluble (secreted) APP; Shh, Sonic Hedgehog; TDP-43, TAR DNA-binding protein 43; TSC, tuberous sclerosis complex; UPS, ubiquitin–proteasome system; VEGF, vascular endothelial growth factor; VLDLR, very-low-density lipoprotein receptor; Wnt, Wingless/Int.

http://dx.doi.org/10.1016/j.neuroscience.2014.03.045
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INTRODUCTION: OVERVIEW OF NEURODEGENERATIVE DISEASES (NDDS) AND SCOPE OF REVIEW

Age-associated cognitive decline is a human experience, which differs in extent between individuals. Such age-related cognitive changes have been ascribed to alterations in synapses and neuronal loss in the brain that are multiplied in pathological brain aging. Experimental evidence suggests a complex scenario, including mitochondrial dysfunction, compromised stress responses, synaptic rearrangements and altered protein expression, to cause age-related brain changes. NDDs were traditionally defined as disorders with selective loss of neurons and distinct involvement of functional systems defining clinical presentation. Current concepts of NDDs can be summarized as follows:

Classification of NDDs is protein-based

Complex alterations of the cytoskeleton and axonal transport systems lead to accumulation or deposition of pathological forms of proteins in the brain. Anatomical areas are involved in a hierarchical way as suggested for different disorders (Thal et al., 2002; Braak et al., 2003, 2006; Brettschneider et al., 2013); thus there are stages or phases in the involvement of anatomical areas. This suggests a prion-like spreading of protein deposits (Polymenidou and Cleveland, 2012). Aggregation of several proteins may be initiated in the same brain (Kovacs et al., 2010, 2013).

Classification of NDDs is based on clinical presentation, anatomical regions and cell types affected, conformationally altered proteins involved in the pathogenetic process (Table 1), and etiology if known, e.g. genetic aberrations. Currently, ''the-winner-takes-it-all'' approach supports classification of diseases according to the predominant protein that is deposited in the brain (Kovacs et al., 2010). The basis of this classification is to evaluate where the deposits composed of particular proteins are found. Extracellular deposits comprise deposits with immunoreactivity for amyloid-β (Aβ) or prion protein (PrP), while proteins that deposit intracellularly include tau, α-synuclein, TAR DNA-binding protein 43 (TDP-43), or so called FET proteins (*F*US, fused in sarcoma; *E*WS, Ewing sarcoma protein; *T*AF15, TATA-binding protein-associated factor 15); (Kovacs et al., 2010; Neumann et al., 2011). These proteins associate with sporadic and inherited forms, while there are further proteins, which are related to genetic diseases, like those linked to trinucleotide repeat disorders. These proteins deposit in various cell types (neuron, astro- and oligodendroglia). Indeed, some NDDs show predominantly oligodendroglial protein deposits (like the α-synucleinopathy multiple system atrophy, or tauopathies with globular glial inclusions) (Kovacs et al., 2008; Wenning et al., 2008), which raise the issue that non-neural cells are also important components of NDD pathology.

The concept of proteinopathies underpins the role of protein processing systems

Two major elimination pathways control the quality of cellular components and maintain cell homeostasis: the ubiquitin–proteasome system (UPS) that degrades short-lived proteins in the cytoplasm and nucleus, and the autophagy–lysosome pathway (ALP) which digests long-lived proteins and abnormal organelles just in the cytoplasm (Nijholt et al., 2011). Ubiquitin is a small stress-induced protein, and is found in diverse filamentous inclusions of NDDs. Several studies indicate that the ubiquitin-binding protein 62/sequestosome 1, a cytosolic 62-kD protein (p62) is also a common component of various inclusions (Wooten et al., 2006). NDD-associated intracellular inclusion bodies or extracellular deposits follow a maturation process from non-ubiquitinated, non-argyrophilic deposits to ubiquitinated (and p62 positive), argyrophilic inclusions (Bancher et al., 1989; Kuusisto et al., 2003).

At basal levels autophagy plays a vital role in keeping the cell homeostasis by digestion of dysfunctional organelles and proteins while defective autophagy pathways or alterations in autophagy-related genes associate to NDDs (Ghavami et al., 2014). The role of the endosomal–lysosomal system has been discussed in various NDDs, including prion diseases (Laszlo et al., 1992; Kovacs et al., 2007, 2012), Alzheimer's disease (AD) (Cataldo et al., 1995), or amyotrophic lateral sclerosis (Matej et al., 2010). Involvement of this system is reminiscent of storage diseases; however there an enzymatic failure causes accumulation of the product, while in some forms of NDDs, constant overloading of the protein processing system impairs the function of lysosomes and lead to accumulation of abnormal protein conformers (Kovacs et al., 2007).

Neuronal loss is associated with a plethora of pathogenetic pathways

In addition to autophagy, several further pathways are extensively examined in NDDs, including apoptosis and neuroinflammation. Autophagy itself may promote neuronal cell death via impairment of protein degradation in lysosomes and inducing either apoptotic or necrotic cell death by the release of cathepsins, or by failure in mitophagy resulting in accumulation of damaged mitochondria leading to cytochrome c release and apoptotic cell death (Nijholt et al., 2011). The pathway of apoptosis is very complex and shows diversity

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