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Between destiny and disease: Genetics and molecular pathways of human central nervous system aging

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ABSTRACT

Aging of the human brain is associated with "normal" functional, structural, and molecular changes that underlie alterations in cognition, memory, mood and motor function, amongst other processes. Normal aging also imposes a robust constraint on the onset of many neurological diseases, ranging from late onset neurodegenerative diseases, such as Alzheimer's (AD) and Parkinson's diseases (PD), to early onset psychiatric disorders, such as bipolar disorder (BPD) and schizophrenia (SCZ). The molecular mechanisms and genetic underpinnings of age-related changes in the brain are understudied, and, while they share some overlap with peripheral mechanisms of aging, many are unique to the largely non-mitotic brain. Hence, understanding mechanisms of brain aging and identifying associated modulators may have profound consequences for the prevention and treatment of age-related impairments and diseases. Here we review current knowledge on age-related functional and structural changes, their molecular and genetic underpinnings, and discuss how these pathways may contribute to the vulnerability to develop age-related neurological diseases. We highlight recent findings from human post-mortem brain microarray studies, which we hypothesize, point to a potential genetically controlled transcriptional program underlying molecular changes and age-gating of neurological diseases. Finally, we discuss the implications of this model for understanding basic mechanisms of brain aging and for the future investigation of therapeutic approaches.

Contents

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's diseases; BPD, bipolar disorder; SCHZ, schizophrenia; ROS, reactive oxygen species; CR, caloric restriction; PFC, prefrontal cortex; SNP, single nucleotide polymorphism; SIRT, sirtuin.

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1. Introduction

Age-gated neurodegenerative and psychiatric diseases affect ~15% of people during their lifespan and are almost uniformly devastating. Current treatments for these diseases are not curative and have limited efficacy for symptom relief. Outside of the disease context, aging by itself is also associated with variable rates of cognitive and motor decline, which can be severely impairing for the most affected individuals. By definition, age is a constraint for the onset and progression of functional declines and age-associated diseases, and thus may represent a key entry point for understanding basic mechanisms of brain aging and for the future investigation of therapeutic approaches for age-related diseases.

Here, we use the term "normal brain aging" to describe aging of the central nervous system in the absence of clinically diagnosed neurodegenerative or psychiatric diseases, or of related pathology. However, as described in this review, it is becoming increasingly clear that molecular changes occurring during normal brain aging substantially overlap with those observed in the context of many diseases. Thus "normal brain aging" actually refers to average successful aging. This somewhat circular parsing of "normal or average disease-free" from disease-associated age-related changes is currently an unavoidable caveat of the field, but is necessary for investigating the contribution of aging to disease processes. Similarly, the line between developmental and age-related changes is unclear. Subjects as young as 14 years of age display molecular changes in the brain on a continuum with age-related changes that extend throughout old age (Erraji-Benchekroun et al., 2005), and it is likely that molecular aging partially extends from developmental processes.

Normal aging of the brain (i.e., in subjects without age-related neurological disorder) is understudied compared with peripheral aging, and has many fundamentally different molecular mechanisms and modulators. Some mechanisms, such as those related to insulin signaling and cellular insult, are shared between the periphery and brain; however, mechanisms related to cellular turnover and depletion, such as telomere shortening and senescence, are not as pertinent in the largely non-dividing brain. Instead, progressive morphological and molecular changes within life-long existing neurons and glia likely underlie age-related cognitive, motor, and mood changes and disease susceptibility (Fig. 1). Brain aging is also subjected to many unique genetic modulators, such as neurotransmitters, neurotrophins, and neurological disease-related genes (Fig. 1). Here, we briefly review current knowledge on the functional correlates of brain aging and discuss their putative biological underpinnings, starting at the gross structural and functional, cellular, and molecular levels,

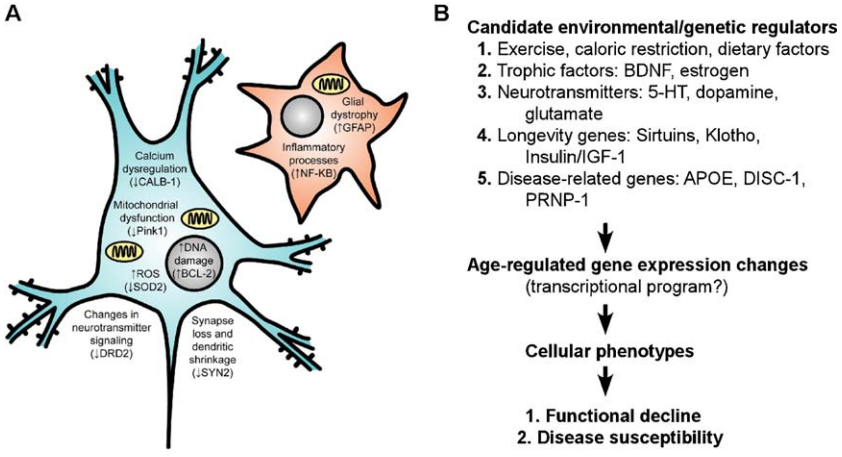

Fig. 1. "Normal" age-related molecular changes in neurons and glia, and putative modulators, mediators, and functional consequences. (A) Known age-related cellular phenotypes in neurons (blue) and glia (red). Cells are depicted as a generic neuron and glia for simplicity, but some information is known about class-specific changes in neurons and glia. Also not shown are changes in brain white matter tract and blood vessel integrity. Many neuronal phenotypes (such as DNA damage) also occur in glia, but are not depicted here for clarity. In parentheses are single representative examples (amongst many) of age-regulated gene expression changes seen by human brain microarray that may contribute to/underlie a particular cellular phenotype. (B) Schematic of putative modulators, mediators, and consequences of brain aging.