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editorial

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Aneuploidy and adult neurogenesis in Alzheimer's disease: therapeutic strategies

The confirmation that neurogenesis occurs in the adult brain and neural stem cells (NSCs) reside in the adult central nervous system (CNS) of mammals reveals that the adult brain has the potential for self-repair. Neurogenesis occurs in discrete regions of the adult mammalian brain, the subventricular zone and the dentate gyrus (DG) of the hippocampus, in various species, including humans. Newly generated neuronal cells in the adult brain originate from a pool of residual NSCs. Adult NSCs contribute to the physiology and pathology of the nervous system [1]. Recent studies show that neurogenesis is enhanced in the brain of patients with Alzheimer's disease (AD) [2]. Enhanced neurogenesis in the brain of AD patients would contribute to regenerative attempts in the CNS, to compensate for the neuronal loss.

AD is a neurodegenerative disease associated with learning and cognitive deficits, and for which aging is the main risk factor. The hippocampus is the main region of the brain affected by the disease. There are two forms of the disease: the late onset form (LOAD) diagnosed after age 65 and the early onset form (EOAD) diagnosed at a younger age. Genetic background and acquired and environmental risk factors are causative factors for LOAD, whereas EOAD is primarily an inherited disease. The presence of the apolipoprotein E varepsilon 4 allele (*ApoE4*) in the genetic makeup of the individuals is the best-established genetic risk factor for LOAD. Mutations in the amyloid precursor protein (*APP*), the presenilin-1 (*PSEN-1*) and the presenilin-2 (*PSEN-2*) genes have been identified as causative for EOAD. Amyloid plaques, composed of deposits of amyloid proteins, and neurofibrillary tangles, composed of aggregated hyperphosphorylated Tau proteins, are the histopathological hallmarks of AD [3].

AD is also characterized by neurodegeneration and aneuploidy in the adult brain [4]. The increase of aneuploid nerve cells in regions of degeneration in the AD brain contributes to the development of the disease. In regions of degeneration, cell cycle re-entry and DNA duplication, without cell division, are at the origin of aneuploid nerve cells in the brain of patients with AD [5]. These cells are fated to die and may undergo a slow death process, underlying the process of neurodegeneration in AD [6]. The *ApoE*, *PSEN-1*, *PSEN-2* and *TAU* genes are located on chromosomes 19, 14, 1 and 17, respectively. Aneuploidy for chromosomes carrying genes involved in AD promotes the formation of amyloid plaques, neurofibrillary tangles and neurodegeneration in the brain of patients with AD, LOAD or EOAD depending on the genetic and/or risk factors involved.

Dividing cells are the most likely to generate aneuploid cells [7]. Hence, neurogenesis holds the potential to generate new neuronal cells that are aneuploid in the neurogenic regions of the adult brain. Aneuploid new neuronal cells and aneuploid newly generated neuronal cells that would not proceed with their developmental program in the adult brain would be a contributing factor of the pathogenesis of AD in the neurogenic regions. Aneuploidy, for chromosomes carrying genes involved in AD, in newly generated neuronal cells of the adult brain would further promote the pathological process of AD, particularly in the hippocampus [8].

Adult neurogenesis is a relatively low frequency event in the adult brain; it is estimated that 0.004% of the granule cell

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2010.04.001

population is generated per day in the DG of adult macaque monkeys [1]. The hippocampus is one of the neurogenic regions of the adult brain and one of the regions of the brain the most affected in AD. Aneuploid newly generated neuronal cells originating from the nondisjunction of chromosomes during cell division may have their lifespan shortened or may survive for extended period of time. They would contribute to the pathogenesis of AD by promoting the formation of amyloid plaques, neurofibrillary tangles, neurodegeneration and aneuploidy, locally. This suggests that, despite being a low frequency event, the generation of aneuploid new neuronal cells in the hippocampus, in particular, may play a critical contribution to the pathology of AD.

Mutated forms of PSEN-1 are detected in interphase kinetochores and centrosomes of dividing cells, where they may be involved in the segragation and migration of chromosomes during cell division [9]. The hyperphosphorylation of Tau by kinases leads to the dissociation of Tau and tubulin and to the breakdown of microtubles causing the disruption in the mitotic spindle, which promotes aneuploidy during mitosis [10]. Hence, genetic and/or risk factors involved in AD would promote the generation of aneuploid new neuronal cells in the adult brain. Enhanced neurogenesis in the hippocampus of patients with AD, and more generally conditions that promote neurogenesis, would contribute to an increase of aneuploidy newly generated neuronal cells in the adult brain. This reveals that adult neurogenesis may be involved in the pathogenesis of AD.

In all, adult neurogenesis may contribute not only to regenerative attempts in the nervous system, but also to the pathogenesis of neurological diseases and disorders, particularly in AD. The contribution of aneuploid newly generated neuronal cells of the adult hippocampus to the pathogenesis of AD opens new avenues and perspectives for our understanding of and for treating the disease. Therapeutic strategies will aim at specifically targeting aneuploid newly generated neuronal cells of the adult brain, to limit their potential deleterious effects in patients with AD, without disrupting the regenerative capacity of adult neurogenesis.

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