Neurogenesis *versus* neurodegeneration: the broken balance in Alzheimer's disease

Baruh Polis*, Abraham O. Samson

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, eventually manifesting in severe cognitive dysfunction. Despite the recent proliferation of encouraging preclinical studies and clinical trials, scientific society is still far from a complete consensus regarding the AD etiology and pathogenesis. Accordingly, no approved AD-modifying therapies are currently available. Nevertheless, novel concepts predicated upon the latest discoveries and comprehension of the disease as a multifactorial disorder are paving the road to the successful AD treatment.

Accruing evidence indicates the role of systemic and brain metabolic aberrations, in addition to the canonical hallmarks, in AD pathogenesis (Polis and Samson, 2019). The up-to-date description of AD-associated pathology includes neuroinflammation, mitochondrial dysfunction, instigated apoptosis, and chronic oxidative stress. Of note, oxidative damage is one of the earliest events causing and following AD (Nunomura et al., 2001). Moreover, oxidative damage is strongly associated with neurodegenerative processes and it is a connecting factor between β-amyloidosis, τ-protein hyperphosphorylation, and neuronal loss. Oxidative stress due to the disbalance between generation and elimination of reactive oxygen species (ROS) plays a key role in β-amyloid-mediated cytotoxicity via a spectrum of molecular events that eventually lead to a substantial neuronal loss, which is a primary hallmark of AD, clinically manifesting in cognitive decline. In healthy individuals, excessive ROS production is counteracted by physiological antioxidant mechanisms that incessantly maintain redox homeostasis. However, these mechanisms are inadequate in the AD brain tissue and do not provide the necessary protection against highly reactive species, which disrupt membrane function, impair enzymes, break polysaccharides, and damage nucleic acids.

It is worth noting that oxidative stress characterizes normal aging as well, and leads to protein aggregation and misfolding in the brain. The hypothesis concerning the role of ROS and age-related changes in the pro-oxidant brain status, that contribute to the AD pathogenesis, was articulated long ago (Benzi and Moretti, 1995). This theory considers the extreme sensitivity of the brain to oxidative damage, due to its enormous metabolic rate together with a relatively large content of catecholamines and unsaturated lipids, as a prompting neurodegeneration factor. Recent translational studies prove the involvement of ROS in AD-associated pathology and open new treatment avenues.

Continuous life-long neuronal loss was supposed to be irreversible and cause, in some cases, cognitive impairment and neurological diseases. The brain capability to generate new neurons was confined to a distinct developmental period. However, murine and human studies have demonstrated the persistence of adult neurogenesis throughout life in several brain areas. Even though neurogenesis gradually wanes in aging animals and men, strong evidence verifies the presence of newborn cells in the brains of centenarians and AD patients (Tobin et al., 2019). Nevertheless, the density of neuronal progenitors is substantially decreased in cases of clinical AD in comparison with healthy age-matched controls, indicating severe impairment of this natural brain self-repair mechanism in AD (Moreno-Jiménez et al., 2019). Of note, some human-based postmortem studies report a significant increase in the levels of neurogenesis-related markers in AD patients compared to healthy controls (Jin et al., 2004), which is the stage-dependent phenomenon reflecting the compensatory effect to emerging neurodegeneration. However, advanced AD pathology is characterized by a decrease in the rate of neuronal replacement in the hippocampus, pointing to an imbalance between neurogenesis and neurodegeneration in this pathology.

Adult neurogenesis is an intricate multistage process including the proliferation of neural progenitors, migration of newborn cells, and their differentiation into a distinct neuronal phenotype following by functional integration into specific circuits. The newborn neuronal cells originate from neural stem cells of the definite germinal zones and are characterized by self-replication ability and differentiation into several lineages, including neurons and glia. Neuronal precursors have been identified in various adult brain regions; however, active neurogenesis is localized in the subventricular zone and the hippocampal dentate gyrus, both of which unremittingly generate neurons during adulthood and even senescence.

This capability, as a form of neural plasticity, seems to be evolutionary significant for species living in a continually changing environment, providing mammalian brains with a superb capacity to cope with extreme cognitive and emotional challenges. Accordingly, adult neurogenesis is controlled by plenteous behavior-associated factors. Empirical evidence demonstrating the experience-dependent differentiation and functional integration of newborn neurons, proves the neurogenesis contributing role in learning and memory acquisition mechanisms (Deng et al., 2010). Environmental enrichment and physical exercise escalate the rate of neurogenesis in rodents. Voluntary running, in mice, and intense walking in men, have been shown to support neurogenesis in normal aging and halt the AD-related cognitive decline. Aerobic exercise, in particular, modulates the redox brain status and improves the resistance against oxidative stress attenuating the age-associated cognitive decline and the manifestation of AD. Conversely, an artificial extension of the adult-born neurons population in mice improves specific cognitive performances. Moreover, the instigation of adult neurogenesis combined with training upturn exploratory behavior (Sahay et al., 2011). Therefore, therapeutic strategies for manipulating neurogenesis by decreasing the rate of cell death and by increasing generation of newborn neurons are promising to reverse the age or AD-associated cognitive impairments.

Neurogenesis is under precise regulation by delicate physiological mechanisms, which are extremely sensitive to homeostasis alterations. Notably, even in the healthy brain, the vast majority of newborn cells do not survive for more than one month (Mu et al., 2010). Their endurance rate is sensitive to assorted conditions of the brain milieu, which have to be precisely appropriate to physiological development program and support the neuronal integration into the functional brain circuitry.

The hippocampus is a primary memory acquisition domain, which substantially degenerates in AD patients. Therefore, particular attention has been given to a distinct population of the progenitor cells residing in the subgranular zone of the dentate gyrus, producing functional granule postmitotic cells that express typical neuronal markers. These newborn cells have been shown to penetrate the granule layer, differentiate, extend processes, receive functional input, and integrate into the existing neuronal circuitry (**Figure 1A**).

We have mentioned above that AD-related neurodegeneration, and even normal aging, are associated with growing oxidative stress, which reflects imbalances between oxidative and antioxidative factors. Several processes lead to this phenomenon. The brain hypoperfusion due to atherosclerosis and/or endothelial dysfunction, neuroinflammation, traumatic injury, diabetes, and metabolic stress are among them (Polis and Samson, 2019). These conditions do not support neurogenesis and, on the other hand, lead to neurodegeneration (**Figure 1B**). In AD particularly, the mechanism of cell-replacement and integration of novel neurons into the existing networks is seriously deteriorated. Amyloid-β protein impairs the proliferation and differentiation of neural progenitors directly, promotes their apoptosis, and aggravates oxidative stress. Likewise, oxidative stress upsurges β-amyloid production via various transcription, translation, and processing-related mechanisms, which further exacerbates neurogenesis, prompts neurodegeneration, and finally closes the vicious circle of AD pathogenesis (Polis et al., 2020). Numerous animal models of AD substantiate this conception. AD mice are characterized by a significantly decreased density of adult-generated hippocampal neurons that contributes to the cognitive decline observed in these animals. Some models, such as triple-transgenic mice, for instance, show age-dependent neurogenesis deficits, which precede the manifestation of other classical hallmarks of AD pathology and

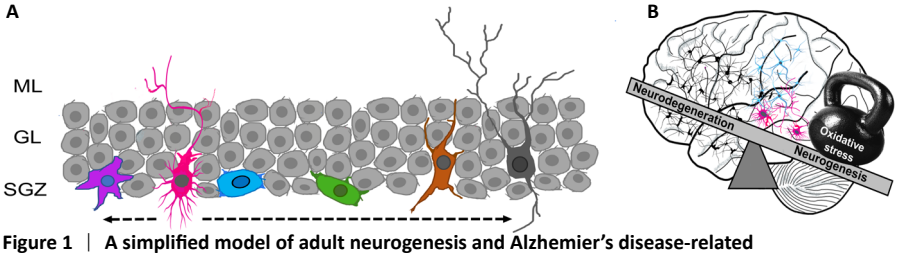

Figure 1 | **A simplified model of adult neurogenesis and Alzhemier's disease-related neuropathological changes.**
(A) A simplified representation of the adult hippocampal neurogenic processes. The radial glia-like cells (red) give rise to astrocytes (purple) and neuronal progenitor cells (blue), which display a dissimilar morphology. Progenitors proliferate, differentiate, express specific markers, and generate neuroblasts (green). The postmitotic neuroblasts differentiate into immature neurons (brown) that undergo postmitotic maturation, send processes via granular layer, and form functional connections. The survived mature neurons (dark gray) further extend their processes towards the molecular layer and integrate into the existing circuitry. Granule layer neurons are shown in gray. Molecular layer (ML), granule layer (GL), subgranular zone (SGZ). (B) The brain tissue is highly vulnerable to oxidative stress that plays a central role in the pathogenesis of Alzhemier's disease. Chronic oxidative stress affects the delicate balance between the two opposite processes. It leads to a substantial reduction in the rate of adult neurogenesis and, on the other hand, upsurges the rate of neurodegeneration, which manifests in clinical dementia.

memory impairment, pointing to neurogenesis insufficiency as an early and sensitive AD hallmark. Remarkably, the treatment strategies correcting oxidative brain status support the survival and differentiation of neuronal precursors and reduce neurodegeneration in these animals (Polis et al., 2020).

Of note, β-amyloid-mediated cytotoxicity is characterized by the activation of numerous apoptotic and necrotic mechanisms. Oxidative DNA damage particularly has been associated with triggering neuronal apoptosis programs in the AD brain. Amyloid-β overproduction significantly reduces the survival rate of newborn neurons and intensifies their death as they approach maturity (Verret et al., 2007). Consequently, decreased integration of newly generated neurons into the hippocampal circuitry correlates with the decline in learning and memory capabilities following AD and normal aging, which indicates the complexity of the disease-associated neurogenesis malfunction.

Of note, as an energy-consuming process, adult neurogenesis is associated with ROS generation. In a healthy brain, with intact mechanisms of ROS removal, it does not lead to oxidative stress. Moreover, short-term ROS accumulation stimulates neural progenitors proliferation, and differentiation; however, long-term exposure leads to cell damage and induces apoptosis. In the advanced pathological states, however, ROS accumulation results in the blood-brain barrier breakdown, severe cellular injury, disordered signaling, and malfunction, which in turn, aggravate oxidative stress due to the loss of balance between ROS production and elimination. Consequently, oxidative damage causes and typifies the AD-related neuronal loss and, on the other hand, leads to neurogenesis insufficiency. We suggest that oxidative stress dramatically reduces and limits the survival rate of newborn cells. For that reason, therapeutic strategies directed at correcting antioxidative brain mechanisms demonstrate potency to improve the neurogenesis rate and halt the AD-associated cognitive decline.

In the context of the discussion on the role of oxidative stress in adult neurogenesis, it is noteworthy to mention the effects of cranial irradiation, which is used in patients with brain tumors, upon neurogenesis. Cranial irradiation is accompanied by serious side effects in cancer survivors. Cognitive impairment represents just one of them and is associated with substantial suppression of hippocampal neurogenesis and escalation of neuronal apoptosis. Notably, the ROS generation is a key cause of radiation-induced tissue damage. Typically, radiation therapy leads to severe several-month-long oxidative tissue stress. Furthermore, long-term radiation-related brain tissue damage leads to an irreversible impairment of the neural precursors' function and reduction in their density in both rodents and men (Monje et al., 2002). Accordingly, antioxidant-based therapies have been proposed to protect the brain after irradiation and preclude these complications. Remarkably, the same approach, utilizing a list of potent antioxidants, represents a recent direction in AD treatment.

In conclusion, we highlight that the role of adult neurogenesis in AD-related cognitive deficiency is still debated in the literature. Even though some pieces of recent evidence are extremely contradictory, there is no doubt that the hippocampal neurogenesis is critical in maintaining cognitive functions in both the healthy and AD brain. Newborn cells definitely contribute to learning and memory, and their malfunction is associated with AD pathogenesis (Moreno-Jiménez et al., 2019).

Adult neurogenesis is extremely responsive to the brain pathology and correlates with its severity. Neurogenesis counteracts neurodegeneration in the aging and AD brains by implicating neural progenitors in the repair mechanisms and replacement of nonfunctional brain tissue. However, the development of AD is followed by an increase in the imbalance between these two counterdirected processes. Notably, oxidative stress due to numerous factors seems to be the main cause of this imbalance. The AD brain is under gradually growing oxidative stress, leading to progressive neuron degeneration and, eventually, death and atrophy of susceptible areas. On the other hand, chronic oxidative stress causes neurogenesis decline that further aggravates clinical dementia, which becomes irreversible. Therefore, early diagnosis and preventive interventions targeted at neurovascular unit function and ROS elimination are the most promising approaches to combat the disease.

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