Adult neurogenesis is the process by which new neurons are generated throughout life. They develop from stem cells, located in two neurogenic niches, i.e., the dentate gyrus of the hippocampus and the subventricular zone (SVZ).

This process appears to take place also in adult humans and is severely reduced during aging, depression, and during neurodegenerative pathologies; the first consequence of this reduction is a decrease of associative memory. In fact, the newly generated neurons within the dentate gyrus are integrated in memory circuits and play an important role in counteracting processes such as aging or neurodegeneration, whereas the new neurons generated in the subventricular zone are redirected, in case of brain trauma, to the damaged neural area to counteract the ongoing degeneration.

In this scenario, in the last years we have investigated the process of adult neurogenesis, seeking to identify neurogenic stimuli as well as the gene network responsible for the maintenance of the quiescence of stem cells and for the migration and differentiation of the new neurons. Stem cells in fact mature into progenitor cells that in turn develop into new neurons.

Concerning the neurogenesis gene network, we identified and studied four genes involved, all cell cycle inhibitors, namely Tis21/Btg2, Btg1, p16Ink4a, p21Cip1, and also the chemokine Cxcl3. We found that the gene Tis21/Btg2 is responsible for the exit from cell cycle of progenitor cells (neuroblasts) and for their differentiation in new neurons. A misregulation of the timing of activation of Tis21/Btg2 generates new neurons unable to encode new memories (1).

We found also that another gene of the Btg family, Btg1, maintains the quiescence of the stem cells in the dentate gyrus as well as in the subventricular zone, as its deletion triggers their proliferation (2).

Recently we showed that p16Ink4a is specifically responsible for preventing the exit from quiescence of aged hippocampal stem cells, in aged mice undergoing the neurogenic stimulus of running. Thus, p16Ink4a appears to prevent the depletion of the pool of stem cells of the hippocampus in aging subjects, since p16Ink4a expression becomes detectable only during aging (3).

On the other hand, we observed that p21Cip1 is required to regulate neurogenesis in the subventricular zone (4).

Moreover, Tis21/Btg2 directly binds and regulates the promoter of cyclin D1 and of the chemokine Cxcl3, which controls the migration of progenitor cells (5). Thus, the coordinated action of all these cell cycle inhibitory genes contributes to orchestrate the process of adult neurogenesis.

In parallel, we analyzed the possibility to activate stem cells by neurogenic stimuli as a function of the intensity of the stimulus (i.e., whether this is physiological or pathological), and of the deregulation of the system (i.e., whether the model is aged or carrying genetic mutations in the gene network controlling quiescence). While neurogenic stimuli such as running or antidepressants (e.g., fluoxetine) or diet nutrients (e.g. hydroxytyrosol) are normally unable to activate stem cells in the dentate gyrus or SVZ, when the system is aged and/or carrying mutations of quiescence-maintaining genes, such as Btg1 or p16Ink4a or p21Cip1, preservation of the quiescent state of stem cells is more critical and stem cells can be activated by neurogenic stimuli ineffective in normal conditions (3,4,6,7). This indicates that stem cells retain a high proliferative capability and plasticity, and suggests that stem cells are protected against the response to stimulus and are resilient to exhaustion (see for review: 8).

We are currently studying different functional degrees of deregulation of the stem cell quiescence-maintaining system. These studies are relevant to find strategies counteracting neural aging and neurodegenerative diseases.

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