Running rescues defective adult neurogenesis by shortening the length of the cell cycle of neural stem and progenitor cells.

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### Abstract

 Physical exercise increases the generation of new neurons in adult neurogenesis. However, only few studies have investigated the beneficial effects of physical exercise in paradigms of impaired  neurogenesis.  Here, we demonstrate that running fully reverses the deficient adult neurogenesis within the hippocampus and subventricular zone of the lateral ventricle, observed in mice lacking the antiproliferative gene Btg1. We also evaluated for the first time how running influences the cell  cycle kinetics of stem and precursor subpopulations of wild-type and Btg1-null mice, using a new method to determine the cell cycle length. Our data show that in wild-type mice running leads to a cell cycle shortening only of NeuroD1-positive progenitor cells. In contrast, in Btg1-null mice, physical exercise fully reactivates the defective hippocampal neurogenesis, by shortening the S-phase length and the overall cell cycle duration of both neural stem (glial fibrillary acidic protein(+) and Sox2(+)) and progenitor (NeuroD1(+)) cells. These events are sufficient and necessary to reactivate the hyperproliferation observed in Btg1-null early-postnatal mice and to expand the pool of adult  neural stem and progenitor cells. Such a sustained increase of cell proliferation in Btg1-null mice after running provides a long-lasting increment of proliferation, differentiation, and production of newborn neurons, which rescues the impaired pattern separation previously identified in Btg1-null mice. This study shows that running positively affects the cell cycle kinetics of specific subpopulations of newly generated neurons and suggests that the plasticity of neural stem cells without cell cycle inhibitory control is reactivated by running, with implications for the long-term modulation of neurogenesis.

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**Significance Statement**

In this paper we studied for the first time the effect of physical activity on the cell cycle kinetics of  proliferating adult newborn neurons in the dentate gyrus of hippocampus.

It is well established that physical exercise has profound benefits for cognitive function and many studies has shown that running is associated with enhanced hippocampal adult neurogenesis and with changes in the expression of plasticity enhanced genes.

In this research we highlight the importance of physical activity in counteracting the defective adult neurogenesis in a mouse model in which the depletion of the antiproliferative gene Btg1 provokes in the neurogenic niches (ie dentate gyrus and subventricular zone) a post natal hyper- proliferation of newly generate neurons followed by a gradual depletion of neural stem cells during the adulthood.

More specifically, we found that a sustained increase in cell proliferation in Btg1 null mice after running is strictly dependent by a shortening of S-phase and consequently of the cell cycle of the neural stem and progenitor cells. On the contrary, in the wild-type mice running induces the shortening of S-phase and cell cycle only of committed progenitor cells. The events described in the Btg1 ko mice results in a long-term increment of neurogenesis and production of newborn neurons, which in turn contributes to improvement of the defective process of hippocampal-dependent pattern separation detected  in Btg1-null mice.

These data indicate for the first time that the replicative potentiality of the neural stem cells is not limited with aging and that a deprived stem cells pool is still ready to be reactivated when the inhibitory cell cycle control is missing. This scenario provides new pivotal information in modulating the dynamics of adult neural stem cells proliferation and neuronal production. In our opinion, these findings could be relevant in the fight against cerebral aging and  neurodegenerative disorders, since  “run-activated neural stem cells” identified by us, could harness the potential to regenerate the pool of neural and might be employed in the neuroregenerative therapies in combination with pharmacological approaches.

**Figure Legend:**

Representation of radial glia-like neural stem cells (rNSC) in the adult hippocampal dentate gyrus of Btg1 knockout mice after 12 days of running. The soma of these cells dwells in the subgranular zone of the dentate gyrus, while a single apical process crosses the GCL and then arborizes profusely in the molecular layer. The rNSCs were characterized by the expression of both GFAP and Nestin (scale bar 15 mm).

