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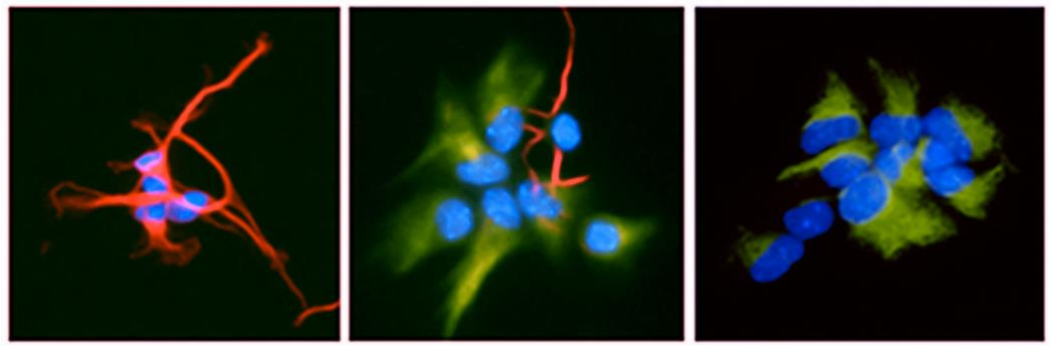
PRESS RELEASE

The origins of astrocytes: the brain's star cell

A new SISSA study investigates the unexplored dynamics behind the production of these special cells, which are essential for neuronal activity and implicated in a number of diseases, with interesting implications for research and therapeutic treatments



Trieste, 27 July 2022

Astrocytes are a particular subgroup of star-shaped brain cells. Although less well-known than neurons, astrocytes are essential for neuronal activity and play a role in various neurological diseases. A new study led by Antonello Mallamaci from the Trieste-based International School for Advanced Studies (SISSA), recently published in *Cerebral Cortex*, demonstrates that as an embryo develops, these cells are produced according to different programs in different parts of the brain. This discovery has revealed new mechanisms for regulating stem cells in the brain and may have implications for therapeutic treatments.

As the embryo develops, all stem cells, including neural stem cells, give rise to more specialized progenitor cells, which in turn can multiply and differentiate into, for example, only astrocytes or only neurons. However, until now, nobody had ever explored in depth the theory that this process might follow different dynamics in different parts of the brain.

“We thought there should be a discrepancy, as the stem cells that make up the hippocampus, which is a relatively small structure, are found in proportionately larger numbers than those in the neocortex, which is a larger structure. Nobody, however, had ever investigated the underlying mechanism” explains Manuela Santo, one of the first two authors of the study.

Using mice as models for the study, the research team observed that the stem cells from specific parts of the cortex had a different propensity to generate astrocytes and followed two distinct dynamics. In the hippocampus and in the medial areas of the brain in general, neural stem cells produce a large number of progenitors, which are poorly prone to proliferate and quickly differentiate into astrocytes. Conversely, in the anterolateral parts of the cortex, the progenitor cells produced by the stem cells are few in number, and differentiate into astrocytes relatively late, after high proliferation. This dynamic was right under everyone’s nose but had never been explored until now.

Underlying this difference is the early exposure of stem cells to different doses of the *Emx2* transcription factor, which was already known to be involved in astrogenesis. The gene *Emx2* is expressed in very high levels in the hippocampus area, which is precisely where the astrocytes are produced earlier than in other areas of the cerebral cortex.

“One of the most interesting things we discovered is that the hippocampus stem cells not only know they have to generate more commissioned progenitors, but they can even programme the molecular behaviour of these progenitors, ‘teaching’ them to proliferate less,” explains Laura Rigoldi, another primary author of the recently-published *Cerebral Cortex* study, the result of a collaboration between Italian and US researchers.

The team found that this behaviour can be reproduced in vitro by forcing a neurostem cell to express the *Emx2* gene, as happens in the hippocampus. This signal is all it takes to induce the production of many progenitors programmed for short proliferation, even in the descendant cells.

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"This study on astrogenesis has added to the list of mechanisms involving this important growth gene. It also opens up interesting avenues for new research projects into the regional specialisation of astrocytes" commented Manuela Santo. However, that is not all: the results of this study could, in the future, have potential implications for the treatment of glioblastoma, a highly aggressive form of brain tumour.

"At the moment it is purely speculation, so we are very cautious, but from past studies we know that if we over-express the *Emx2* gene specifically in glioblastoma stem cells, we greatly reduce tumor growth capacity" explains Mallamaci. He continues "This can reflect the fact that if the gene is highly expressed in the stem cells, such cells 'instruct' daughter cells to proliferate less, and that teaching is handed down to the next generations."

It appears that the tumor behaves like a pathological caricature of what occurs in nature: the same mechanisms observed in this study might explain the functioning of those attempts at experimental treatment.

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Full paper: Cerebral Cortex

IMAGE
Credits: Manuela Santo

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