Discovered key gene for the formation of new neurons

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Scientists discovered a gene - called AP2gamma - crucial for the neural development of the visual cortex, in a discovery that can have implications for the therapeutics of neural regeneration as well as provide new clues about how the brain evolved into higher sophistication in mammals. The article will come out in the journal *Nature Neuroscience* today.

The cerebral cortex is the folded, outside layer of the brain, involving it like a tree bark. It is also the most recent brain structure having appeared with mammals - where is responsible for higher brain functions including memory, thought and reasoning but also sensory responses - and is organized in several layers of neurons, with different cortical areas (with distinct neural anatomy) performing different functions.

To understand how these different areas with different functions have evolved is one of today´s biggesr questions in science. We already know, for example, that cortical neurons originate from two groups of precursor cells - neuroepithelial cells (NEC) and radial glial cells (RGC) on one hand, and basal progenitors - which develop from NEC and RGC- on the other, although is still unclear how this happens. Basal progenitors are particularly interesting to understand because when they divide they create new neurons - only very rarely they originate more basal progenitors - what gives them a special potential for treatments in neural regeneration.

And it is exactly this step - from basal progenitors to neurons - that is

investigated by Luisa Pinto and Magdalena Götz at the Institute for Stem Cell Research, Neuherberg/Munich, Germany and colleagues in the article now published. The group of researchers have previously identified a protein in RGCs - called AP2gamma - which seemed particularly promising to further investigation since it was shown to be linked to Tbr2, a transcription factor existent in basal progenitors and known to be involved in neuron formation (neurogenesis). Transcription factors are proteins that bind DNA to activate or suppress other genes.

The researchers started by investigating AP2gamma expression in the brain of mouse embryos to find that the gene was only active in the cortex, suggesting a specific function in this structure. And in fact, they went to show that mice without a functional AP2gamma presents a smaller caudal (occipital) cortex, exactly where the visual cortex is located. When this “shrinkage” was investigated Pinto and colleagues discovered that, contrary to what they expected, this was not the result of a reduction in cellular division (which seemed to be even increased) but, instead, of a neural “maturation” issue. In fact, these mice´s caudal basal progenitors lacked most of the normal transcription factors necessary for neurogenesis - including Tbr2 - while retaining features of RGCs (their precursors), apparently staying “immature”.

Since the visual cortex is located in the cortex caudal area the next logical question was to investigate for functional problems that effectively existed in the form of lack of visual clearness and proper binocularity (ability to focus upon an object with both eyes).

In conclusion, Pinto and colleagues show that changes in AP2gamma result in loss of neurons and reduced cortical (or caudal) cortex. This happens because AP2gamma is crucial for the regulation of most transcription factors necessary for the passage from basal progenitor to neuron. So when AP2gamma is not functional, basal progenitors, incapable of generating neurons, re-enter instead the cell cycle dividing

again and forming more basal progenitors. Eventually, later in development, these basal progenitors seem to die. The researchers also show that these changes create visual issues, which, very interestingly, resembled the characteristics of very young mice. It was almost like if mice with no AP2gamma maintained an immature cortex what supportedthe molecular data.

Luisa Pinto a Portuguese researcher and the first author of the work explains the importance of these results “we already knew another gene, Pax6, which seemed to be involved in neural regeneration after brain lesions but its manipulation resulted in small numbers of apparently immature neurons what made us suspect that other genes had to be involved. AP2gamma fits the bill perfectly”

Pinto, Götz and colleagues help to unveil some of the mysteries of the development of one of our most important and complex brain areas: the cortex. Their work has many implications, for a start, by showing that changes in AP2gamma can make a neural precursor re-enter the cell cycle to further multiply and they open the possibility that manipulation of this protein can be used in neural regeneration. This is also particularly important because all Pinto’s results were seen in glutamatergic neurons, which are renowned by their incapacity to naturally regenerate and are also associated to several diseases such as Alzheimer’s where they are known to be the first to die. Not only that, but illnesses like autism, schizophrenia and epilepsy are still explained in terms of an imbalance between the inhibitory and excitatory (mediated by glutamatergic neurons) systems in the cerebral cortex.

“The next step - says Pinto now working at the Life and Health Sciences Research Institute in the University of Minho, Portugal - is to study the function of AP2gamma in neurogenesis modulation after a brain lesions and in stress-related disorders. We will also be collaborating with researchers looking for the function of AP2gamma in primates and

humans, since the gene is expressed in both organisms".

Finally, it is known that the evolution of the cortex - towards more and more complexity - in mammals is not due to changes in the number or types of cortical areas but, instead, in the number of neurons within them raising the possibility that AP2gamma could have been/is a key player in the process.

More information: *Nature Neuroscience* - 2009 Online Early Edition; DOI: 10.1038/nn.2399 ; "AP2γ regulates basal progenitor fate in a region- and layer-specific manner in the developing cortex"

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