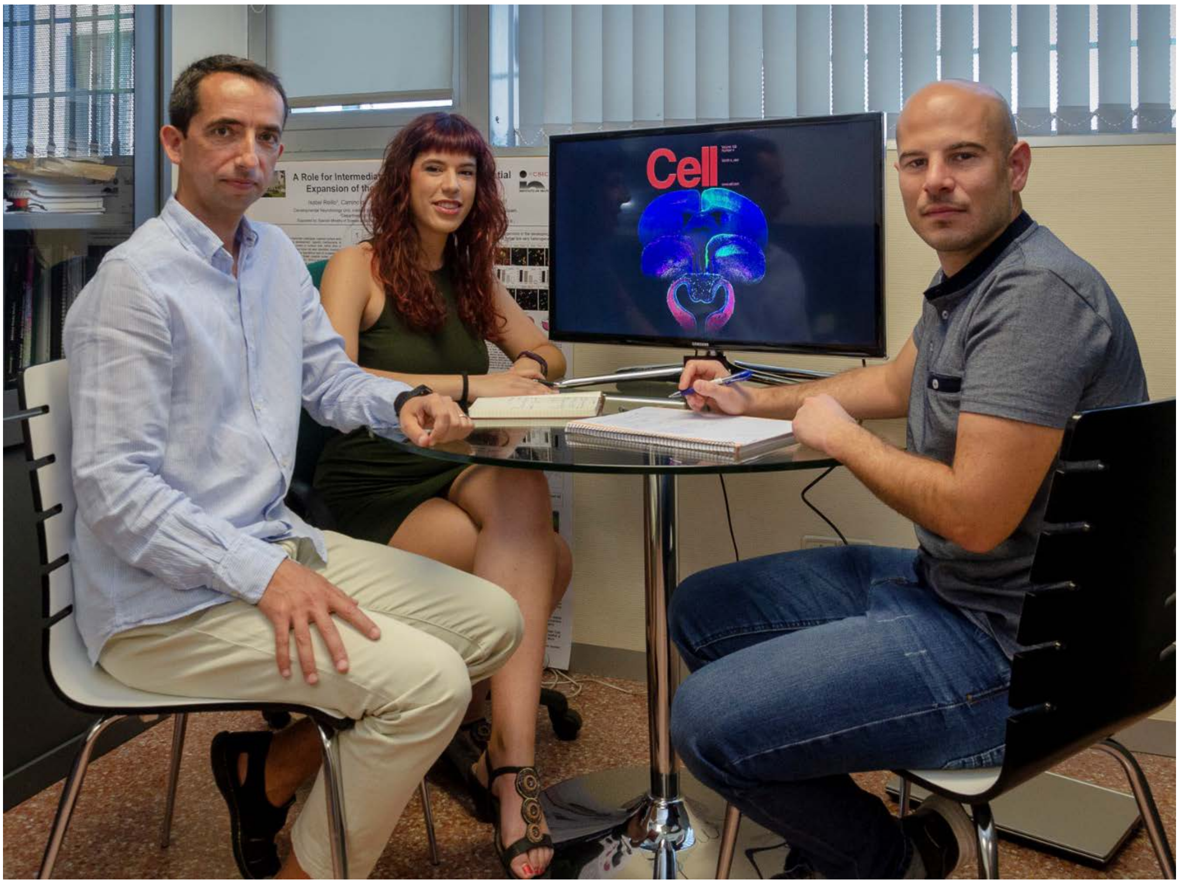
IDENTIFIED A GENETIC MECHANISM THAT ALLOWED THE UNPRECEDENTED INCREASE IN THE NUMBER OF NEURONS AND THE APPEARANCE OF CAPACITIES THAT DEFINE US AS HUMAN

The laboratory of Dr. Víctor Borrell, from the Instituto de Neurociencias in Alicante, Spain, a joint center of the Miguel Hernández University of Elche and the CSIC, has identified for the first time a key molecular signal for the expansion of the cerebral cortex and the acquisition of its complex architecture in the evolution of mammals. This finding is of unprecedented importance because it shows that this evolution was not due to the appearance of new genes, as has recently been suggested, but rather to the fine regulation of genetic mechanisms already existing in reptiles, and common to all amniotes. The study led by Dr. Borrell's lab in Spain has also involved researchers from the University of Geneva (Switzerland), Max Planck Institute (Germany), Stanford University and Thomas Jefferson University (USA).



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The size of the brain is radically different between reptiles, birds and mammals due mainly to the difference in size and complexity of the cerebral cortex, which reaches its maximum exponent in our species. Composed of six layers, in contrast to three layers in reptiles and birds, our cerebral cortex allows us to control characteristics that are uniquely human, such as creativity, language, writing, laughter, the arts or the ability to plan actions and anticipate their consequences.

The expansion of the cerebral cortex began with the passage of vertebrates to dry land in the Cambrian, about 500 million years ago, when the diversity of life forms experienced a great explosion. At that time amniotes appeared (reptiles, amphibians and birds), whose embryo is provided with a cavity filled with liquid (amnion) that allowed them to become independent from water for reproduction and development.

Leaving the aquatic environment was a great challenge for the primitive brain, which underwent profound modifications to integrate the new visual, acoustic and olfactory information that it received out of the water, as well as to adapt to the new terrestrial locomotion, which needed the development of a musculature specific body to move the anterior and posterior limbs.

All these modifications evolved the small and primitive cerebral cortex of amphibians to become the much larger and complex cortex of mammals. This happened thanks to an unparalleled increase in the number and types of neurons, which allowed the passage of a crust formed by three layers of cells, called paleocortex (ancient cortex) typical of reptiles, to another more evolved and with six layers, typical of mammals, called neocortex (new cortex). This great qualitative leap was fundamental for the progressive increase in cognitive abilities in the different species of mammals, ultimately reaching the highest level in primates and humans.

NEURAL STEM CELLS

The development of the cerebral cortex depends to a large extent on radial glia cells, the stem cells responsible for generating neurons and guiding them during embryonic development to their final destinations within the brain. The increase in embryonic neurogenesis throughout evolution depended on a binary decision of radial glia cells: to generate neurons directly or indirectly.

In reptiles and birds, most cortical neurons are produced directly from the radial glia cells, whereas in the neocortex of mammals most neurons are produced indirectly through intermediate progenitor cells, which are grouped in the so-called subventricular zone, exclusive of the mammalian brain. This process for generating new neurons, although slower, allowed an exponential amplification of the production of new neurons that drove the evolution of the cortex to the brain.

Until now, the mechanisms that regulated this expansion of the cerebral cortex from the three layers of reptiles and birds to the six layers of mammals were unknown. The laboratory of Dr. Víctor Borrell, of the Institute of Neurosciences in Alicante, joint center of the Miguel Hernández University of Elche and the CSIC, has taken a very important step precisely to understand, both at the cellular and genetic levels, how this evolution took place, fundamental to endow us with our unique characteristics.

In particular, they have identified for the first time a key molecular signal for the expansion of the cerebral cortex and the acquisition of its complex architecture in mammals (neocortex). This finding is of outmost importance because it shows that this evolution was not due to the appearance of new genes, as has recently been suggested, but rather to the fine regulation of genetic mechanisms existing already in reptiles, and that are common to all amniotes.

It was the regulation of activity levels of a highly conserved signaling pathway, that of the Robo gene (abbreviation of Roundabout), which made possible the change in the way of generating new neurons, going from a direct neurogenesis with low efficiency to another indirect, very productive. While direct neurogenesis, typical of reptiles and birds, limits the number of new neurons and, therefore, the size of the cerebral cortex, the appearance of indirect neurogenesis allowed the production of an unprecedented volume of neurons. This was achieved by decreasing the expression of the Robo gene during the evolution of the amniotes, as the primary mechanism that promoted the expansion and complexity of the cerebral cortex along the evolutionary scale.

Dr. Borrell's team has used experiments of gain and loss of gene function in embryos of mice, chickens and snakes, and also in human brain organoids, to show that low levels of the gene Robo, combined with high levels of the gene Dll1, are necessary and sufficient to lead to indirect neurogenesis, which allowed the development of the increasingly larger and more complex cerebral cortex of mammals. In addition, they have experimentally verified in snakes and birds that the decrease in the signal of Robo and the potentiation of Dll1 recapitulates this evolutionary process, giving rise to the formation of stem cells that only form in the mammalian brain, and that are necessary for indirect neurogenesis, also exclusive of mammals.

Víctor Borrell is a Scientific Researcher of the CSIC and Deputy Director of the Instituto de Neurociencias in Alicante. His laboratory is a world leader in the study of the evolutionary expansion of the cerebral cortex and its folding. His discoveries and innovative experimental approaches have paved the way for a whole field of research currently in effervescence, mainly due to his knowledge and vision of the evolutionary process. Awarded with an European Research Council grant, he has discovered multiple fundamental cellular and genetic mechanisms in this process (Cerebral Cortex 2011, Cell 2013, EMBO J 2015, Nat Comm 2016). The last one, published in May of last year (Cell 2017), identified a hitherto unknown mechanism that allows the formation of folds in the cerebral cortex to increase its surface area.