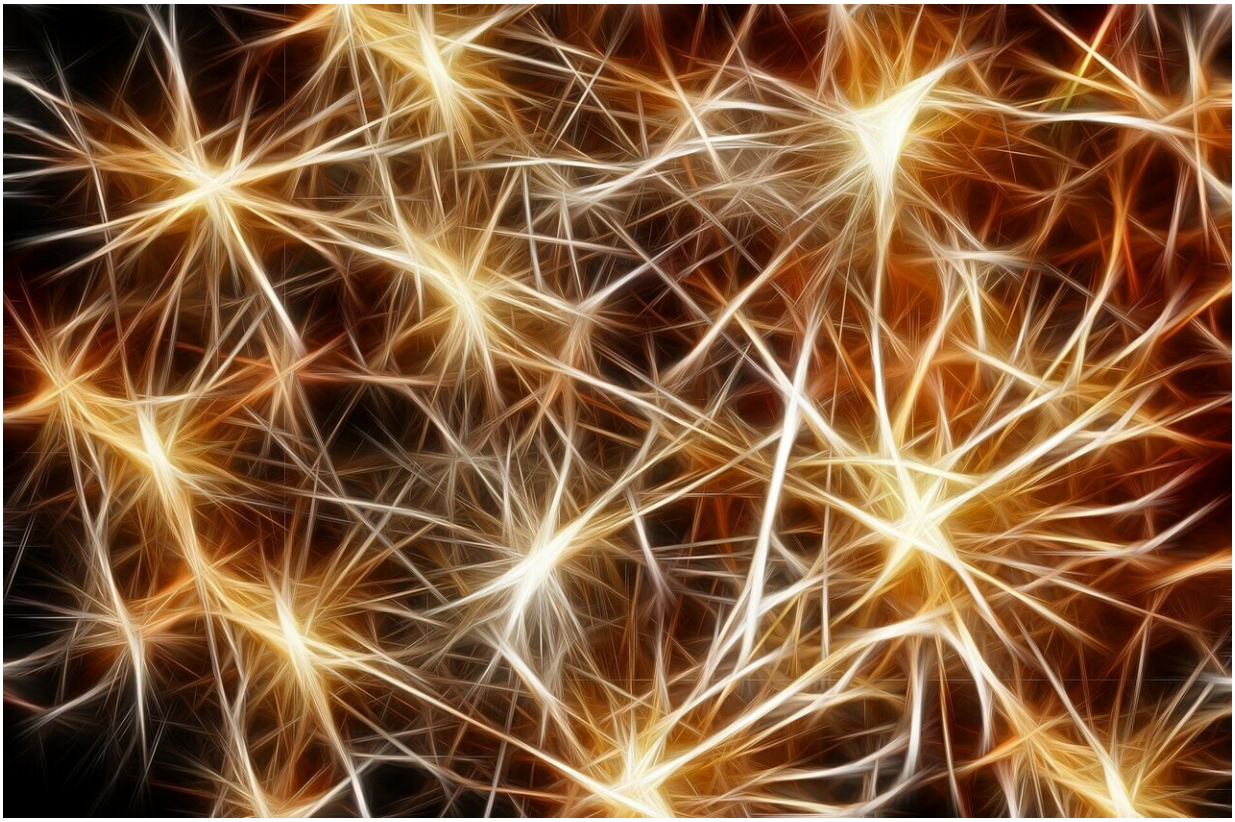
To become, or not to become a neuron

July 25 2019



Credit: CC0 Public Domain

Researchers led by Pierre Vanderhaeghen and Jérôme Bonnefont (VIB-KU Leuven and ULB) have unraveled a mechanism controlling the switch between growth and differentiation of neural stem cells during brain development. They discovered a specific factor that makes stem cells 'deaf' to proliferative signals, which in turn causes them to

differentiate into neurons. The findings, published in this week's edition of *Neuron*, shed new light on the understanding of brain developmental processes and have important implications for stem cell biology.

The brain is an incredibly complex organ consisting of billions of cells with a diverse range of functions. The mechanisms that orchestrate the formation of this intricate network during development have kept neuroscientists awake for decades.

One such neuroscientist is Prof. Pierre Vanderhaeghen (VIB-KU Leuven), whose team studies the development of the brain cortex, the outer layer of neuronal tissue that contributes in an essential way to who we are, as a species and as individuals.

"During neural development, a complex cocktail of signals determines the fate of neuronal progenitor cells," explains Vanderhaeghen. "These stem cells receive many 'proliferative' signals that instruct them to keep on dividing, generating more and more cells for the growing brain, but at some point, they also need to stop doing this and differentiate. In other words, they need to specialize to become a specific type of brain cell."

Turning deaf at the right time to mature into a nerve cell

Vanderhaeghen's team set out to understand how this switch between growth and differentiation is regulated and identified a molecular factor, called Bcl6, that essentially makes progenitor cells "deaf" for the proliferative signals that tell them to keep on dividing, thereby ensuring that differentiation occurs efficiently.

Jérôme Bonnefont, a postdoctoral researcher in Vanderhaeghen's lab, says, "We used an extensive set of genomic and cellular tools and found

that a protein called Bcl6 acts as a global repressor of a repertoire of signaling components and pathways that are known to promote self-renewal. Since Bcl6 is expressed only in specific subsets of progenitors and neurons during brain development, it allows for the precise fine-tuning of brain developmental processes."

Fate transition, stem cells, and cancer

Vanderhaeghen is enthusiastic about the findings: "These results provide important insight into the molecular logic of so-called neurogenic conversion. Thanks to this ingenious switch, differentiation can occur in a robust way despite the presence of many, and sometimes even contradictory, extrinsic cues."

"We made this discovery focusing on neural stem cells, but I would predict that similar factors act in many stem cells in the embryo and even in adults to ensure proper differentiation," he continues. "This may be also important in the context of cancer biology, since stem cells and cancer cells usually respond to the same proliferative cues that are precisely inhibited by Bcl6."

Future work should determine whether and how other repressors in other parts of the nervous system and body can modulate responsiveness to extrinsic cues in a similar way. This will reveal more about differentiation, not only during development, but also beyond in the adult brain and in cancer cells.

More information: Cortical neurogenesis requires Bcl6-mediated transcriptional repression of multiple self-renewal-promoting extrinsic pathways, Bonnefont et al. *Neuron* 2019

Provided by VIB (the Flanders Institute for Biotechnology)