The migration of cortical interneurons

11/9/12

Initially known for its ability to promote cell cycle exit, protein p27 has now been found to have other talents. Laurent Nguyen’s team at the GIGA-Neurosciences unit has revealed the involvement of p27 in controlling the migration of cortical interneurons through its action on actin and microtubules.

If we think about the complexity of the human body, the billions of cells composing it, the way in which they are organised and orchestrated to form this perfectly functional whole, it is sometimes difficult to remember that all of this results from one initial cell (this sentence is grammatically correct but do not sound English). But nevertheless, after the fusion of sperm and egg, the first cell starts to divide and the resulting daughter cells will follow suit, and so on.
Embryonic cells are undifferentiated cells and they will gradually exit the cell cycle, to specialise and migrate to constitute the various tissues such as the epithelium, muscle, nerve, conjunctive tissue, etc. Every cell reaches its specific location in due course thanks to a vital and highly controlled process: cell migration. If a grain of sand interferes with the process, this can have dramatic consequences on the body's development preventing it from developing or functioning properly. Depending on the severity of the abnormality and the type of cell concerned, various pathologies may appear. For instance some epilepsy, autism and lissencephaly result from impaired neuron migration during embryogenesis.

**Two types of cortical neurons**

Laurent Nguyen (a research associate of the FRS-FNRS and a WELBIO investigator) and his team at the University of Liège's GIGA-Neurosciences unit, are studying the molecular regulation of neurogenesis. One of aspect of their research is to uncover the mechanisms that control the development of the cerebral cortex. The latter is composed of two classes of neurons: projection neurons and GABAergic interneurons. The first ones are excitatory neurons with far-reaching axons that create connexions with motor neurons in the spinal cord, among other things. Interneurons are inhibitors neurons that play a crucial role in controlling the activity of neuronal ensembles. These two types of cortical nerve cells come from different progenitor domains in the telencephalon. To settle to their final location within the developing cerebral cortex, the projection neurons and interneurons use two distinct migration modes.

In 2009, Laurent Nguyen and his colleagues showed the contribution of the elongator complex to the migration of projection neurons in the cerebral cortex (read: La migration des neurones sous l'aile d'Elongator). In a study published in the journal Developmental Cell (1), the researchers from Liège have recently demonstrated the key role of protein p27 in controlling the migration of the cortical interneurons.
p27 (green) interacts with the small GTPase RhoA (red) in actin-enriched (blue) domains in interneurons.
The unexpected localisation of p27 in the cortex

Known for its involvement in the regulation of the cell cycle, p27 is a small protein that allows stem cells to exit the cycle and give birth to differentiated cells, such as neurons. It inhibits enzymes from the family of cycline-dependent kinases (CDKs). It is expressed in different cell types and tissues of the human body. "We decided to study this protein because we were intrigued by its localisation in the developing cortex", explains Laurent Nguyen. "At the beginning, we thought that p27 only played a role in controlling the cell cycle in stem cells and progenitor cells. But analyses of this protein's distribution pattern in the brain showed that p27 was also located in neurons and, therefore, in post-mitotic cells," , continues the scientist. "Among other things, our research revealed that p27 was expressed by migrating neurons in the cortex". In view of these observations, the researchers concluded that aside from cell cycle exit, p27 may play a role in neuronal maturation.
Taking their research one step further, Laurent Nguyen's team was able to confirm this hypothesis. p27 does indeed control the migration of cortical interneurons thanks to novel molecular domains that are not involved in cell cycle regulation.
Objectives: actin contraction and microtubule polymerization

"The protein p27 controls cortical interneuron migration through two different molecular pathways. These pathways target two components of the cell cytoskeleton: actin and microtubules", Laurent Nguyen points out. "Two distinct domains of the protein independently control the microtubules on one hand, and the actin on the other.", continues Juliette Godin, a researcher in Laurent Nguyen's team and the first author of the study. The regulation of actin depends on a domain of p27 that interacts with the protein RhoA known to activate myosin that regulates actin contractions, following a series of intermediate molecular steps. "By interacting
with RhoA, p27 controls the activation of myosin and thus the contractions and movements of the actin in migrating neurons", Juliette Godin explains. In addition, the scientists showed that another domain of p27 plays an important role in the polymerization of microtubules.

"This novel activity of p27 is required for proper extension of neurites - the projections formed by the neurons - during migration", the researcher points out. This study is the first to reveal the role of p27 in controlling the dynamics of microtubules.

**Revisiting the role of p27 in the cell cycle**

Having a better understanding of the development of the cerebral cortex and, in this particular case, the migration of interneurons, will make it easier in the long term to develop novel strategies to treat certain neurological disorders. "This is fundamental research, creating a basis for providing critical information that will serve to develop novel therapeutical strategies in the future", Laurent Nguyen points out.