Neuronal regeneration: CIBIO takes new approach

Researchers aim to counteract motor neuron degeneration by stimulating neuronal growth. The results of an international five-year study have recently appeared in “Molecular Cell”. The research team found out that the growth stimulation factor in mature motor neurons is blocked by another molecule, and when you try to set it free it displays enormous strength and excellent functioning.

Trento, 20 July 2018 – This time researchers did not focus on a specific condition, but on the mechanisms that regulate the neuronal maturation process. In other words, they concentrated on how this process begins and increases, which could be fundamental to address a number of motor neuron diseases, the most widespread and severe of which are amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), which affect the nerves controlling muscles causing progressive paralysis.

The researchers of the Laboratory of Translational Genomics at CIBIO – Centre for Integrative Biology, headed by Alessandro Quattrone, have abandoned the traditional approach and addressed the problem from a different angle. They did not start from the causes of motor neuron degeneration, focusing instead on the factors involved in neuronal maturation. “Our idea is that by stimulating the maturation of already mature neurons we could counteract degeneration, regardless of the conditions that cause it, and trigger the process that neurologists have been searching for years for their patients: neuronal regeneration”, affirmed Quattrone.

The study is the result of an international collaboration and lasted five years, leading to unexpected results. “We focused on a factor named HuD, which is known for its ability to induce nerve growth”, the researchers explained. Analysing all the genes controlled by this factor we have demonstrated that it affects the group of cell growth inducing factors by stimulating the protein synthesis machinery. The most interesting aspect is that this factor operates independently of other processes that are known to cause this fundamental phenomenon. Like a sort of overdrive factor, it boosts the machinery’s performance to a level that is much higher than the basic one. Yet, the big advancement came later, when we observed that the overdrive factor in motor neurons is “blocked”, suppressed by another molecule called Y3. The close association of HuD and Y3 prevents HuD from operating at excellent levels in motor neurons”.

“In other words”, continued Quattrone, “we have found out that a very powerful protein in establishing innervation in the early stages of development is then suppressed in the mature neuron, ‘glued’ to another molecule that inhibits it. When we tried to separate the former from the latter, we were surprised by the strength and
precision of its powerful force. To better understand this point let's go back to the NGF, the famous discovery of Rita Levi Montalcini, the first identified factor that promotes neuronal maturation from the outside. Unfortunately, because of various reasons, almost half a century later we have not been able to develop it into a drug. Now we have found this other protein, within neurons, asleep, and its awakening has an effect that is equivalent to that of the NGF. We must therefore find a way to overcome this inhibition in patients with motor neuron diseases because we expect that this protein stimulates regeneration. The implications of this discovery are not limited to the field of neuro-degenerative diseases, because central nervous system tumours are characterized, in a way, by something that prevents cell maturation”.

The results of the study were published in the US journal “Molecular Cell”. They are the result of the collaborative work of CIBIO with three other laboratories, the Biophysics Institute of CNR in Trento, the Institute for Molecular Medicine of Martin Luther University in Halle, and the Wellcome Centre for Cell Biology and the School for Informatics of the University of Edinburgh. The principal authors of the study, funded through the Grande Progetto AxonomiX of the Autonomous Province of Trento and Fondazione Cassa di Risparmio di Trento e Rovereto, are: Daniele Peroni, Paola Zuccotti, Toma Tebaldi, who were all at CIBIO in the course of the project, and Marcel Kohn.

Tebaldi, who currently holds a research position at the Cancer Center of the Yale School of Medicine, added: «Y3, the molecule that blocks the neuronal maturation factor, belongs to a class of molecules that is very common in the genome, but whose function was unknown and considered useless. Yet these factors are proving fundamental to understand the great complexity of life. It is fascinating to think that Y3 is a paradigmatic example of the potential that is hidden in the dark matter inside cells”.

The team concluded: “The suppressed overdrive factor in motor neurons breaks new ground in the fight against serious diseases for which there is no cure. This discovery, which is the result of basic research, opens the opportunity to find new therapeutic applications, but to get there scientists must find a way to separate the two factors and reveal the potential of the inhibited one. Another challenge for researchers is to understand if the inhibited factor is missing, as we would expect, in organisms like fish and some amphibians, that are able to effectively regenerate their nerves, something that humans are unable to do”.

The article, “HuD Is a Neural Translation Enhancer Acting on mTORC1-Responsive Genes and Counteracted by the Y3 Small Non-coding RNA”, appeared in “Molecular Cell” and is available here: https://www.cell.com/molecular-cell/fulltext/S1097-2765(18)30507-0 with the journal's comment: https://www.cell.com/molecular-cell/fulltext/S1097-2765(18)30554-9