THE FRONT ROW
at Scripps Research

Micro molecules, big impact: New approaches to neurodevelopmental disorders

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ABOUT THE LECTURE

The human brain is a remarkably complex organ, and one class of tiny molecules plays an outsized role in shaping its complexity: microRNAs. In his Front Row lecture, Scripps Research professor Giordano Lippi walked through how microRNAs fine-tune where, when and how much protein is produced as the brain develops. Lippi shared examples from his lab of how to harness microRNA biology to restore protein production in neurodevelopmental disorders where too little protein is made —and how this could eventually lead to new therapies.

TOP TAKEAWAY POINTS

- The sequence of DNA provides the blueprint for all cellular structures. To build those structures, DNA is transcribed into messenger RNA, then translated into protein. But not all genes code for proteins—some produce what are called “non-coding RNAs,” which help regulate how much and how often proteins are produced from messenger RNA.

- For human brains to develop such vast and complex architecture, non-coding RNAs play a substantial role. MicroRNAs in particular contribute to the development of different cell types, each of which performs distinct functions. Lippi described his team’s work showing how a certain type of microRNA, called miR-206, helps sculpt the iconic and highly branched dendrite structure of the brain’s Purkinje cells (which help coordinate movement).

- MicroRNAs also help instruct brain development. Lippi’s lab demonstrated how microRNAs decrease ITGB1 protein levels, allowing for neurons’ axons to grow from one side of the brain and connect with neurons on the other. This connection between the two hemispheres is essential for brain function.

- MicroRNAs regulate many genes linked to neurodevelopmental disorders. In SPTBN1 haploinsufficiency syndrome, a loss of one functional copy of the SPTBN1 gene causes too little production of βII-spectrin protein, which is important for the development of the structural connection between brain hemispheres. This results in developmental delay, intellectual disability and seizures. Lippi described how preventing microRNA binding to the SPTBN1 messenger RNA helps restore βII-spectrin protein to more normal levels, improving the connection between brain hemispheres in a preclinical model.

- Going forward, Lippi’s goal is to use knowledge of these mechanisms to make feasible therapies. He described how his lab is working with collaborators to test out an approach using antisense oligonucleotides (ASOs) in human neurons derived from patients with the disease. These ASOs are tiny molecules that can increase protein production by sitting on the messenger RNA and blocking microRNA binding. Some ASO drugs are already approved for clinical use, paving a much clearer potential path to therapy development.

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