New cytoplasmic role for proteins linked to neurological diseases, cancers

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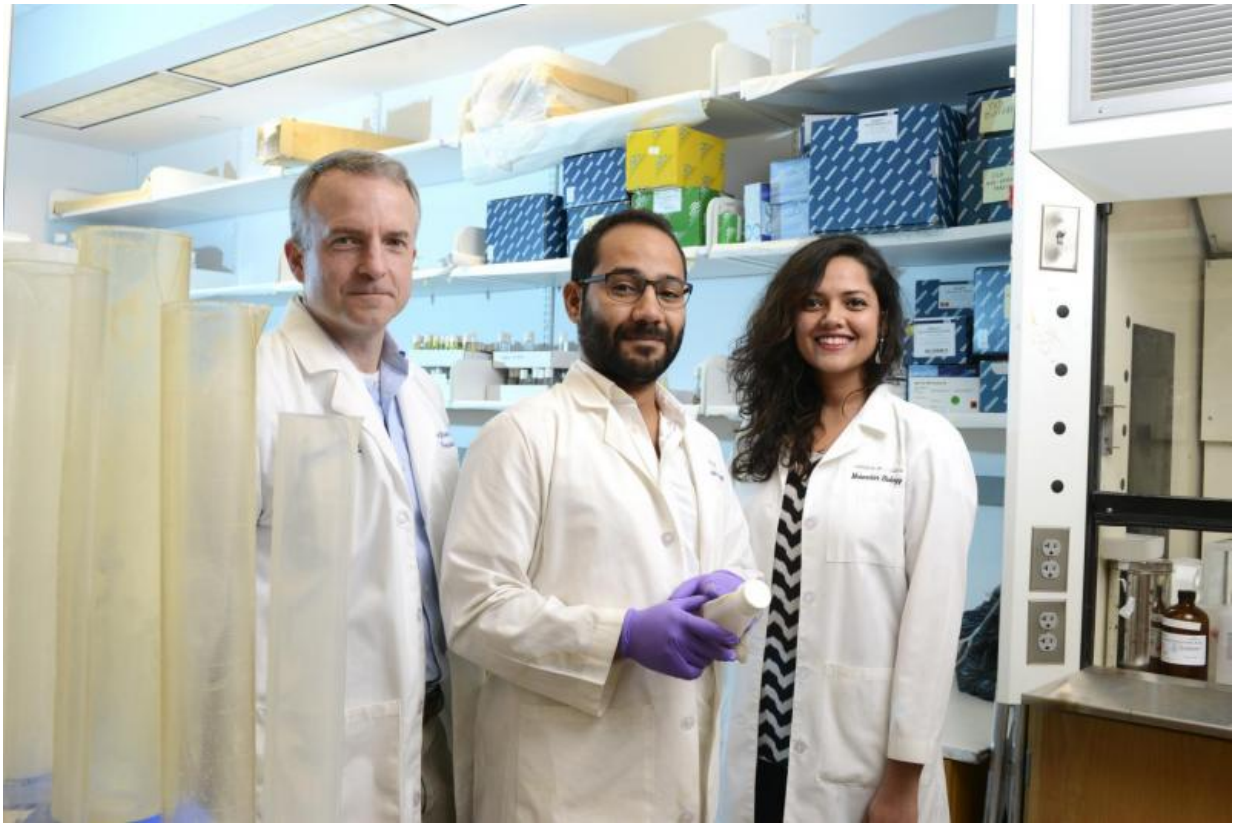

Dr. Michael Buszczak and graduate students Arnaldo Carreira-Rosario and Varsha Bhargava (l-r) contributed to a study that identified a new role for a protein linked to a variety of neurological disorders and cancers. Credit: UT Southwestern Medical Center

Researchers at UT Southwestern Medical Center have identified a

second role for a class of RNA-binding proteins, revealing new insights about neurological diseases and conditions associated with this protein such as autism, epilepsy, and certain types of cancer.

"These data should promote a re-evaluation of those diseases to see if this new function that we've identified contributes to those defects," said senior study author Dr. Michael Buszczak, Associate Professor of Molecular Biology and with the Hamon Center for Regenerative Science and Medicine at UT Southwestern.

The study, published recently in *Developmental Cell*, indicates that RNA-binding fox (Rbfox) proteins oversee translation of messenger RNA, or mRNA, into proteins. Using the fruit fly *Drosophila* as a model, researchers showed that the Rbfox1 protein, in particular, has this regulatory role.

Rbfox1 proteins were known to play a key role in splicing together coding portions of genes called exons to form mRNA, which is subsequently translated to form proteins. Splicing largely takes place within the nucleus of cells, where many Rbfox1 proteins are found. But there are also variants of Rbfox1 proteins found in the cytoplasm - the portion of the cell outside the nucleus - and the function of those cytoplasmic proteins had not been understood.

"We found that cytoplasmic Rbfox1 represses the production of specific proteins," Dr. Buszczak said.

The lead author of the study, UT Southwestern Molecular Biology graduate student Arnaldo Carreira-Rosario, found that Rbfox1 binds to specific elements at the ends of mRNA molecules, preventing these mRNAs from being translated into proteins. If Rbfox1 proteins are lost and mRNA is no longer repressed, that could lead to aberrant growth of cells, or cancers.

The researchers found that cytoplasmic forms of Rbfox1 were required for germ cell development in *Drosophila*. "Without this protein, the germ cells are blocked in a very specific stage of differentiation and just linger there. They can't differentiate into mature eggs," said Dr. Buszczak, an E.E. and Greer Garson Fogelson Scholar in Medical Research.

This block leads to sterility in female *Drosophila* and, in other contexts, can result in an inappropriate proliferation of cells, which underlies cancer.

Work by co-author Dr. Mani Ramaswami of Trinity College Dublin in Ireland points to a link between the newly identified function of Rbfox1 proteins and neuronal development and function, which could have important implications for a number of the neuronal disorders linked to disruption of Rbfox1.

"The idea is that loss of Rbfox1 causes disease by disrupting protein expression, not RNA splicing," Dr. Buszczak said. "If this interpretation is correct, then it has implications for how one would develop therapeutics to treat the disease in question."

Provided by UT Southwestern Medical Center

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