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Press Release:**BRAIN LOGISTICS: Missing link explains mRNA delivery in brain cells**

Teaser: Teams from MPI Institutes in Dresden, Dortmund, Frankfurt am Main and Göttingen have joined forces to gain the first evidence of a protein complex responsible for the transport of messenger RNA in neurons

Brain cells manufacture proteins in every corner, including their long branches. Neurons missing this ability cause severe neurological disorders like disability and epilepsy. The groups of Marino Zerial, Max Planck Institute (MPI) of Molecular Cell Biology and Genetics in Dresden, and Stefan Raunser, MPI of Molecular Physiology in Dortmund, together with colleagues from the MPI for Brain Research in Frankfurt am Main and the MPI for Biophysical Chemistry in Göttingen have discovered a new delivery mechanism that brings messenger RNA (mRNA), the proteins' blueprint, to the point of need in neurons. Using an array of techniques, the researchers have identified a protein complex, named FERRY, which links mRNA to intracellular carriers, and elucidated its role and structure. The discovery may lead to a better understanding of neurological disorders caused by FERRY malfunction and possibly to new medical targets. The results are detailed in two recent works, published back-to-back in the journal *Molecular Cell*.

Faraway, so close!

"These publications provide a major advancement to elucidate the mechanisms underlying mRNA distribution in brain cells," Marino Zerial says. Cells produce vital proteins using mRNA as a blueprint and ribosomes as 3D printers. Yet, brain cells have a logistic challenge to overcome: A tree-like shape with branches that can span centimeters in the brain. "This implies that thousands of mRNAs need to be transported far away from the nucleus, resembling the logistic effort of properly supplying supermarkets in an entire country," Jan Schuhmacher says, first author of the study.

So far, researchers attributed the carrier role to spherical compartments inside the cell, called Late Endosomes. However, MPI scientists argue that a different form of the compartments, called Early Endosomes (EEs), are also suitable as mRNA carriers, due to their ability to travel in both directions along intracellular road networks. In the first publication, led by Marino Zerial from MPI in Dresden, scientists discovered the function of a protein complex that they called FERRY (Five-subunit Endosomal Rab5 and RNA/ribosome intermediarY). In neurons, FERRY is linked to EEs and works similarly to a tie-down strap during transport: It interacts directly with mRNA and holds it onto EEs, which hence become logistic carriers for mRNA transport and distribution in brain cells.

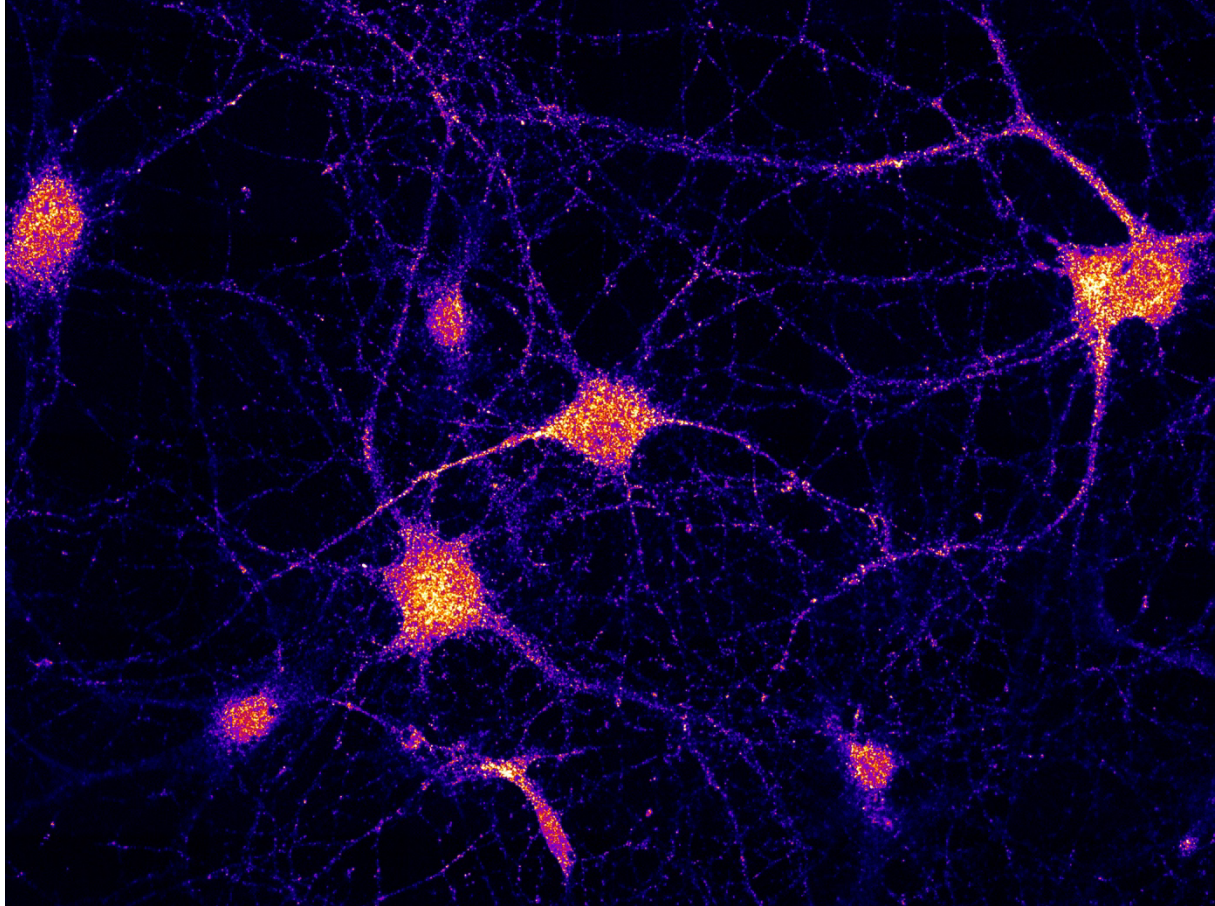
Complex details

But how does FERRY bind to mRNA? That's when Stefan Raunser's group from the MPI Dortmund comes into play. In the second publication, Dennis Quentin et al. used cryo-electron microscopy (cryo-EM) to infer the structure of FERRY and the molecular features that allow the complex to bind to both EEs and mRNAs. The new 3D atomic model of FERRY, with a resolution of 4 Ångstroms, shows a novel mode of binding RNA, which involves coiled-coil domains. Scientists also explained how some genetic mutations affect FERRY's ability to link mRNA thus leading to neurological disorders. "Our research sets the groundwork for a more



comprehensive understanding of neurological disorders caused by a failure of mRNA transport or distribution that might also lead to the identification of therapeutically relevant targets,” Raunser says.

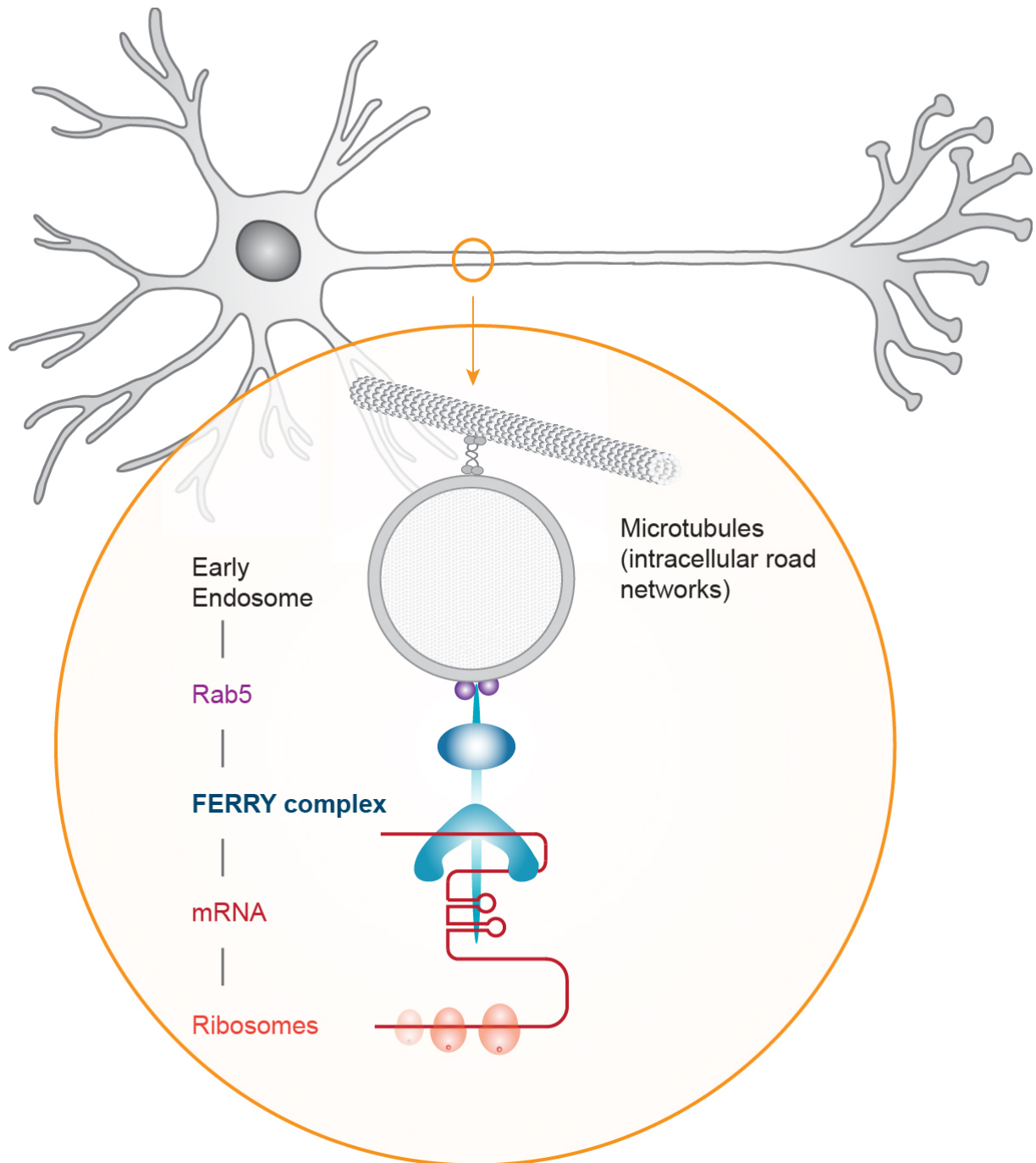
Teaser:



Localization of the FERRY complex in neurons. (Copyright: Schuhmacher et al. (2023) / MPI-CBG)



Image 1 :



Transport of mRNA in neurons along intracellular road networks (Microtubules) by the FERRY complex.
(Copyright: Schuhmacher et al. (2023) / MPI-CBG)



Original Publication:

Quentin D, Schuhmacher S, Klink BU, Lauer J, Shaikh TR, Huis in't Veld PJ, Welp LM, Urlaub H, Zerial M, Raunser S (2023). Structural basis of mRNA binding by the human FERRY Rab5 effector complex. ***Molecular Cell***

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Schuhmacher JS, tom Dieck S, Christoforidis S, Landerer C, Gallesio JD, Hersemann L, Seifert S, Schäfer R, Giner A, Toth-Petroczy A, Kalaidzidis Y, Bohnsack KE, Bohnsack MT, Schumann EM, Zerial M (2023). The Rab5 effector FERRY links early endosomes with mRNA localization. ***Molecular Cell***

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