Blood–brain barrier integrity depends on a protein that is altered in some neurodegenerative diseases, study reveals

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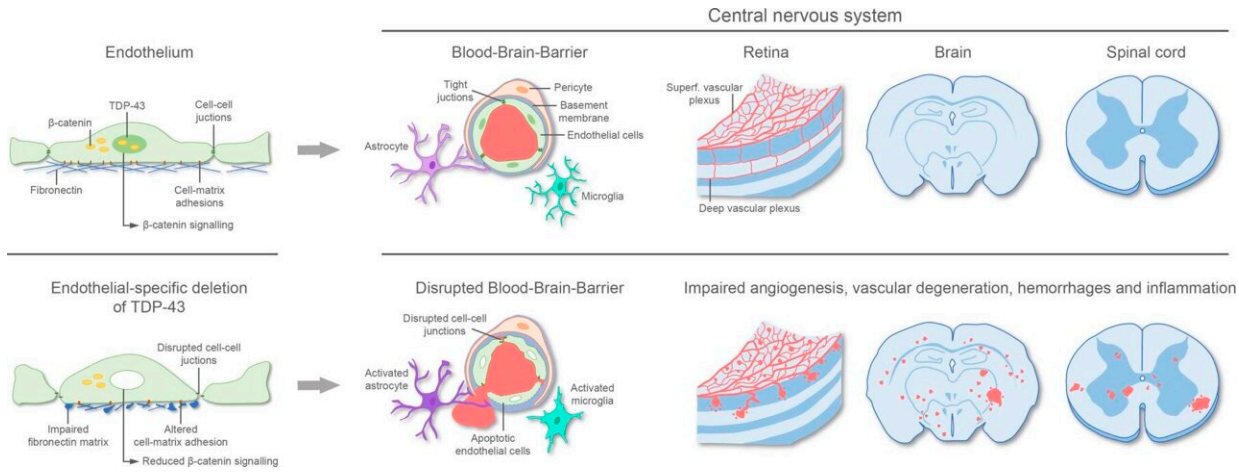


Credit: *JCI Insight* (2024). DOI: 10.1172/jci.insight.177819

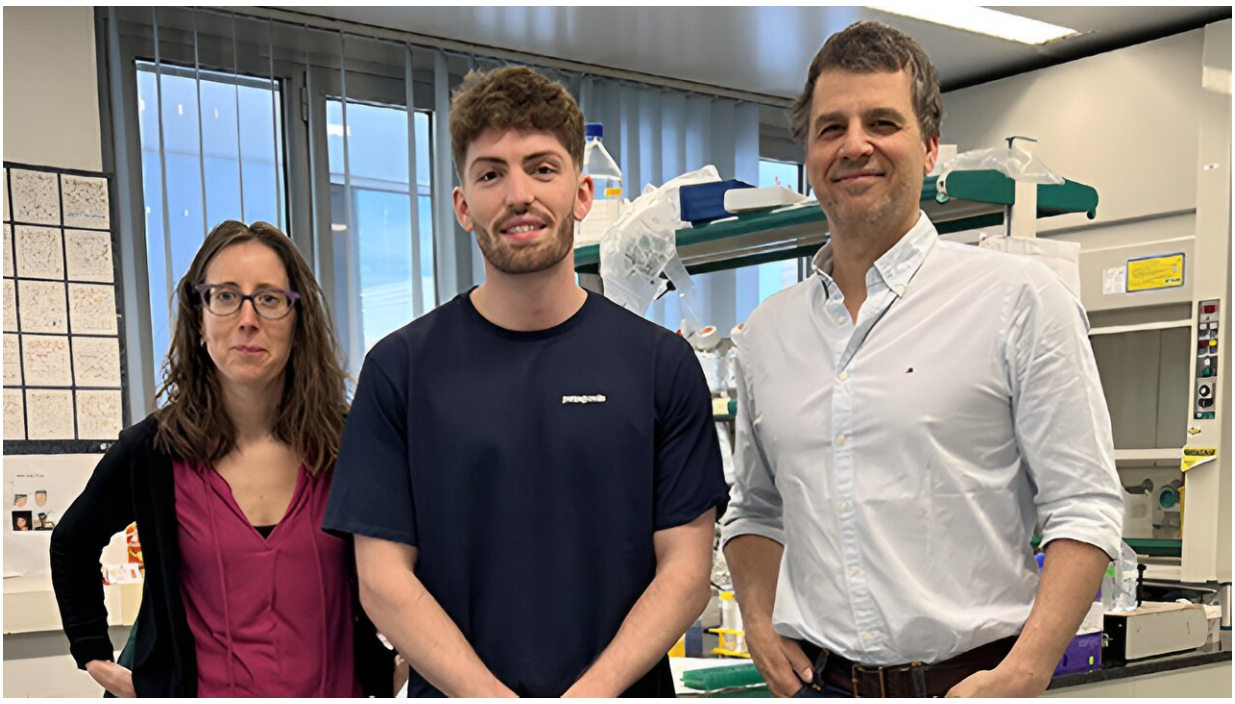
Defects in the blood vessel network of the central nervous system have been linked to early symptoms of neurodegenerative diseases such as Alzheimer's disease and amyotrophic lateral sclerosis (ALS). It is this complex vascular network that provides the necessary nutrients—especially glucose and oxygen—to activate all neuronal functions.

Now, a study led by the University of Barcelona and the Bellvitge Biomedical Research Institute (IBIDELL) reveals that the TDP-43

protein is essential for forming a stable and mature blood vessel network in the central nervous system.

According to the study, featured on the cover of the journal *JCI Insight*, the TDP-43 protein is also critical in maintaining the integrity of the blood–brain barrier, which prevents toxins and pathogens from reaching the central nervous system.

The project was led by Professor Eloi Montañez, from the Faculty of Medicine and Health Sciences of the University of Barcelona and IDIBELL, and involves teams from the Faculty of Biology and the Institute of Biomedicine of the UB (IBUB), the Josep Carreras Leukemia Research Institute, and the National Center for Genomic Analysis (CNAG-CRG).



From left to right, Pilar Villacampa, Víctor Arribas and Eloi Montañez. Credit: University of Barcelona

What is the role of the TDP-43 protein in the vascular system?

The TDP-43 protein is a key factor in nervous system function and neuronal plasticity. It is a DNA- and RNA-binding protein that regulates gene expression, and its dysfunction has been associated with various neurodegenerative disorders.

Although much progress has been made recently in understanding the functions of TDP-43 in neurons, its exact role in the endothelial cells that make up the circulatory system, the formation of new blood vessels (angiogenesis) and vascular function was not yet known.

"The study reveals for the first time that TDP-43 is essential for the formation and stability of blood vessels in the central nervous system, and for the integrity of the blood–brain barrier," says Professor Montañez, from the UB's Department of Physiological Sciences.

The vascularization of the central nervous system and the formation of the blood–brain barrier are regulated by different signaling pathways. For example, the integrin signaling pathway that regulates the interaction of cells with the extracellular matrix and the signaling carried out by the transcription factor β-catenin.

"In the study, we found that TDP-43 deficiency alters the extracellular matrix that surrounds blood vessels and reduces β-catenin signaling in endothelial cells," says the researcher. "Thus, mice without endothelial TDP-43 protein show multiple hemorrhages and vascular degeneration in the brain and spinal cord."

The authors also identify TDP-43 in endothelial cells as a potential contributing factor to the vascular defects that trigger the inflammatory

response observed in patients diagnosed with TDP-43-associated diseases.

Some alterations in the blood vessels of the central nervous system—defects in the integrity of the blood–brain barrier or degeneration of endothelial cells—are associated with inflammatory and immune responses that can cause neuronal loss. This process of neuronal degeneration underlies the origin or progression of various neurological disorders—stroke, diabetic retinopathy—and some neurodegenerative diseases such as Alzheimer's disease, ALS or LATE (Limbic-predominant age-related TDP- 43 encephalopathy).

The study will help to better understand the molecular mechanisms linking vascular defects and neuroinflammation. "Our goal now is to analyze whether defects in TDP-43 protein function in the endothelium of mature vessels could be involved in ALS or other TDP-43-associated pathologies due to increased vascular permeability or inflammatory processes," Montañez concludes.

More information: Víctor Arribas et al, Endothelial TDP-43 controls sprouting angiogenesis and vascular barrier integrity, and its deletion triggers neuroinflammation, *JCI Insight* (2024). DOI: 10.1172/jci.insight.177819

Provided by University of Barcelona

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