Scientists identify first negative regulator of NOX4 translation

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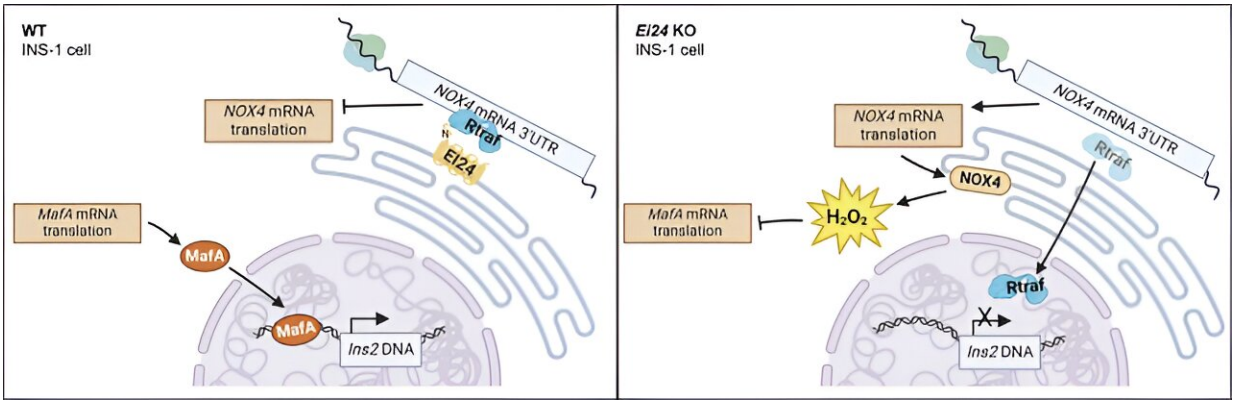

EI24 interacts with the RNA-binding protein RTRAF and Nox4 mRNA 3′-UTR to inhibit the translation of Nox4 in INS-1 cells. Credit: Xu Pingyong's group

Nicotinamide adenine dinucleotide phosphate oxidase 4 (NADPH oxidase 4, NOX4) is an important member of the NADPH oxidase family that is primarily responsible for the production of H_2O_2. The regulation of NOX4 activity is predominantly through protein expression. However, the precise mechanisms by which highly secreting cells maintain NOX4 expression and activity while balancing H_2O_2 levels within the appropriate physiological range remain unclear.

On March 15, a research team led by Prof. Xu Pingyong from the Institute of Biophysics of the Chinese Academy of Sciences published a

study in *Redox Biology*, introducing the first negative regulator of NOX4 translation, the pivotal factor EI24.

They uncovered the molecular mechanism by which EI24 precisely regulates H_2O_2 production by controlling NOX4 translation, and its implications for maintaining the redox equilibrium of pancreatic beta cells and insulin synthesis.

The researchers discovered that the endoplasmic reticulum-resident protein EI24 responds to fluctuations in H_2O_2 levels. Targeted deletion of the Ei24 gene in pancreatic beta cells significantly increased NOX4 protein expression and endoplasmic reticulum H_2O_2 levels.

Using dual fluorescent reporter systems and immunoprecipitation assays, the researchers showed how EI24 binds to the RNA-binding protein RTRAF and anchors it to the 3'-UTR region of the Nox4 mRNA. This interaction inhibits the translation process, effectively controlling the excessive generation of H_2O_2.

Deletion of EI24 caused RTRAF to translocate to the nucleus, releasing the NOX4 translation inhibition and subsequently affecting the translation of the downstream transcription factor MAFA. As a result, Ei24 knockout reduced the binding capacity of MAFA to the Ins2 promoter, which impaired insulin production and perturbed blood glucose levels in mice.

This study reveals a novel co-translational regulatory system and elucidates how endoplasmic reticulum proteins precisely control the co-translation of membrane-located proteins by modulating the localization of RNA-binding proteins. This regulatory process is of remarkable physiological importance and plays a critical role in maintaining the redox balance and vital functions of secretory cells.

More information: Xintong Pei et al, ER-tethered RNA-binding protein controls NADPH oxidase translation for hydrogen peroxide homeostasis, *Redox Biology* (2024). DOI: 10.1016/j.redox.2024.103126

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