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Technology Offer

Tet-inducible “gePSI” protein reversibly regulates eukaryotic ribosomal protein synthesis in a cell-type specific manner allowing to impose and release protein synthesis inhibition in a select subset of cells in mixtures

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Proteins are the main functional units within cells. Their regulated synthesis and degradation are crucial for controlling biological processes. In all cells, protein synthesis is used to respond to extra- and/or intracellular cues to remodel cellular function. Previous studies probing the role of protein synthesis have used chemical inhibitors, often common antibiotics, which are effective but lack functional and cell-type specificity when applied to a mixture of cells.

Technology

Scientists from the Max-Planck Institute for Brain Research in Frankfurt/Main designed two separately expressed polypeptide chains forming together a **g**enetically **e**ncoded **P**rotein **S**ynthesis **I**nhibitor (**gePSI**) (1). gePSI allows for a cell-type selective, tetracycline inducible and hence reversible inhibition of protein synthesis.
The basis for the gePSI system is a class of bacterial and plant toxins from the Shiga and Ricin families that are also known as **ribosome inactivating protein**s (RIPs). These highly potent proteins trigger a complete shutdown of protein synthesis by **depurinating a specific adenine on the ribosomal 28S-rRNA**. The scientists harnessed the toxicity, that might be exhibited by leaky expression already, by splitting the protein in two domains, each domain being inactive in isolation. The gePSI plasmid-based system provides expression of the Tet-dependent transcriptional activator targeting to the gePSI expression cassettes under a cell-type specific promoter allowing for the intended spatial and temporal control of gePSI formation and function.
The system was successfully tested in neurons and was shown to interfere effectively with protein synthesis in a cell-type-specific manner. Neighboring cells in direct physical contact with gePSI-expressing cells showed no change in protein synthesis. The expression of gePSI in such neurons was time-controlled, protein synthesis inhibition was achieved after 2-4 hours and removal of the gePSI-expression-inducing agent (tetracycline) allowed functional recovery of protein synthesis.
In summary, gePSI is a highly effective tool to impact on protein synthesis in a subset of cells in a complex mixture or tissue (e.g. cell cultures, organoids, tissue- or animal models) allowing for disease modelling (e.g.: Parkinson or else) and/or drug screenings that rely on or need interrupted protein synthesis in selected cell-types in a mixture.

Reference

(1) Heumüller M. et al., Nature Methods 2019, doi: 10.1038/s41592-019-0468-x

Patent Information

A PCT application is pending.

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