Novel Discovery Reveals How Brain Protein OTULIN Controls Tau Expression and Could Transform Alzheimer's Treatment

Groundbreaking research identifies unexpected role for deubiquitinase enzyme in regulating toxic tau protein accumulation

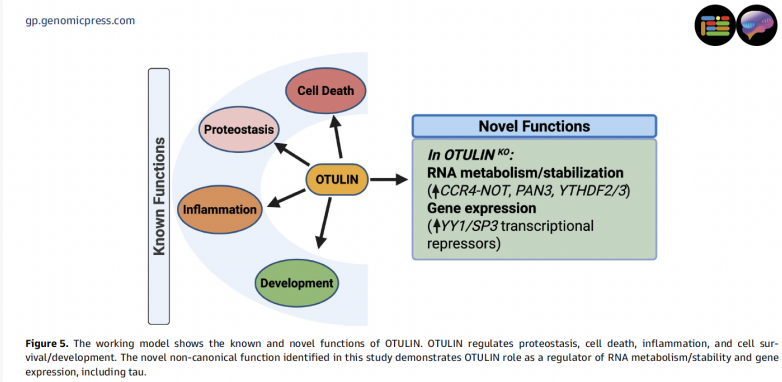

Figure 5. The working model shows the known and novel functions of OTULIN. OTULIN regulates proteostasis, cell death, inflammation, and cell survival/development. The novel non-canonical function identified in this study demonstrates OTULIN role as a regulator of RNA metabolism/stability and gene expression, including tau.

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ALBUQUERQUE, NM, UNITED STATES, November 25, 2025 / EINPresswire.com/ -- Scientists have uncovered a surprising mechanism by which a brain enzyme called OTULIN controls the expression of tau, the protein that forms toxic tangles in Alzheimer's disease. The findings, published today in Genomic Psychiatry, reveal that OTULIN functions not only as expected in protein degradation pathways but also plays a previously unknown role as a master regulator of gene expression and RNA metabolism.

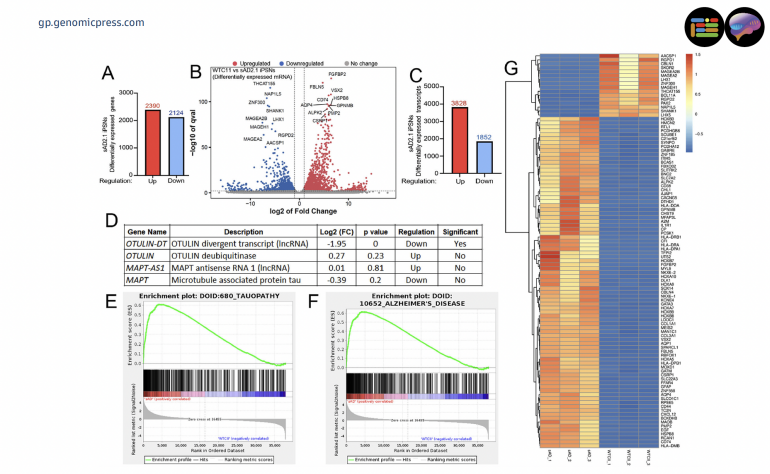
The research team, led by Dr. Kiran Bhaskar at the University of New Mexico Health Sciences Center and Dr. Francesca-Fang Liao at the University of Tennessee Health Science Center, made the discovery while investigating how neurons clear abnormal tau aggregates. Their unexpected findings could open new therapeutic avenues for Alzheimer's disease and related dementias affecting millions worldwide.

"We set out to test whether stabilizing a specific type of ubiquitin chain would help clear toxic tau from neurons," explained Dr. Karthikeyan Tangavelou, the paper's first author. "Instead, we discovered something completely unexpected – that OTULIN acts as a master switch controlling whether tau is even produced in the first place."

The Revolutionary Discovery: The research team initially hypothesized that inhibiting OTULIN's enzyme activity would enhance tau clearance through cellular garbage disposal systems. However, when they completely knocked out the OTULIN gene in neurons, tau disappeared entirely, not because it was being degraded faster, but because it wasn't being made at all.

"This was a paradigm shift in our thinking," said Dr. Liao. "We found that OTULIN deficiency causes tau mRNA to vanish, along with massive changes in how the cell processes RNA and controls gene expression."

The study used neurons derived from a patient with late-onset sporadic Alzheimer's disease, which showed elevated levels of both OTULIN protein and phosphorylated tau compared to healthy control neurons. This correlation suggested OTULIN might be contributing to disease progression.



Gene Name	Description	Log2 (FC)	p value	Regulation	Significant
OTULIN-DT	OTULIN divergent transcript (lncRNA)	-1.95	0	Down	Yes
OTULIN	OTULIN deubiquitinase	0.27	0.23	Up	No
MAPT-AS1	MAPT antisense RNA 1 (lncRNA)	0.01	0.81	Up	No
MAPT	Microtubule associated protein tau	-0.39	0.2	Down	No

The sporadic Alzheimer's disease (sAD2.1) iPSC line-derived neurons (iPSNs) show significantly altered gene expression profile with increased OTULIN long noncoding RNA (OTULIN lncRNA) levels.

Key Findings – The research revealed several crucial insights:

First, when OTULIN was completely removed from neuroblastoma cells, comprehensive RNA sequencing showed dramatic changes in gene expression, 13,341 genes were downregulated and 774 were upregulated, with even more dramatic effects on RNA transcripts (43,003 downregulated, 1,113 upregulated). Comparing Alzheimer's patient neurons to healthy controls revealed over 4,500 genes and 5,600 transcripts were differentially expressed.

> This discovery opens up an entirely new research direction. We need to determine whether targeting OTULIN therapeutically can safely reduce tau accumulation without disrupting key cellular functions."
>
> *Dr. Kiran Bhaskar, University of New Mexico Health Sciences Center*

Second, pharmacological inhibition of OTULIN's enzymatic activity with a novel small molecule inhibitor (UC495) reduced phosphorylated tau levels in Alzheimer's disease neurons, suggesting potential therapeutic benefit without complete gene elimination.

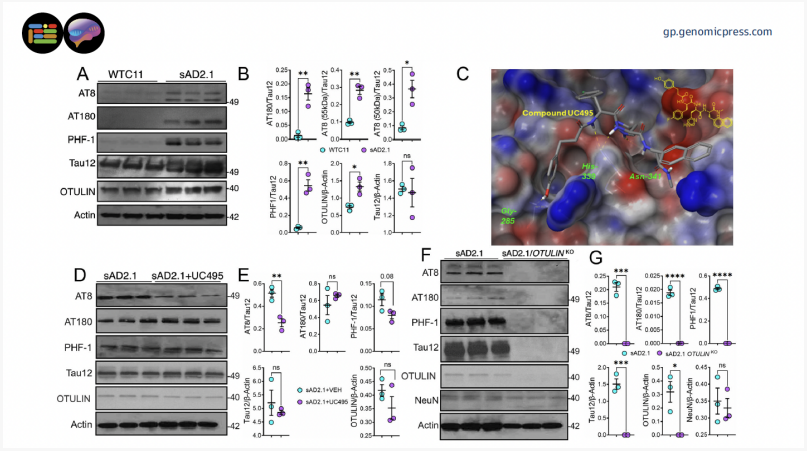
Third, the absence of OTULIN upregulated numerous genes associated with RNA degradation and stability regulation, including components of the CCR4-NOT complex and various RNA-binding proteins implicated in neurodegenerative diseases.

Fourth, bulk RNA sequencing of Alzheimer's neurons revealed significant downregulation of OTULIN long noncoding RNA alongside decreased expression of melanoma antigen gene (MAGE) family members, which activate ubiquitin ligases involved in protein quality control.

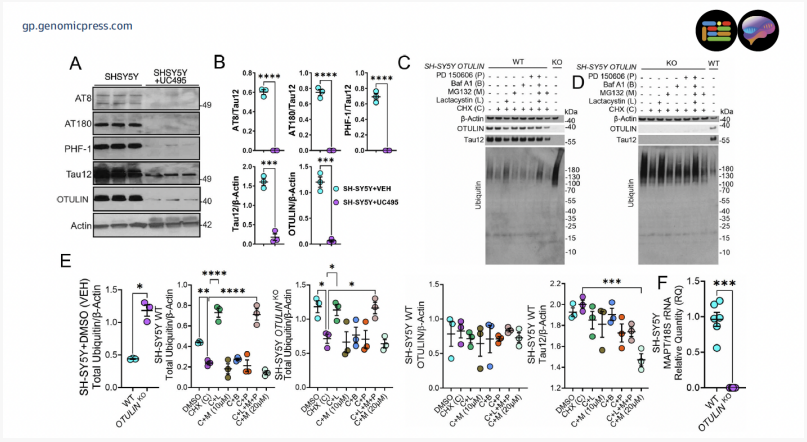
Clinical Implications: These findings have profound implications for treating tauopathies, a group of more than 20 neurodegenerative diseases characterized by toxic tau accumulation.

"OTULIN could serve as a novel drug target, but our findings suggest we need to modulate its activity carefully rather than eliminate it completely," Dr. Bhaskar noted. "Complete loss causes widespread changes in cellular RNA metabolism that could have unintended consequences."

The research demonstrated that partial inhibition with UC495 reduced pathological tau forms without eliminating total tau or causing apparent toxicity to neurons. This suggests a therapeutic window exists where OTULIN activity could be tuned to beneficial levels.



The sporadic sAD2.1 iPSNs increase the levels of OTULIN and phosphorylated tau, whereas inhibition of OTULIN deubiquitinase or deletion of OTULIN gene decreases phosphorylated tau levels.



Pharmacological inhibition of OTULIN deubiquitinase or deletion of OTULIN gene decreases tau levels in human neuroblastoma cell line, SH-SY5Y

The team also discovered that OTULIN deficiency prevents the development of autoinflammation in neurons by downregulating inflammatory pathway components, providing additional insight into how cells balance protein quality control with inflammatory responses.

Broader Impact on RNA Biology: Beyond Alzheimer's disease, the findings illuminate fundamental mechanisms of RNA metabolism regulation in neurons. The researchers identified upregulation of transcriptional repressors like YY1 and SP3 in OTULIN-deficient cells, along with changes in RNA-binding ubiquitin ligases RC3H2 and MEX3C that control mRNA stability.

"We're essentially looking at a previously unknown checkpoint in gene expression," explained Dr. Liao. "OTULIN appears to influence which genes get expressed and how long their RNA messages survive in cells."

The study also revealed connections between OTULIN and multiple neurodegenerative disease-

associated RNA-binding proteins, including TDP-43, FMR1, ATXN2, and MSI1, suggesting broader implications for understanding various brain disorders.

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RESEARCH ARTICLE

The deubiquitinase OTULIN regulates tau expression and RNA metabolism in neurons

Karthikeyan Tangavelou[1], Virginie Bondu[1], Mingqi Li[2], Wei Li[3], Francesca-Fang Liao[2], and Kiran Bhaskar[1,4]

The degradation of aggregation-prone tau is regulated by the ubiquitin-proteasome system and autophagy, which are impaired in Alzheimer's disease (AD) and related dementias (ADRD), causing tau aggregation. Protein ubiquitination, with its linkage specificity determines the fate of proteins, which can be either protein degradative or stabilizing signals. While the linear M1-linked ubiquitination on protein aggregates serves as a signaling hub that recruits various ubiquitin-binding proteins for the coordinated actions of protein aggregate turnover and inflammatory nuclear factor-kappa B (NF-κB) activation, the deubiquitinase OTULIN counteracts the M1-linked ubiquitin signaling. However, the exact role of OTULIN in neurons and tau aggregates clearance in AD are unknown. Based on our quantitative bulk RNA sequencing analysis of human inducible pluripotent stem cell–derived neurons (iPSNs) from an individual with late-onset sporadic AD (sAD2.1), a downregulation of the ubiquitin ligase activating factors (MAGE-A2/A2B/H1) and OTULIN long noncoding RNA (OTULIN lncRNA) was observed compared to healthy control WTC11 iPSNs. The downregulated OTULIN lncRNA is concurrently associated with increased levels of OTULIN protein and phosphorylated tau at p-S202/p-T205 (AT8), p-T231 (AT180), and p-S396/p-S404 (PHF-1) in sAD2.1 iPSNs. Inhibiting the deubiquitinase activity of OTULIN with a small molecule, UC495 reduced the phosphorylated tau in iPSNs and SH-SY5Y cells, whereas the CRISPR-Cas9–mediated *OTULIN* gene knockout (KO) in sAD2.1 iPSNs decreased both the total and phosphorylated tau levels. CRISPR-Cas9–mediated *OTULIN* KO in SH-SY5Y resulted in a complete loss of tau at both mRNA and protein levels, and increased levels of polyubiquitinated proteins, which are being degraded by the proteasome as confirmed with an inhibitor, Lactacystin. In addition, SH-SY5Y *OTULIN* KO cells showed downregulation of various genes associated with inflammation, autophagy, ubiquitin-proteasome system, and the linear ubiquitin assembly complex that consequently may prevent development of an autoinflammation in the absence of *OTULIN* gene in neurons. Together, our results suggest, for the first time, a noncanonical role for OTULIN in regulating the gene expression and RNA metabolism, which may have a significant pathogenic role in exacerbating tau aggregation in neurons. Thus, OTULIN could be a novel potential therapeutic target for AD and ADRD.

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Keywords: Alzheimer's disease, tau, neurofibrillary tangles, LUBAC, OTULIN, M1-linked ubiquitin, autophagy, ubiquitin, proteasome, autoinflammation, RNA metabolism, RNA-binding proteins, RNA degradation

The deubiquitinase OTULIN regulates tau expression and RNA metabolism in neurons.

Research Methodology: The team used cutting-edge techniques including CRISPR-Cas9 gene editing, induced pluripotent stem cell-derived neurons from Alzheimer's patients and healthy controls, comprehensive bulk RNA sequencing, and computational drug design to identify the OTULIN inhibitor UC495. They validated their findings across multiple cell types, including patient-derived neurons and human neuroblastoma cells, ensuring reproducibility and relevance to human disease.

Next Steps: The researchers are now working to understand precisely how OTULIN influences gene expression and RNA metabolism at the molecular level. They're also testing whether carefully calibrated OTULIN inhibition can reduce tau pathology in animal models of Alzheimer's disease.

"This discovery opens up an entirely new research direction," said Dr. Bhaskar. "We need to determine whether targeting OTULIN therapeutically can safely reduce tau accumulation without disrupting essential cellular functions."

The team is also investigating why OTULIN long noncoding RNA is reduced in Alzheimer's neurons and whether restoring its levels could normalize OTULIN protein expression and tau pathology.

About the Research: This study was funded by the National Institutes of Health and involved collaboration between the University of New Mexico Health Sciences Center, the University of Tennessee Health Science Center, and other institutions. The comprehensive RNA sequencing data have been deposited in publicly accessible databases to enable further research by scientists worldwide.

The findings represent years of meticulous work combining molecular biology, cell biology, genomics, and computational approaches to unravel the complex relationship between protein quality control systems and neurodegenerative disease.

About Alzheimer's Disease and Tauopathies: Alzheimer's disease affects more than 6 million

Americans and is characterized by two pathological hallmarks: amyloid plaques and tau tangles. Tau pathology correlates more closely with cognitive decline than amyloid accumulation, making it a critical therapeutic target.

Tauopathies encompass more than 20 brain diseases where tau forms toxic aggregates, including frontotemporal dementia, progressive supranuclear palsy, and chronic traumatic encephalopathy. Current treatments provide only modest symptomatic relief without addressing underlying disease mechanisms.

The discovery that OTULIN regulates tau at the gene expression level, rather than simply controlling its degradation, represents a fundamental advance in understanding how tau pathology develops and suggests novel intervention strategies.

Article citation: The peer-reviewed Research Article titled “The deubiquitinase OTULIN regulates tau expression and RNA metabolism in neurons,” by Tangavelou K, Bondu V, Li M, Li W, Liao FF, Bhaskar K. The is freely available via Open Access starting on 25 November 2025 in Genomic Psychiatry at the following hyperlink: https://doi.org/10.61373/gp025a.0116

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