

EXACERBATED RIBOSOMAL METABOLISM PATHWAYS IN THE 3XTG-AD MOUSE MODEL OF ALZHEIMER'S DISEASE

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INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
The 3xTg-AD Murine Model: A triple-transgenic model incorporating human mutations in APP, Psen1, and Tau genes to reproduce AD neuropathology integrally. Early Pathogenic Markers: This model exhibits synaptic dysfunction, early cognitive deficits, and cerebral hypometabolism before the full appearance of neurofibrillary tangles. The RQC System (Ribosome-associated Quality Control): A mechanism that acts as a "proteostasis crossroads," degrading aberrant proteins during translation to maintain a healthy nervous system.	The objective of this work is to compare a 3xTg-AD model with a control model to describe the main alterations present that can serve as guidance for a better understanding of the disease. Animals comparison was performed using hippocampal tissue, with all the present pathophysiological alterations. The animal development period is 8 months, a critical period to capture disturbances before neurofibrillary tangles. 1. ANIMAL MODEL 3xTg-AD mice (Jackson Laboratory) vs. Wild Type (WT) 3xTg-AD vs. Wild Type (WT) Age: 8 months Sex: Both Background: B6;129 3xTg-AD model expresses human mutations associated with Alzheimer's disease: - APP^{SwE} - PS1^{M146V} - Tau^{P301L} 3xTg-AD Model: A Timeline of Pathogenic Progression and the Critical Window 1 Month: No synaptic changes 4 Months: Cognitive impairment and intraneuronal Aβ accumulation 6 Months: Extracellular Aβ deposition and decreased Long-Term Potentiation (LTP) 7 Months: Increased gliosis (astrocyte and microglia density) 8 Months (The Critical Window): Captures translational disturbances before extensive neurofibrillary tangle formation 12 Months: Onset of neurofibrillary tangles and severe tau pathology 18+ Months: Advanced progression of pathology Insight: Intervening at 8 months allows observation of the cellular machinery failing before the resulting debris (plaques/tangles) obscures the root cause. 2. TISSUE COLLECTION Mice were euthanized at 8 months of age. Hippocampi were rapidly dissected on ice, flash-frozen in liquid nitrogen and stored at -80°C. Hippocampus - All subregions - Preserving all present pathophysiological Total RNA extraction Transcriptome profiling (RNA-seq) Quality control - Quantity (NanoDrop/Qubit) - Integrity (Bioanalyzer) Paired-end sequencing High depth Illumina platform 4. DATA PROCESSING & NOMENCLATURE CONVERSION Raw data quality control (FastQC) Read trimming & filtering (Trimmomatic) Alignment to reference genome (STAR/Hisat2) Gene-level quantification (featureCounts) Nomenclature conversion (mouse gene IDs → human orthologs) (biomaRt / Ensembl) Output: Gene expression matrix (human nomenclature) for downstream analyses	In particular, dysregulation of the E3 ubiquitin ligase Listerine, a central component of the Ribosome-associated Quality Control (RQC) mechanism, was verified. These alterations were associated with cellular processes previously implicated in the pathophysiology of neurodegenerative diseases. Differential expression analysis (3xTg-AD vs. WT) (DESeq2) Upregulated in 3xTg-AD: 226 Shared altered genes: 2455 Downregulated in 3xTg-AD: 1348 Venn diagram of differentially expressed genes (Adjusted p < 0.05 log2FC ≥ 0.5) Functional & pathway enrichment - Gene Ontology (GO) - KEGG / Reactome Top enriched pathways (KEGG) Synaptic function Neuroinflammation Axon guidance Mitochondrial dysfunction Amyloid processing Cell-type / cellular deconvolution - CIBERSORTx / xCell - Estimation of cell population changes in hippocampus Protein-protein interaction network (STRING) LTN1: The Central Executor Failure Significant dysregulation was found in Listerin (LP11), the E3 ubiquitin ligase that bridges the stalled ribosome to the Ubiquitin-Proteasome System (UP3).	Consistent alterations in 3xTg-AD cellular metabolism have been better elucidated and are present particularly in critical steps of ribosomal biogenesis. With this information, the possibilities for treatment and etiopathogenesis of Alzheimer's disease expand and can be highlighted in future studies.	Chu J, et al Natl Acad Sci U S A. 2009 Feb 17;106(7):2097-103. doi: 10.1073/pnas.0812819106. Epub 2009 Feb 5. PMID: 19196968; PMCID: PMC2650114. Leijie Chen, et al. Current Medicinal Chemistry; Volume 32, Issue 32, Year 2025, e09298673317789. doi: 10.2174/0109298673317789240807055740. Wang J, et al. J Gerontol A Biol Sci Med Sci. 2025 Mar 7;80(4):glae304. doi: 10.1093/gerona/glae304. PMID: 39719885.
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