How are researchers investigating the nucleus–mitochondria communication axis as potential therapeutic target by manipulating nuclear regulation of mitochondrial gene expression in Neurodevelopmental and Psychiatric Disorders?

Researchers Target **Nucleus–Mitochondria Crosstalk** in Neurodevelopmental and Psychiatric Disorders

The mitochondria and nucleus communicate bidirectionally to coordinate energy production and utilization, providing potential for therapeutics by manipulating nuclear regulation of mitochondrial gene expression (Pei & Wallace, 2017; Darfarin & Pluth, 2025; Eisenberg-Bord & Schuldiner, 2017). Since the vast majority of mitochondrial proteins are nuclear-encoded, this inter-genomic relationship is vital for neuronal function and is increasingly implicated across neurodevelopmental and psychiatric disease spectra (Fairbrother-Browne et al., 2021; Pei & Wallace, 2017; Walker & Moraes, 2022).

Transcriptional and Epigenetic Mechanisms

Nuclear transcription factors NRF-1 and NRF-2 regulate both nuclear- and mitochondrial-encoded cytochrome c oxidase subunits, coupling mitochondrial bioenergetics to neural activity via concomitant regulation of NMDA receptor subunits (Uittenbogaard & Chiaramello, 2014). The psychiatric risk gene BRD1 encodes an epigenetic regulator that targets nuclear genes encoding mitochondrial proteins; its modulation alters mitochondrial physiology, metabolism, and bioenergetics in an isoform-dependent manner, linking genetic variation to psychopathology through mitochondrial dysfunction (Paternoster et al., 2022). Nuclear-encoded epigenetic factors including DNA and histone modifiers also localize to mitochondria, where they modulate mtDNA stability, gene expression, and metabolic flux, establishing a bidirectional regulatory axis (Xu et al., 2026).

Therapeutic Target	Mechanism	Disease Context	Evidence Stage
AMPK-SIRT1-PGC-1α axis	Small molecules enhance mitochondrial biogenic response	Neurodevelopmental & neurodegenerative disorders	Preclinical (mouse models) (Uittenbogaard & Chiaramello, 2014)
ERRγ / PGC1α activation	Up-regulate mitochondrial biogenesis and bioenergetics	Broad neuropsychiatric disorders	Proposed strategy (Pei & Wallace, 2017)
BRD1 modulation	Co-repression of PPAR-mediated transcription of mitochondrial genes	Schizophrenia, bipolar disorder	Cell-line & developmental data (Paternoster et al., 2022)
MFN2 overexpression	Restores mitochondrial dynamics in nucleus accumbens	Anxiety, depression	Preclinical (AAV in rats) (Gebara et al., 2020)
MOTS-c peptide	Mitochondrial-encoded peptide translocates to	Metabolic stress response	Cell-based (Kim et al., 2018)

Therapeutic Target	Mechanism	Disease Context	Evidence Stage
	nucleus, regulates gene expression via NRF2		

FIGURE 1 Therapeutic targets along the nucleus–mitochondria communication axis under investigation for neurodevelopmental and psychiatric disorders.

Pharmacological and Gene-Therapy Strategies

Pharmacological tools acting as effectors of the AMPK-SIRT1-PGC-1α axis have shown promising but mixed results in mouse models, with variability attributable to nuclear background as a key modulator of mitochondrial biogenesis (Uittenbogaard & Chiaramello, 2014). Activation of ERRγ or PGC1α to up-regulate mitochondrial biogenesis may hold promise for treating neuropsychiatric disorders, achievable through exogenous ligands, AMPK-mediated post-translational modifications, or viral-mediated transduction (Pei & Wallace, 2017). A recent study using iPSC-derived neurons from schizophrenia patients suggested enhancement of mitochondrial biogenesis as a treatment strategy (Paternoster et al., 2022).

Epigenetic modifications of mtDNA are reversible, enabling therapeutic interventions that change target modifications to repair or prevent mitochondrial insufficiency by reversing altered gene expression (Kumar et al., 2024). Allotopic gene expression—expressing mitochondrially encoded genes from nuclear transfected constructs—and mtDNA editing enzymes represent additional strategies for correcting mtDNA mutations (Walker & Moraes, 2022).

Emerging Tools and Disease Models

- **Mitochondria-targeted AID degron** systems enable acute, selective depletion of mitochondrial proteins, overcoming conventional knockout limitations to establish causal links between mitochondrial perturbations and nuclear epigenetic remodeling (Xu et al., 2026).
- **Multi-omics integration** (transcriptomics, proteomics, metabolomics, epigenomics) is being applied to reveal how mitochondrial perturbations reshape nuclear gene expression and chromatin states in real time (Xu et al., 2026; Calame & Emrick, 2024).
- **iPSC and organoid technologies** are being expanded to model specific mutations associated with mitochondrial genetic disorders, facilitating study of disease phenotypes and post-treatment changes (Wen et al., 2025; Calame & Emrick, 2024).
- **MitoNuclearCOEXPlorer** is a publicly available tool to interrogate key mitochondria–nuclear relationships in multidimensional brain data, enabling analysis of co-expression profiles across CNS regions (Fairbrother-Browne et al., 2021).

Patients with major depressive disorders show **altered expression of nuclear-encoded mitochondrial genes**, directly linking bioenergetics to psychiatric risk (Verbal et al., 2026). Mitochondrial-nuclear relationships are highly perturbed in Alzheimer's disease, particularly through synaptic and lysosomal pathways, implicating energy balance regulation and removal of dysfunctional mitochondria in disease etiology (Fairbrother-Browne et al., 2021). No existing small-molecule drugs targeting this axis have been tested in patients with mitochondrial respiratory diseases, and the field of mitochondrial pharmacology remains nascent (Uittenbogaard & Chiaramello, 2014).

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