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COMMENTARY

Silencing excessive stress response of neurons — a new approach to treat neurodegeneration diseases

KEY WORDS

Neurodegenerative diseases;
Mitochondrial protein import;
Stress response;
SIFI;
UBR4

Mitochondria contain over 1000 types of proteins, most of which are imported from the cytosol[1]. This import process is intricate and energy-dependent, in which mitochondrial energy deficits and oxidative stress pose significant threats to the import efficiency. When the import is compromised, it can initiate mitochondrial import stress, potentially triggering the integrated stress response (ISR). Persistent ISR may escalate into broader cellular stress[2,3]. Under normal conditions, the body maintains mitochondrial and cellular equilibrium through intricate stress response pathways. However, during aging or in pathological conditions like neurodegeneration, impaired mitochondrial function and stress signal transduction can disrupt protein homeostasis, leading to uncontrolled stress responses. The precise mechanisms of stress response regulation and their role in neurodegenerative disease pathogenesis are not well understood[2-7]. A recent study published in *Nature* has uncovered a potential mechanism where a stress response silencing system modulates the stress arising from the mitochondrial protein import disorders. This study revealed that defects in this system can lead to neuronal death due to excessive stress responses[8], offering new insights into neurodegenerative disease mechanisms.

Stress responses, such as those induced by disruptions in mitochondrial protein import, serve a dual purpose. They are crucial for maintaining homeostasis but can also become detrimental if overly activated. In mammals, cells continually face a variety of environmental stressors, triggering responses like heat shock proteins, DNA repair, apoptosis, secretion of cytokines and chemokines, etc. These temporary responses are cells' short-term strategies for environmental adaptation and homeostasis maintenance. However, chronic activation of stress pathways can lead to prolonged cellular stress, potentially prompting the body to initiate cell death programs to remove damaged or tumorigenic cells[8,9]. In neurodegenerative diseases, neurons endure ongoing stress due to aging or pathological changes, necessitating precise control of stress responses for cellular protection. The mechanisms behind this control, however, remain elusive. In 2017, Rapé's team identified UBR4 (ubiquitin protein ligase E3 component *n*-recognin 4), an E3 ubiquitin ligase, as vital for degrading aggregation-prone proteins within cells[10]. Subsequent findings linked its mutations to neurodegenerative diseases like ataxia and early-onset dementia[11,12]. In the new study, It was found to be part of a larger E3 ligase complex, termed "SIFI" (silencing factor of the integrated stress response) which mainly contains UBR4, potassium channel modulatory factor 1 (KCMF1) and calmodulin and regulates neuronal stress under mitochondrial import disruptions, introducing a novel concept in stress response regulation[8].

In the study, researchers established a UBR4-mutated (ΔUBR4) cell line to investigate the loss-of-function effects. Through whole-genome screening and genetic interaction analysis, they identified a novel, larger E3 ligase complex, named SIFI. Absence of SIFI activity led to impaired protein import into mitochondria and subsequent cell death. Next, they found two core substrates of SIFI—DELE1 (DAP3 binding cell death enhancer 1) and HRI (the heme-regulated inhibitor), DELE1 acts as a sensor for mitochondrial protein import stress, while HRI is a kinase integral to ISR. When cells undergo mitochondrial import stress, DELE1 detects abnormal proteins, activating HRI, which then phosphorylates eukaryotic initiation factor-2α (eIF2α), thereby inhibiting the translation initiation factor eIF2. This inhibition halts new protein synthesis, allowing cells to address the stress. Under normal conditions, SIFI facilitates the degradation of these substrates through ubiquitination, thereby terminating the

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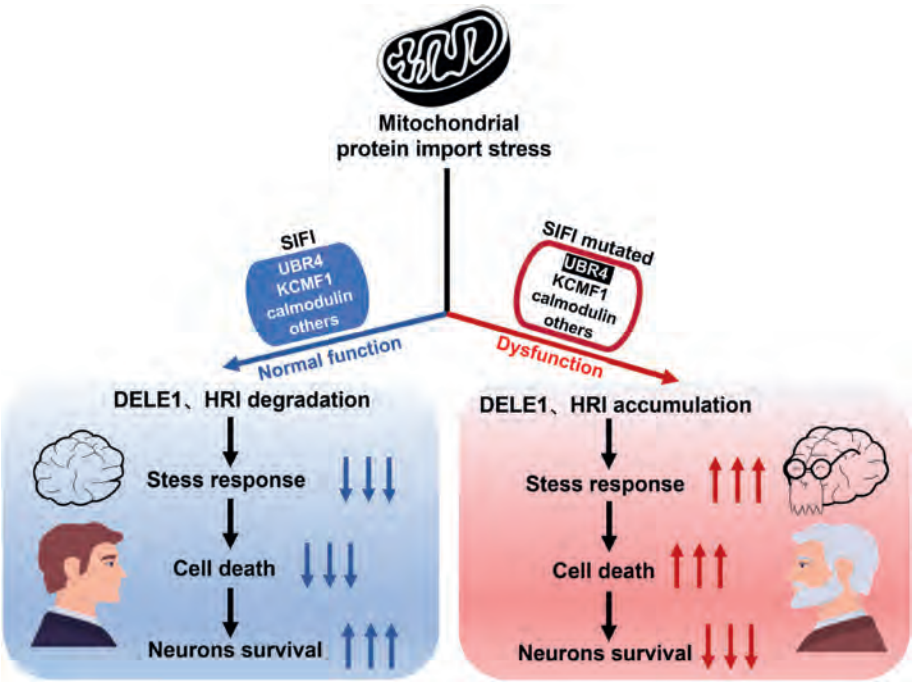

Figure 1 SIFI activity in the control of neuron stress response in the normal and abnormal conditions.

stress response. However, when mitochondrial protein import is disrupted, the unimported mitochondrial precursor proteins disassociate the SIFI complex from its substrates, enhancing the stress response. The findings suggest that mitochondrial precursor proteins compete with DELE1 and HRI to suppress SIFI activity, prolonging the stress response until mitochondrial protein import stress is resolved.

Moreover, the author explored the molecular mechanism of SIFI activity in the pathogenesis of neurodegenerative diseases, such as ataxia and early-onset dementia[8]. Using UBR4 mutant cell lines, they found that SIFI inactivation led to the aggregation of mitochondrial precursor proteins and sustained activation of the stress response. Inhibition its substrates alleviated the stress response in UBR4-deficient cells and restored cell proliferation without affecting mitochondrial import. These results suggest that the sustained stress response activation, rather than the aggregation of mitochondrial precursor proteins, is the primary cause of cell death in cells with SIFI inactivation. To verify this, they employed the small molecule compound ISRIB, which inactivates HRI to stop the stress response. They found that the compound effectively controlled the stress response in ΔUBR4 cells by inhibiting HRI and its downstream effects, akin to inducing SIFI activity, thereby enhancing the survival of mutant cells without correcting mitochondrial import defects. These findings suggest that pharmacologically blocking the stress response may restore cell survival even in the presence of aggregated proteins, potentially offering therapeutic benefits for neurodegenerative diseases.

In summary, the research discovered a new E3 ligase complex named SIFI that regulates mitochondrial protein import stress. SIFI degrades mitochondrial precursor proteins and silences the integrated stress response by recognizing and degrading its substrates (DELE1 and HRI) until the import problem is resolved. In neurodegenerative diseases, such as ataxia and early-onset dementia, mutations in UBR4 disrupt SIFI's function, leading to sustained stress response in neurons due to the impaired clearance of its substrates. However, directly silencing the stress response with drugs may rescue neurons from stress-induced cell death even in the presence of sustained protein aggregation. The major findings are outlined in the figure below (see Fig. 1).

The study provides an innovative mechanism for controlling mitochondrial stress response in the context of neuronal death related to the neurodegenerative diseases, and presenting possible new breakthrough ideas for the prevention and treatment of neurodegenerative diseases. However, the findings are currently confined to cellular models, and the absence of animal model data somewhat limits the conclusions. Future research may consider extending these findings to animal models of neurodegeneration, such as Alzheimer's and Parkinson's disease mouse models, to bolster the evidence. Moreover, the effectiveness of current pharmaceutical interventions for neurodegenerative diseases such as Alzheimer's, has been somewhat constrained. While clinical trials for ISRIB-derived compounds are underway, effective and safe clinical trial outcomes in neurodegenerative diseases treatment are warranted. Pursuing of such research may potentially lead to transformative treatments that significantly improve patient outcomes.

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Author contributions

Chunyang Li made the draft and edited the manuscript. Hongkai Lian, Xiwen Ma, and Jianping Ye provided the concept, ideas and edits to the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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