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Targeting MCL1 to induce mitophagy is a potential therapeutic strategy for Alzheimer disease

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ABSTRACT

Mitochondrial dysfunction is associated with the occurrence of a variety of neurodegenerative diseases, especially Alzheimer disease (AD). As a mitochondrial quality control process, mitophagy is greatly inhibited in AD; increasing evidence shows that the induction of mitophagy is an effective therapeutic intervention strategy. However, the lack of more safe, effective, and clear mechanisms for mitophagy inducers has limited the clinical application. In recent studies, we have identified a small molecule compound, UMI-77, that can safely and effectively induce mitophagy. UMI-77 is an established BH3-mimetic for MCL1 and was developed to induce apoptosis in cancer cells. We found that UMI-77 can bind MCL1 and enhance its function as a mitophagy receptor protein, thus enhancing its interaction with LC3A to induce mitophagy. UMI-77 effectively improves the cognitive decline seen in an AD mouse model. Our findings shed light on the novel mechanisms of mitophagy, reveal that MCL1 is a mitophagy receptor that can be targeted to induce mitophagy, and identify MCL1 as a drug target for therapeutic intervention in AD.

Alzheimer disease (AD) is a serious neurodegenerative disease with the progressive degeneration of cognitive function as its main symptom. A large number of damaged mitochondria, MAPT/Tau tangles, and extracellular Aβ plaques are accumulated in the neurons of AD patients. Current studies suggest that the accumulation of damaged mitochondria occurs prior to the accumulation of Aβ plaques, and accelerates the deposition of Aβ, suggesting that mitochondrial dysfunction may be the main pathogenic factor of AD. Promoting mitochondrial function recovery may be a promising strategy for the treatment of AD. Mitochondria homeostasis is strictly controlled and composed of two parts: mitochondrial biogenesis and mitophagy, which are both inhibited in AD patients. Because the homeostasis of mitochondria is a cycle-controlled process, increasing mitophagy can promote the biogenesis of mitochondria.

In recent studies, we developed a high-throughput method for screening mitophagy inducers [1]. We used mt-Keima protein, which was previously established as a robust sensor of mitophagy, to construct a stable expression cell line. High-throughput imaging was used to detect the proportion of mitochondria entering lysosomes to define the occurrence of mitophagy. We screened FDA-approved drugs or drug candidates and found several apoptosis inducers that can effectively induce mitophagy, including BH3 mimics. Most of these drugs inhibit BCL2-family proteins, thereby allowing apoptosis to occur. Interestingly, a specific inhibitor of MCL1, UMI-

77, shows the potential to induce mitophagy, suggesting that MCL1 may mediate mitophagy activation. Most of the known mitophagy inducers, such as CCCP, that have been used in previous studies mainly act by damaging mitochondria, thus forcing cells to undergo mitophagy; thus, the safety of these compounds is the main consideration. In our study, we did not find that UMI-77 damages mitochondria. Conversely, UMI-77 can cause selective degradation of damaged mitochondria, which shows the possibility of clinical application.

As an anti-apoptotic protein, MCL1 participates in many biological processes. Previous studies suggest that loss of MCL1 in adult myocytes results in mitochondrial dysfunction, defective PINK1-PRKN/PARK2 signaling, and impaired initiation of autophagy. MCL1 is also suggested to function in embryonic development and synapse formation, lifespan regulation, and diverse cellular processes (including mitochondrial dynamics), suggesting its important physiological function. Many studies have found that MCL1 is abnormally expressed in many tumors and has been used as a target for the development of anti-cancer drugs. UMI-77 is an MCL1-specific compound that blocks the interaction between MCL1 and BAX-BAK1, thereby allowing BAX-BAK1 to induce apoptosis. Moreover, UMI-77 is a drug candidate for the treatment of pancreatic cancer. However, we did not find that UMI-77 can induce apoptosis at the sublethal 5 μM dose that we used, which implies that MCL1 has a novel and undiscovered function.

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MCL1 is mainly located in mitochondria, and has three BH domains, BH1 to BH3, which mediate the interaction between MCL1 and other pro-apoptotic proteins containing a BH domain, and this protein plays an anti-apoptotic role. Interestingly, MCL1 has a functional LC3-interacting region (LIR) motif located in the BH1 domain, which mediates the interaction between MCL1 and LC3A, resulting in mitophagy. Moreover, MCL1 can interact with other Atg8-family proteins, such as the GABARAP-family proteins. The LIR motif ([W/Y/F]XX[I/L/V]) exists in autophagy-related receptor proteins, and our study revealed that MCL1 is a novel mitophagy receptor. We postulate that MCL1 recruits LC3A via its LIR motif to the surface of mitochondria, leading to the expansion of the phagophore membrane around the mitochondria and the formation of nascent mitophagosomes. The interaction between MCL1 and GABARAP proteins subsequently mediates the closure of the phagophore membrane, thereby engulfing the mitochondria. LIR motif mutants prevent UMI-77-mediated mitophagy, indicating that the LIR motif is necessary, which suggests that there is a relationship between MCL1 mitophagy receptor function and anti-apoptotic function. Because the LIR is located in the BH1 domain, UMI-77 blocks the interaction between MCL1 and BAX-BAK1, thereby exposing the LIR motif to enhance the interaction between MCL1 and LC3A, which causes MCL1 to play the role of a mitophagy receptor. We speculate that, in the physiological process, MCL1 is in the regulatory center of apoptosis and mitophagy; MCL1 inhibits apoptosis through its function as a mitophagy receptor, thus achieving a balance between apoptosis and autophagy.

UMI-77 can induce mitophagy *in vivo* and significantly improve the cognitive impairment of APP-PSEN1/PS1 mice. This is not only reflected in the positive evaluation of APP-PSEN1 mice in the water maze test but also the inhibition of extracellular Aβ plaque deposition and Inflammatory cytokine levels in the brain. In addition, the morphology of mitochondria of neurons in the brain is restored. Risk factors in AD patients, such as genetic mutation, aging, and environmental factors, promote the production of reactive oxygen species (ROS) and lead to mitochondrial dysfunction, as well as the production of Aβ plaques and inflammatory cytokines. Conversely, Aβ can be transported into cells and accumulate in mitochondria, and this interaction inhibits mitochondrial function, elevates ROS levels, and alters mitochondrial dynamics. UMI-77 reduces the production of Aβ plaques and inflammatory cytokines by degrading the damaged mitochondria, which suggests that mitochondrial damage may play a central role in the occurrence of AD, and further suggesting that promoting mitophagy and restoring mitochondrial function is a promising strategy for the treatment of AD.

Our study demonstrates that MCL1 is a novel mitophagy receptor protein, and that the FDA-approved drug candidate BH3 mimetic UMI-77 can induce mitophagy via releasing MCL1, which can reverse the pathology of Alzheimer disease. Our findings suggest that MCL1 is a novel drug target for the treatment of AD, and further confirm that the induction of mitophagy is an effective strategy for the treatment of this disease.

Disclosure statement

No potential conflict of interest was reported by the authors.

Reference

[1] Cen X, Chen Y, Xu X, et al. Pharmacological targeting of MCL-1 promotes mitophagy and improves disease pathologies in an Alzheimer's disease mouse model. Nat Commun. 2020 Nov 12;11(1):5731.