New Results

Pharmacological inhibition of MCL-1 disrupts mitochondrial cristae and depletes the human neural progenitor cell pool

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Abstract

Myeloid Cell Leukemia-1 (MCL-1) is canonically an anti-apoptotic protein that is crucial for early neurodevelopment. Loss of MCL-1 results in embryonic-lethal neurodevelopmental defects that cannot be rescued by other anti-apoptotic proteins of the B-cell lymphoma 2 (BCL-2) family. Here, we pharmacologically inhibit MCL-1 in human neural stem cells and find non-apoptotic roles for MCL-1 in sustaining mitochondrial cristae integrity, fatty acid oxidation, and neural progenitor identity. MCL-1 inhibition disrupts mitochondrial ultrastructure, leading to swollen mitochondria with disorganized cristae and destabilization of the OPA1-MICOS machinery that maintains inner membrane architecture. These structural defects are accompanied by impaired lipid droplet accumulation and altered expression of β-oxidation enzymes, revealing a tight link between cristae architecture and metabolic competence. Functionally, in the absence of caspase-mediated cell death, MCL-1 inhibition selectively depletes intermediate progenitor cells without affecting proliferation, indicating a direct role in lineage progression. Together, our findings identify MCL-1 as a modulator of cristae organization, linking lipid metabolism to neural progenitor fate. This work establishes mitochondrial inner membrane architecture as an instructive determinant of human neurogenesis and highlights the non-canonical MCL-1 functions as critical regulators of human brain development.

Competing Interest Statement

The authors have declared no competing interest.

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Back to top

Previous Next

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