# Stimulation of mitochondrial Endonuclease G by natural polyphenols to degrade damaged DNA

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Endonuclease G (EndoG) is an evolutionarily conserved mitochondrial protein, exhibiting non-specific endonuclease activity bearing a His-Me finger motif in the active site. EndoG is widely known for its pro-apoptotic function in degrading chromosomal DNA in the mitochondrion-dependent programmed cell-death pathway in mammals and nematodes. In non-apoptotic adult cells, EndoG has multiple essential roles in DNA metabolism, including participating in mitochondrial DNA replication and removing oxidatively-damaged mitochondrial DNA. By screening a group of natural compounds from plants that possess the ability to promote mitochondrial functions, herein we show that a couple of polyphenol compounds directly bind EndoG with a high nanomolar affinity to exert opposite effects, either enhancing or inhibiting EndoG's activity. We determined the crystal structure of the C. elegans EndoG (CPS-6) bound with one of the polyphenol compounds, providing the molecular basis for how this compound is bound at the His-Me finger motif and thus competitively inhibits the endonuclease activity of EndoG in degrading DNA with single-strand breaks. Given that EndoG is a key player in apoptosis and its functional impairment and activity are linked to various heart and neurodegenerative diseases, our study opens up new directions for targeting EndoG via these polyphenols for treating diseases arising from diminished or increased activity of EndoG.