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Mitochondrial dysfunction in Cockayne syndrome: the role of DRP1 protein

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Cockayne syndrome (CS) is a rare genetic progeroid disorder characterized by growth and development defects, severe cutaneous photosensitivity, cachectic dwarfism, progressive neurological dysfunction, and precocious aging.
The molecular basis of these clinical traits are still unknown. Cells derived from CS patients present as pathological hallmarks excessive oxidative stress, intense glycolytic metabolism, mitochondrial fragmentation and apoptosis associated with hyperactivation of the mitochondrial fission Dynamin related protein 1 (DRP1). By using human cell models, we investigated the interplay between DRP1 and CSA and we determined whether pharmacological or genetic inhibition of DRP1 could ameliorate the molecular traits of CS patients and thus the disease progression. Both reactive oxygen and nitrogen species are in excess in CS-A cells and when the mitochondrial translocation of DRP1 is inhibited a reduction of these species is observed together with a recovery of mitochondrial integrity. Moreover, a significant decrease of apoptosis was also observed. A causal link between modulation of DRP1 activation by CSA and regulation of metabolism, mitochondrial health and apoptosis is suggested, indicating DRP1 as a potential therapeutic target in the treatment of CS patient.
Finally, we propose that the dual role of CS proteins in both repair of oxidatively-induced DNA lesions and modulation of metabolic pathways activated by chronic oxidative stress/energy failure converge into mitochondrial dysfunction that is a prominent feature of neurodegeneration onset and progression.

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