Cadmium elicits alterations in mitochondrial morphology and functionality in C3H10T1/2Cl8 mouse embryonic fibroblasts

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Abstract:

Background: Cadmium is a widespread carcinogen. We previously showed that the administration of low $CdCl_2$ doses for 24 h to healthy C3H10T1/2Cl8 mouse embryonic fibroblast cell line at the beginning of Cell Transformation Assay (CTA), up regulates genes involved in metal scavenging and antioxidant defense, like metallothioneines, glutathione S-transferases and heat shock proteins. Still, although most cells thrive normally in the following weeks, malignancy is triggered by $CdCl_2$ and leads to the appearance of foci of transformed cells at the end of the CTA. In this work we aim at elucidating the early metabolic deregulation induced by cadmium, underlying healthy cell transformation into malignant cells.

Methods: Respiratory metabolism was investigated through Seahorse Agilent assays, while oxidative stress level was assessed through fluorescent probes; DNA damage was evaluated by Comet assay, and mitochondrial morphology was analyzed in confocal microscopy.

Results: Results show that the initial response to $CdCl_2$ involves mitochondria rearrangement into a perinuclear network. However, SOD1 and SOD2 activities are inhibited, leading to increased superoxide anion level, which in turn causes DNA strand breaks. From the metabolic point of view, cells increase their glycolytic flux, while all extra NADH produced is still efficiently reoxidized by mitochondria.

Conclusions: Our results confirm previously shown response against cadmium toxicity; new data about glycolytic increase and mitochondrial rearrangements suggest pathways leading to cell transformation.