

Titolo: Impaired enzymatic defensive activity, mitochondrial dysfunction and proteasome activation are involved in RTT cell oxidative damage.

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Abstract:

A strong correlation between oxidative stress (OS) and Rett syndrome (RTT), a rare neurodevelopmental disorder affecting females in the 95% of the cases, has been well documented although the source of OS and the effect of a redox imbalance in this pathology has not been yet investigated. Using freshly isolated skin fibroblasts from RTT patients and healthy subjects, we have demonstrated in RTT cells high levels of H₂O₂ and HNE protein adducts. These findings correlated with the constitutive activation of NADPH-oxidase (NOX) and that was prevented by a NOX inhibitor and iron chelator pre-treatment, showing its direct involvement. In parallel, we demonstrated an increase in mitochondrial oxidant production, altered mitochondrial biogenesis and impaired proteasome activity in RTT samples. Further, we found that the key cellular defensive enzymes: glutathione peroxidase, superoxide dismutase and thioredoxin reductases activities were also significantly lower in RTT. Taken all together, our findings suggest that the systemic OS levels in RTT can be a consequence of both: increased endogenous oxidants as well as altered mitochondrial biogenesis with a decreased activity of defensive enzymes that leads to post translational oxidant protein modification and a proteasome activity impairment.