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High-fat diet, oxidative damage and susceptibility to obesity: a study in transgenic mice

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Several lines of evidence show that an increase in body fat mass is linked to oxidative stress and that the accumulation of radical oxygen species (ROS) contributes to develop the metabolic syndrome.
ROS induce DNA damage with a consequent activation of DNA damage response, an orchestrated set of proteins which trigger a systemic inflammatory response.
Mice defective in DNA damage processing genes are highly susceptible to obesity if exposed to high-fat diet (HFD), suggesting a link between genomic instability and metabolic dysfunction.
In our laboratory we obtained a transgenic mouse which expresses high levels of the human MutT homologue (hMTH1). MTH1 is a hydrolase which protects cells by oxidative damage by removing oxidized precursors from pool of nucleotides, thus avoiding their incorporation in DNA. Interestingly, when compared with wild-type counterpart, our transgenic mouse (hMTH1-Tg) shows: a) protection against neurodegeneration induced by treatment with 3-nitropropionic acid, which causes symptoms that resemble those of Huntington's disease; b) a decrease in oxidative damage, both in nuclear and in mitochondrial DNA; c) an increased longevity; d) a delay in the ageing process; e) a reduced anxiety and an enhanced investigation of environmental and social cues; f) a best mitochondrial functionality.
Our preliminary data suggest that MTH1 plays a pivotal role in modulating oxidative DNA damage in response to HFD. Moreover, we obtained data by magnetic resonance spectroscopy (MRS) that show a higher interscapular brown adipose tissue in hMTH1-Tg mouse compared to wild type, which is correlated to a low cardiovascular disease risk.

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