PRINCIPE FELIPE
CENTRO DE INVESTIGACION

Seminario CIPF

Metabolic reprogramming involved in the pathomechanisms of OXPHOS diseases related to hypomodification of mitochondrial tRNAs

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Abstract: Defective mitochondrial translation is recognized as a cause of human diseases associated with severe dysfunction of oxidative phosphorylation (OXPHOS). However it is unclear how this type of alterations may lead to different nosological entities. Thus, mutations in nuclear and mitochondrial genes involved in mitochondrial translation are cause of encephalopathies, myopathies, cardiomyopathies, liver failure, neurosensorial hearing loss, etc. We hypothesize that retrograde signaling from mitochondria to nucleus is different in each entity, thus generating a tissue-specific maladaptive response that is responsible of the clinical phenotype. To this end, we have characterized the retrograde signaling in cell models of the MTO1 and GTPBP3 defects. The nuclear encoded proteins MTO1 and GTPBP3 are jointly involved in the post-transcriptional modification of mitochondrial tRNAs (mt-tRNAs). Mutations in MTO1 and GTPBP3 lead to hypomodification of mt-tRNAs, impairment of mitochondrial translation, dysfunction of the oxidative phosphorylation (OXPHOS) and infantile hypertrophic cardiomyopathy.

We demonstrate that the MTO1 defect triggers the inactivation of the AMPK/UCP2 retrograde signaling, which drastically affects the expression of metabolic genes, and leads to the uncoupling of OXPHOS from glycolysis and to an impairment of fatty acid oxidation. Strikingly, this response is different from that found after stable or transient silencing of GTPBP3, represented by an AMPK-mediated induction of UCP2 and, accordingly, of fatty acid oxidation.

Our results support the idea that MTO1 may have a second function, which would explain the different nuclear expression pattern observed between the MTO1- and GTPBP3-defective cells. If so, and against expected results, MTO1 and GTPBP3 mutations trigger different pathogenic mechanisms leading to a similar clinical phenotype.

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