Título del Proyecto	**Novel therapeutic perspectives for mitochondrial DNA depletion and deletion syndrome due to defective dNTP homeostasis: The specific case of TK2 deficiency**
Nº de expediente asignado	Trampoline Grant: 19965
Abstract	TK2 mutations cause a severe infantile myopathy due to profound muscle mitochondrial DNA (mtDNA) depletion. Progressive muscle weakness with histological hallmarks of both dystrophy and mitochondrial myopathy most often occur in the first year of life. To-date, in the absence of any efficient treatment, early involvement of proximal muscles and diaphragm leads to death in early childhood due to respiratory insufficiency. Recent description of several adult or slow-progressive cases of myopathy due to TK2 mutations has demonstrated the existence of mechanisms that are able to ameliorate clinical presentation. These mild phenotypes are associated with accumulation of multiple mtDNA deletions in muscle without the marked mtDNA depletion occurring in severe pediatric forms of the disease. Residual TK2 activity does not account for the milder phenotypes since at least some of the mutations totally abolish TK2 activity. In addition some homozygous mutations have been commonly found in either mildly-affected adult or severe infantile patients. This observation suggests that the improved clinical condition is due to specific gene variants or differential gene expression patterns, either due to environmental or epigenetic factors. TK2 catalyzes the first and rate-limiting step of the deoxypyrimidine salvage pathway that ultimately generates dCTP and dTTP in mitochondria. Recently, a bypass therapy based on the administration of deoxypyrimidine monophosphates (dNMPs), which are the products of the TK2-catalyzed reaction, has provided positive results on a mouse model of the disease and has led to try dNMPs as a compassionate treatment in TK2-deficient patients. However the synthesis of dNMPs is complex and thus expensive. In addition, we think that the efficiency of dNMPs-based therapy is likely hampered by the difficult entry into cells of these charged compounds, in the absence of any known transporter. Furthermore, dNMPs are highly unstable in vivo. Our preliminary results suggest that dNMPs act essentially as prodrugs that are incorporated in their dephosphorylated form as deoxyribonucleosides (dNs).
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