Treatment of mitochondrial disease pathology in a Leigh syndrome mouse model by metallothionein 1 overexpression: is there still a role for redox active compounds?

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Introduction: Leigh syndrome (LS) results from a complex I deficiency in the mitochondrial OXPHOS system and is one ofthe most prevalent and devastating mitochondrial diseases, affecting brain and muscle. With no effective therapies for patients living with LS, and considering its pathophysiology, several approaches have been investigated with redox active modulators considered as prime targets. Based on their neuroprotective effects against other neurodegenerativediseases in vivo and their proven impact against complex I deficiency in vitro, we investigated the potential therapeutic effect of the endogenous redox and metal modulator, metallothionein 1 (MT1), using genetically modified mouse models.

Methodology: Whole-body Ndufs4 (complex I) knockout mice (B6.129S4-Ndufs4$^{tm1.1Rpa}$/J) and Mt1 overexpressing mice (B6.Cg-Tg(Mt1)174Bri/J) were crossed and four genotypes selected (n = 12 each): WT (wild type), OVER (Mt1 overexpressing), KO (Ndufs4$^{-/-}$), and KO OVER (Mt1 overexpressing + Ndufs4$^{-/-}$) mice. A wide range of phenotypic, biochemical, histochemical and metabolomics analyses where performed on brain and muscle to evaluate the effect of MT1 overexpression on mitochondrial pathology.

Results: With the exception of subtle reductions in the expression of neuro-inflammatory markers, GFAP and IBA1 in the vestibular nucleus and hippocampus, no improvement in survival, growth, locomotor activity, balance, or motor coordination in the KO OVER mice where observed, compared to KO mice. Furthermore, at a cellular level, no significant differences were detected in the metabolomics profile or gene expression of selected one-carbon metabolism and oxidative stress genes, performed in brain and quadriceps, nor in the ROS levels of macrophages derived from these mice. With concerns on the putative role of redox metabolism and oxidative stress in the pathology, brain region-specific metabolomics investigations in KO mice further revealed a link between the severity of CI deficiency and the degree of distinct metabolic perturbations in different Ndufs4 KO brain regions. The metabolic data indicates that, amongst other findings, the level of redox imbalance impacts brain regional capacity to bypass CI deficiency and maintain homeostasis.

Discussion and conclusions: Metallothioneins, as redox and metal modulators that structurally and functionally resemble glutathione, have shown great promise as redox active compounds in vitro and in vivo. Similar to other redox active compounds tested in whole body NDUFS4 KO mice such a idebenone and the trolox analogue, KH176, but with the exception of NAD^+-precursor, NMN, no significant improvement in pathology or life span where observed when overexpressing MT1. Further metabolomics investigations confirmed a significant tissue-specific variation in this disease model and that metabolic redox state is clearly a key perturbation linked to the level of complex I deficiency. However, other therapeutic studies which targeted tissue oxygenation, mitochondrial biogenesis, and adaptive bioenergetics (including mtOR), suggest that metabolic and cellular dysregulation – compared to oxidative damage – may be more prominent in the pathophysiology of LS and should thus be the focus of future therapeutic interventions.

References:

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