Spatial and LC MS/MS Based Quinomics Reveals Novel Therapeutic Impact of BPM31510 For the Treatment of CoQ10 Deficiency Using the Coq4$^{KI/KI}$ Mouse Model

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ABSTRACT

Introduction

Coenzyme Q10 (CoQ10) is vital for mitochondria, playing a central role in energy production and antioxidant defense. Dysregulated CoQ10 metabolism contributes to mitochondrial diseases and deficiency syndromes, yet the mechanisms remain poorly understood. To address this, we developed a novel LC-MS/MS and MALDI-MSI quinomics workflow to comprehensively profile CoQ10 and related metabolites. Using this platform, we examined a lipid nanoparticle CoQ10 formulation (BPM31510) in a CoQ-deficient mouse model (Coq4 $^{KI/KI}$), uncovering novel aspects of quinone regulation, metabolic regulation, and potential therapeutic strategies for mitochondrial diseases.

Methods

CoQ-deficient mice were administered BPM31510 (200 mg/kg CoQ10) via intraperitoneal injection every other day over two weeks. Serum was collected throughout the study and at termination liver, brain, muscle, kidney, heart, adipose, and ear (skin) were harvested. Quinones were extracted from serum and tissues using isopropanol and deuterium-labeled CoQ10 as an internal standard. Samples were analyzed by HPLC-MS/MS on Agilent LC with Waters Acquity HSS-T3 column and Thermo Q-Exactive Plus mass spectrometer. Data were acquired using scheduled parallel reaction monitoring (PRM) to semi-quantify ~30 quinones. MALDI MSI was performed on tissue sections to map the spatial distribution of CoQ10, related quinones, and metabolites.

Result and Conclusion

BPM31510 treatment effectively restored and significantly increased the CoQ pool in brain (cerebellum), kidney, heart, muscle as well as other tissues of Coq4$^{KI/KI}$ mice compared to vehicle treated Coq4$^{KI/KI}$ mice mouse controls. CoQ10 deficiency represents a heterogenous metabolic disorder in which oral CoQ10 provides sub-optimal clinical benefit due to poor absorption and biodistribution. Treatment with BPM31510 restored the CoQ pool impacting metabolic adaptation in a CoQ deficient mouse model, demonstrating its therapeutic potency, bioactivity and biodistribution overcoming these challenges.

CoQ BIOSYNTHETIC PATHWAY, SPATIAL QUINOMICS, AND PRIMARY CoQ10 DEFICIENCY

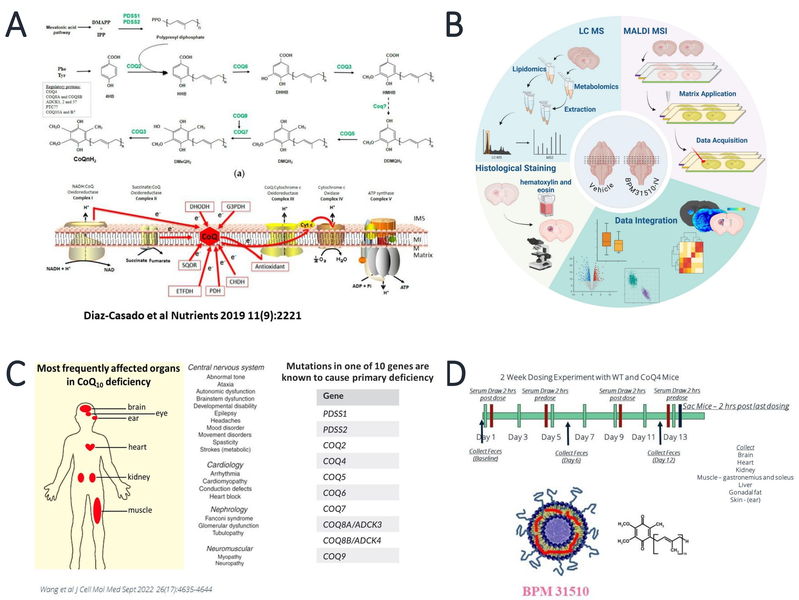

FIGURE LEGEND 1: CoQ10 biosynthetic pathway which regulates the CoQ pool is critical for integrating multiple enzymatic aspects of mitochondrial function (A). LC MS/MS and spatial quinomics workflow, which quantifies quinone metabolites (B). Primary CoQ10 deficiency predominantly impacts neurological, muscle, and kidney physiology and is caused by several different mutations in the CoQ10 pathway genes. Study design treating WT and CoQ4KI mice with BPM31510 over the course of two weeks of dosing to evaluate CoQ10 tissue distribution.

BPM31510 INCREASES SERUM AND TISSUE CoQ10 LEVELS IN Coq4$^{KI/KI}$ MOUSE MODEL

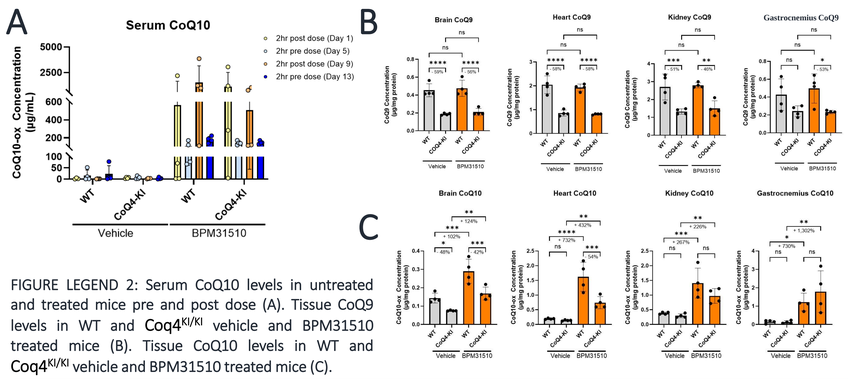

FIGURE LEGEND 2: Serum CoQ10 levels in untreated and treated mice pre and post dose (A). Tissue CoQ9 levels in WT and Coq4$^{KI/KI}$ vehicle and BPM31510 treated mice (B). Tissue CoQ10 levels in WT and Coq4$^{KI/KI}$ vehicle and BPM31510 treated mice (C).

BPM31510 DELIVERED CoQ10 TO THE BRAIN AS WELL AS THE CEREBELLUM OF Coq4$^{KI/KI}$ MICE

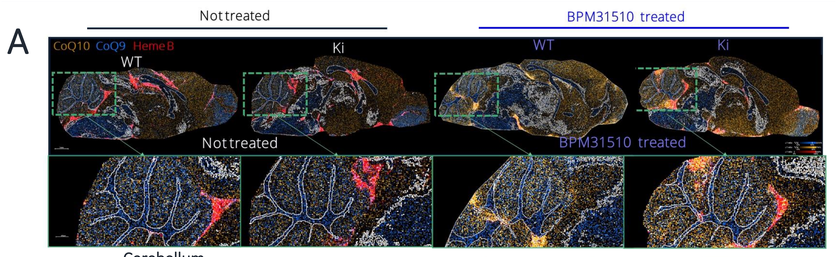

FIGURE LEGEND 3: Single cell spatial CoQ levels in WT and Coq4$^{KI/KI}$ vehicle and BPM31510 treated mice (A). BPM31510 increased CoQ10 levels in cerebellum (B) and in different brain enriched regions (C).

SPATIAL QUINOMICS REVEALED INCREASE IN CARDIAC CoQ10 UPTAKE FROM BPM31510 TREATMENT

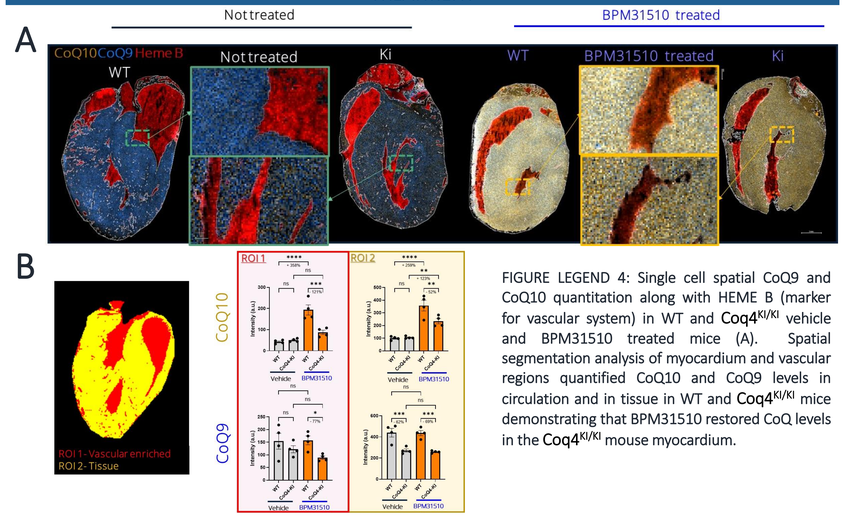

FIGURE LEGEND 4: Single cell spatial CoQ9 and CoQ10 quantitation along with HEME B (marker for vascular system) in WT and Coq4$^{KI/KI}$ vehicle and BPM31510 treated mice (A). Spatial segmentation analysis of myocardium and vascular regions quantified CoQ10 and CoQ9 levels in circulation and in tissue in WT and Coq4$^{KI/KI}$ mice demonstrating that BPM31510 restored CoQ levels in the Coq4$^{KI/KI}$ mouse myocardium.

BPM31510 INCREASED CoQ10 IN KIDNEY SUBREGIONS

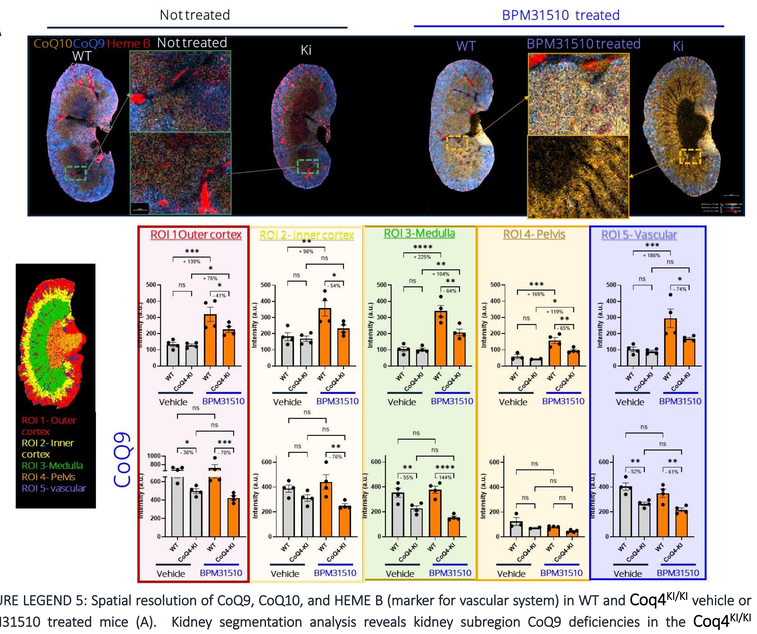

FIGURE LEGEND 5: Spatial resolution of CoQ9, CoQ10, and HEME B (marker for vascular system) in WT and Coq4$^{KI/KI}$ vehicle or BPM31510 treated mice (A). Kidney segmentation analysis reveals kidney subregion CoQ9 deficiencies in the Coq4$^{KI/KI}$ compared to WT mice. BPM31510 treatment increased CoQ10 levels in WT and Coq4$^{KI/KI}$ mouse kidney subregions increasing the overall CoQ pool (B).

BPM31510 INCREASES CoQ POOL IN GASTROCNEMIUS MUSCLE

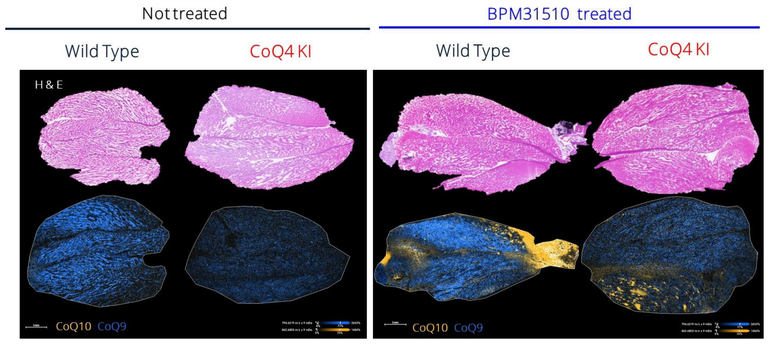

FIGURE LEGEND 6. Spatial assessment of CoQ9 and CoQ10 in WT and CoQ4KI vehicle and BPM31510 treated mice. BPM31510 increased CoQ10 levels in different regions of the gastrocnemius muscle and throughout the myofibrils.

CONCLUSIONS

- Primary CoQ10 deficiency is a complex metabolic disorder in which LC MS/MS based quinomics and spatial quinomics approach offers novel insight into therapeutic development strategies
- Oral CoQ10 therapeutic approaches results in poor bioavailability, however, BPM31510 treatment has demonstrated enhanced bioavailability and tissue distribution.
- Coq4$^{KI/KI}$ mouse model exhibits significant CoQ9 deficiencies in brain, heart, kidney, and muscle and BPM31510 was able to increase CoQ levels through the increase of CoQ10 in these tissues.
- Cerebellar delivery represents a predominant goal of therapeutic intervention in primary CoQ10 deficiency due to this disorder often presenting with ataxia. Utilizing spatial quinomics, we quantified a statistical increase in CoQ10 levels in the cerebellum increasing the CoQ pool.
- In other tissues, such as heart, kidney, and muscle, BPM31510 significantly increased CoQ10 levels in various subregions demonstrating the enhanced tissue distribution and restoration of the CoQ pool.
- BPM31510 demonstrated significant CoQ10 delivery in an animal model of primary CoQ deficiency resulting in the rescue of CoQ levels.