#500: Pan-cancer Assessment Reveals Deletions in COQ Biosynthesis Pathway Genes Associated With Poor Prognosis in Kidney Cancers That May Benefit From BPM31510 Intervention

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BACKGROUND

Defective energy metabolism has been established as a hallmark of cancer; however, the specific genetic basis underlying this relationship across cancers remains unclear. Ubiquinone (CoQ10) plays an essential role in regulating efficient mitochondrial ATP generation and reactive species levels. Maintenance of CoQ10 levels is orchestrated by 13 CoQ10 biosynthetic genes that, when altered, results in severe metabolic dysfunction. However, the mutational, deletion/amplification, methylation, or mRNA expression status across cancers has not been thoroughly investigated. Integrated molecular analysis revealed that KIRP and KIRC are enriched in deletions in the CoQ10 biosynthetic pathway associated with PFS and OS, likely associated with metabolic alterations in these kidney cancers.

Methods/Experimental Approach

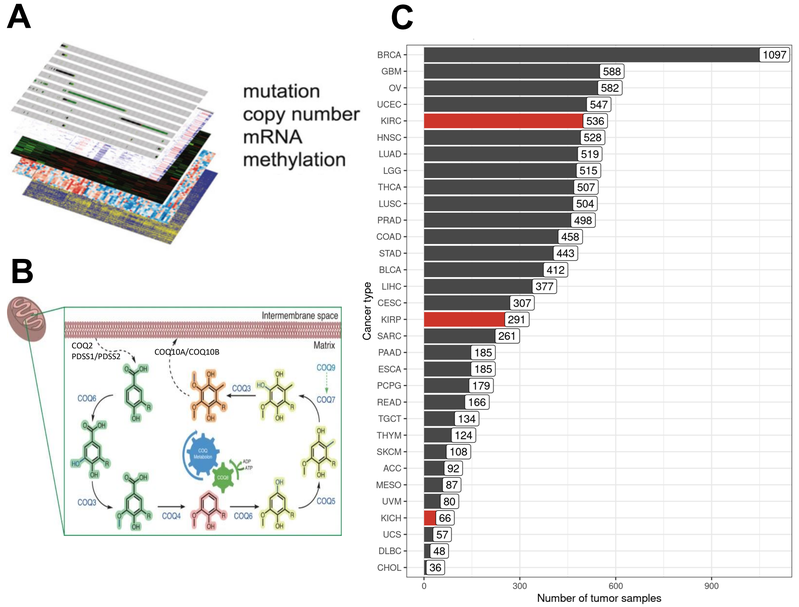


Figure 1: (**A**) Pan-cancer in-silico analysis of TCGA molecular data. (**B**) CoQ10 levels are regulated by 13 CoQ10 biosynthetic genes. (**C**) Distribution of tissue samples in the 33 cancer types investigated. Kidney cancer tissue types are denoted by red shading.

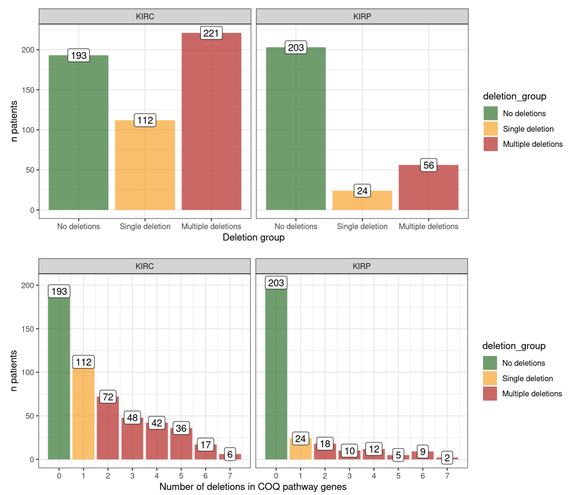
Conclusions

- Across the 33 tumor types profiled in TCGA, we identified Clear Cell Carcinoma (KIRC) and Papillary renal cell carcinoma (KIRP) as primary cancers that demonstrate a significantly poor prognosis with deletions in COQ10 biosynthesis genes.
- Deletions in COQ2, COQ4, and COQ6 were associated with decreased PFI and OS in KIRC and KIRP.
- Further, KIRC demonstrated that up to 42% of tumors had one or more deletions in the CoQ10 biosynthetic pathway
- This unbiased pan-cancer analysis clearly demonstrates that kidney cancers (KIRC/KIRP) may predominantly exhibit a genetic basis for altered mitochondrial metabolism due to a loss of ability to produce COQ10, further pushing the cells into glycolysis over aerobic respiration rendering them susceptible to metabolic interventions.

Deletion of COQ2, 4, 6, and OS/PFI Outcome

Indication	Gene	Overall Survival HR	Overall Survival q	Progression Free Interval HR	Progression Free Interval q
KIRC					
KIRC	COQ6	1.69 (1.25 - 2.28)	0.01728	1.66 (1.21 - 2.26)	0.03070
KIRC	COQ4	1.76 (1.29 - 2.38)	0.00986	2.66 (1.95 - 3.65)	0.00000
KIRC	COQ2	2.35 (1.64 - 3.37)	0.00034	2.99 (2.08 - 4.31)	0.00000
KIRP					
KIRP	COQ6	3.49 (1.83 - 6.65)	0.00713	3.27 (1.86 - 5.75)	0.00166
KIRP	COQ4	3.27 (1.64 - 6.51)	0.01894	3.68 (1.99 - 6.8)	0.00166
KIRP	COQ2	5.86 (2.97 - 11.58)	0.00005	5.46 (2.95 - 10.1)	0.00000

Table 1: Hazard ratios (HR) and q-values associated with copy number deletion (homozygous or heterozygous) of COQ2, COQ4, or COQ6, in KIRC or KIRP and either overall survival or progression-free interval.



KIRC

- **63%** patients had deletions
- **42%** patients had more than one COQ deletion

KIRP

- **28%** patients had deletions
- **20%** patients had more than one COQ deletion

COQ Pathway Gene Deletions in KIRC

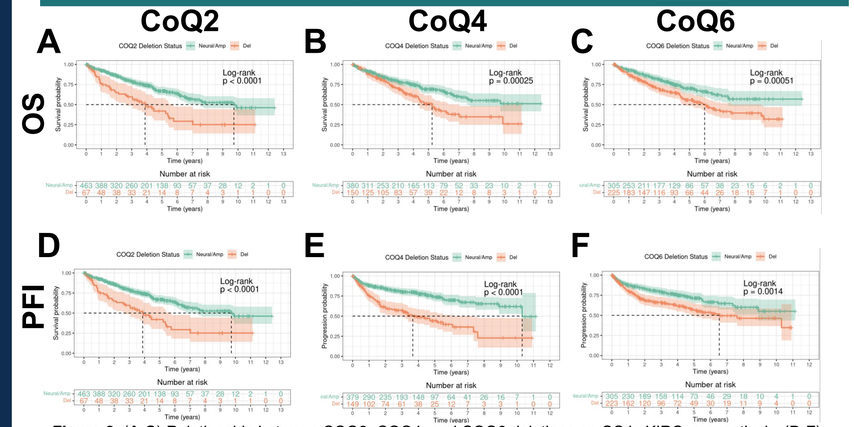


Figure 2: (**A-C**) Relationship between COQ2, COQ4, and COQ6 deletions on OS in KIRC, respectively. (**D-F**) Relationship between COQ2, COQ4, and COQ6 deletions on PFI in KIRC, respectively.

COQ Pathway Gene Deletions in KIRP

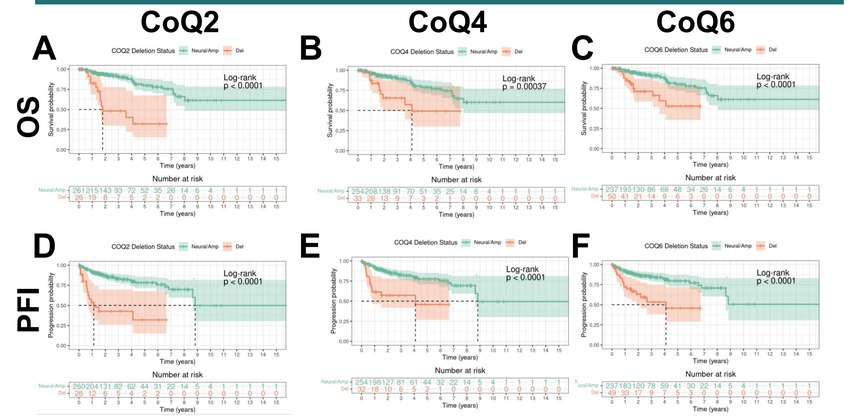


Figure 3: (**A-C**) Relationship between COQ2, COQ4, and COQ6 deletions on OS in KIRP, respectively. (**D-F**) Relationship between COQ2, COQ4, and COQ6 deletions on PFI in KIRP, respectively.

Future Directions for Research

Currently, we are developing a nanodispersion formulation of oxidized CoQ10 (BPM31510) that delivers supraphysiological levels of CoQ10 into circulation and into tumors, which is currently being investigated in Phase 2 clinical trials that might act as a therapeutic fulcrum point for tumors that have metabolic inefficiencies due to CoQ biosynthetic enzyme insufficiency.