#35: De Novo Synthesis from Tryptophan in the Absence of a QPRTase Homolog Contributes to NAD+ Biosynthesis in *C. elegans*

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NAD+ biosynthesis has proven to be an attractive and promising therapeutic target for influencing health-span and obesity-related phenotypes as well as tumor growth. It's a necessity to elucidate exactly how manipulating NAD+ biosynthetic pathways can lead to therapeutic benefits to fully utilize this target for drug discovery. The goal of my research is to understand how NAD+ homeostasis is maintained to support its core metabolic roles and its signaling and regulatory roles involving NAD+ consumers. It's been reported in the literature that *C. elegans* lack the de novo NAD+ biosynthetic pathway because quinolinic acid phosphoribosyltransferase (QPRTase) is not present in the genome. However, all genes coding for the key enzymes required for production of quinolinic acid (QA) from tryptophan are present in the *C. elegans* genome. Therefore, we hypothesized that de novo synthesis from tryptophan in *C. elegans* contributes to NAD+ biosynthesis. In order to investigate if de novo synthesis is indeed active in the absence of the QPRTase homolog, we first asked if QA gets incorporated into NAD+ in *C. elegans*. Using stable isotope/mass spectrometric flux analysis, I observed that label incorporated into QA was subsequently incorporated into NAD+ as well; supporting the notion de novo NAD+ synthesis is active. I further hypothesized that if QA were an endogenous precursor for NAD biosynthesis, then blocking this pathway would compromise NAD+ levels in vivo. Target metabolomics revealed a decrease in NAD+ and QA levels when this pathway was blocked. This data supports the hypothesis that this pathway is active and required for maintenance of global NAD+ levels. Next, I investigated if supplementation with QA could reverse a phenotype associated with NAD+ deficiency. Consistent with the previous results, supplementation with QA rescued the developmental phenotype and increased NAD+ levels in mutants that lack salvage NAD+ biosynthesis. This evidence suggests that boosting this pathway can lead to homeostatic mechanisms when salvage synthesis is blocked, further supporting its core role in maintaining NAD+ homeostasis. Finally, we've identified key candidate enzymes that may play the role of the missing QPRTase in *C. elegans*. Using genetics, I am currently investigating the role of these potential enzymes in NAD+ de novo synthesis. This data will outline the mechanisms by which tryptophan de novo synthesis is functioning in *C. elegans*. This work has implications for efforts to therapeutically target individual NAD+ biosynthetic pathways providing key insight into compensatory homeostatic mechanisms.