Oxidative stress induced suppression of metabolism pathways in Dahl Salt-Sensitive rat

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Introduction: A high-salt (HS) diet has been shown to enhance glycolysis in normal Sprague Dawley (SD) rats, as demonstrated by flux measurements of kidney metabolites using sequential renal arteriovenous sampling and tissue transcriptomic analysis (PMID: 37575482). In this study, we examine kidney cortical (Cx) and outer medullary (OM) transcriptomic responses to a HS diet in Dahl salt-sensitive (SS) rats compared to $SS^{Nox4-/-}$ rats, which have a global knockout of NADPH oxidase 4 (Nox4) to reduce oxidative stress, and SD rats.

Method: Male SS, $SS^{Nox4-/-}$ and SD rats were fed either a 0.4% diet, a 4% diet for 7 days, or for 21 days (HS21). Cx and OM were removed for mRNAseq analysis (Novogene, Inc). Comparisons with previously published SD data was performed by publicly available software (RNAseqChef and DAVID).

Results: Comparing SS and SD rats at HS21, 1724 mRNAs in Cx and 2775 in OM had an FDR<0.05 and fold change>2. Divisive clustering identified 446 mRNAs in Cx and 1550 in OM that showed distinct responses in SS relative to SD and $SS^{Nox4-/-}$. In Cx, only the “Protein digestion and absorption” pathway was significantly enriched, including genes like *Slc3a1* (amino acid transporter) and *Atp1A4* (Na/K ATPase), which were consistently higher in SS. Collagen mRNAs were also increased in SS on HS. In OM, 11 pathways were enriched, including “carbon metabolism” and “biosynthesis of amino acids,” with genes such as *Aco1* (aconitase), *Pc* (pyruvate carboxylase), *Pklr* (pyruvate kinase), and *Ass1* (argininosuccinate synthase) being consistently lower in SS.

Conclusion: Transcriptomic responses to HS differed in SS versus $SS^{Nox4-/-}$ and SD rats, with carbon metabolism and amino acid synthesis genes suppressed in SS OM, potentially causing lactate accumulation and renal damage due to increased energy demand, driven by oxidative stress absent in $SS^{Nox4-/-}$ and SD rats. Further metabolite analysis is ongoing.