

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

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# Introduction

- Previous research has revealed that reactive oxygen species and  $H_2O_2$  in the renal medulla are significantly involved in the blood pressure salt sensitivity in Dahl salt-sensitive (SS) rats.  
Taylor et al. AJP 2005, Makino et al. AJP 2003, Meng et al. AJP 2002, Cowley et al. AJP 2008

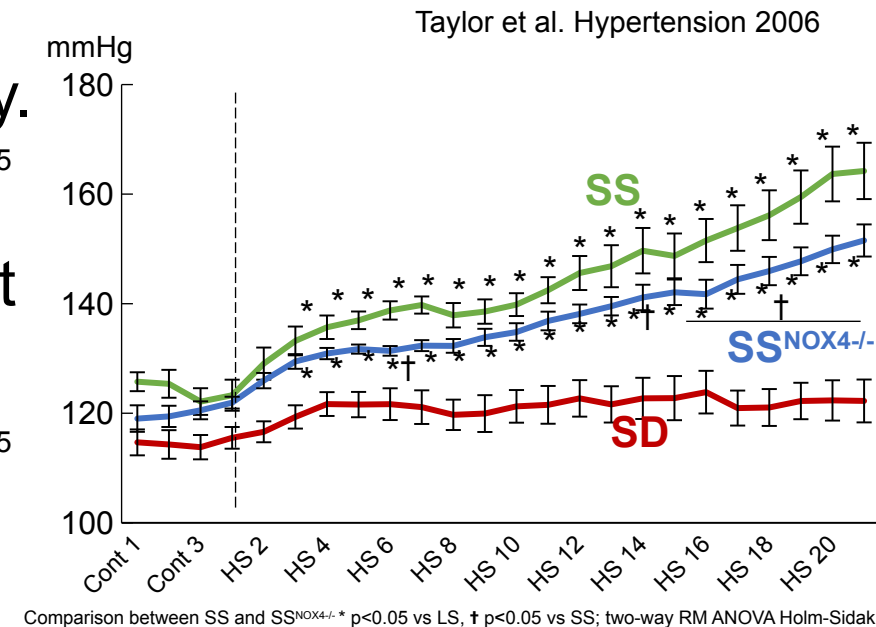
- The primary source of ROS is NADPH oxidase (NOX) in kidney of Dahl SS rats.

- NOX4 is the most abundant NOX isoform in the kidney.

Cowley et al. Hypertension 2015

- Global knock out of NOX4 reduces blood pressure salt sensitivity and kidney damage.

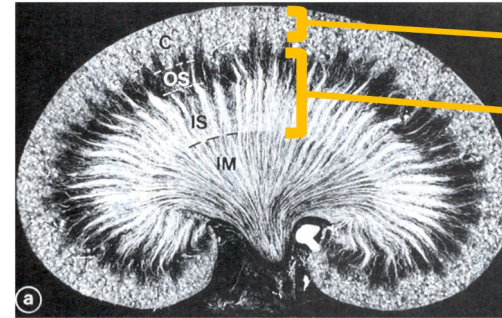
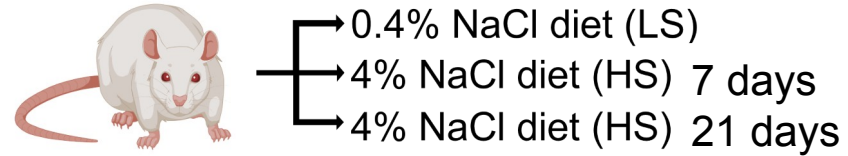
Cowley et al. Hypertension 2015



- The aim of this study was to clarify how knocking out NOX4 to suppress oxidative stress affects the transcriptomic response to salt.

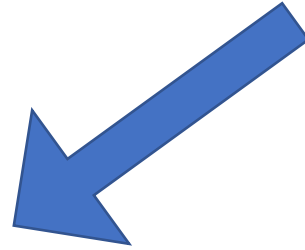
# Method

SD, Dahl SS and SS<sup>NOX4-/-</sup>



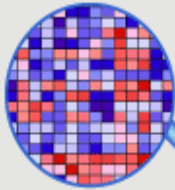
Cortex (Cx)

Outer medulla (OM)



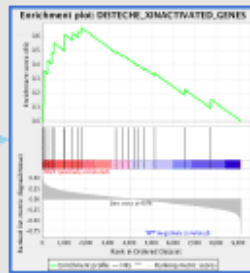
## RNAseq at Novogene

Molecular Profile Data



Run  
GSEA

Enriched Sets



Gene Set Database

DESeq2 Likelihood Ratio Test (LRT) followed by clustering analysis to detect and visualize differentially expressed genes across

- Three strains (SD, SS, SS<sup>NOX4-/-</sup>)
- Three salt conditions

incorporating previously reported SD data

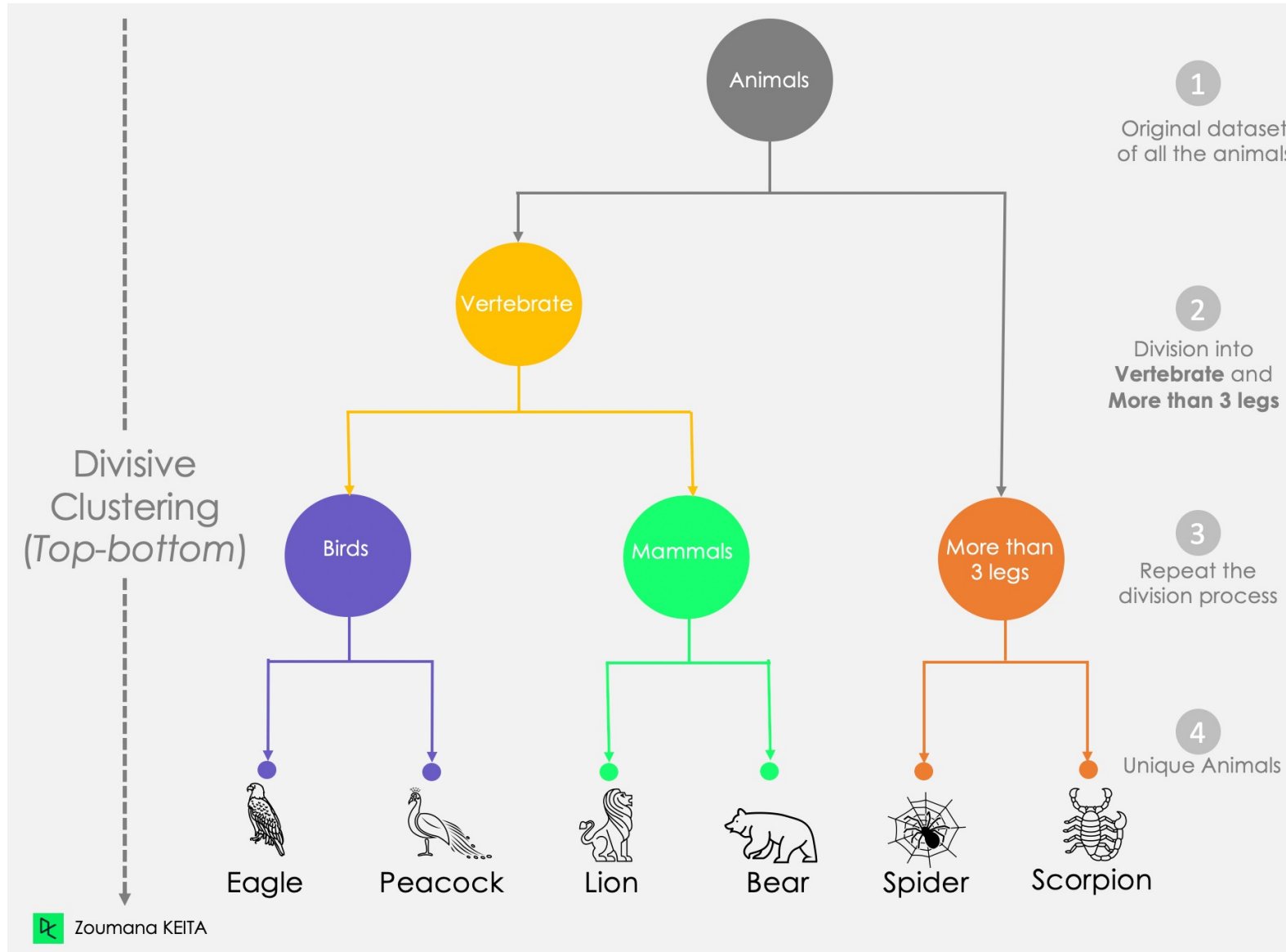
# What are the transcriptomic factors that cause salt sensitivity?

Use divisive clustering analysis to find out genes that share similar expression patterns across different conditions

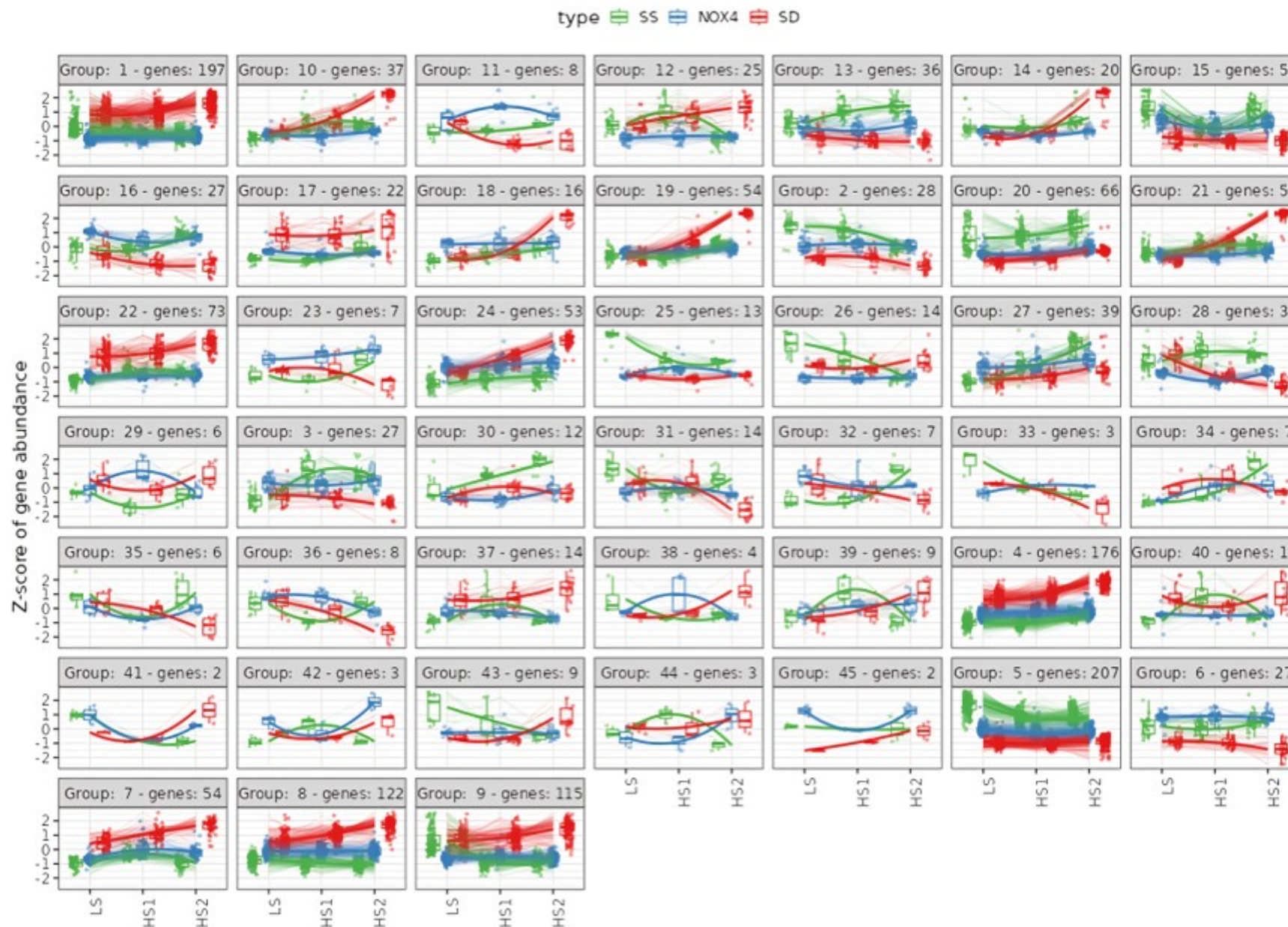


Identify the genes that show a distinct pattern in SS only

# Concept of divisive clustering analysis



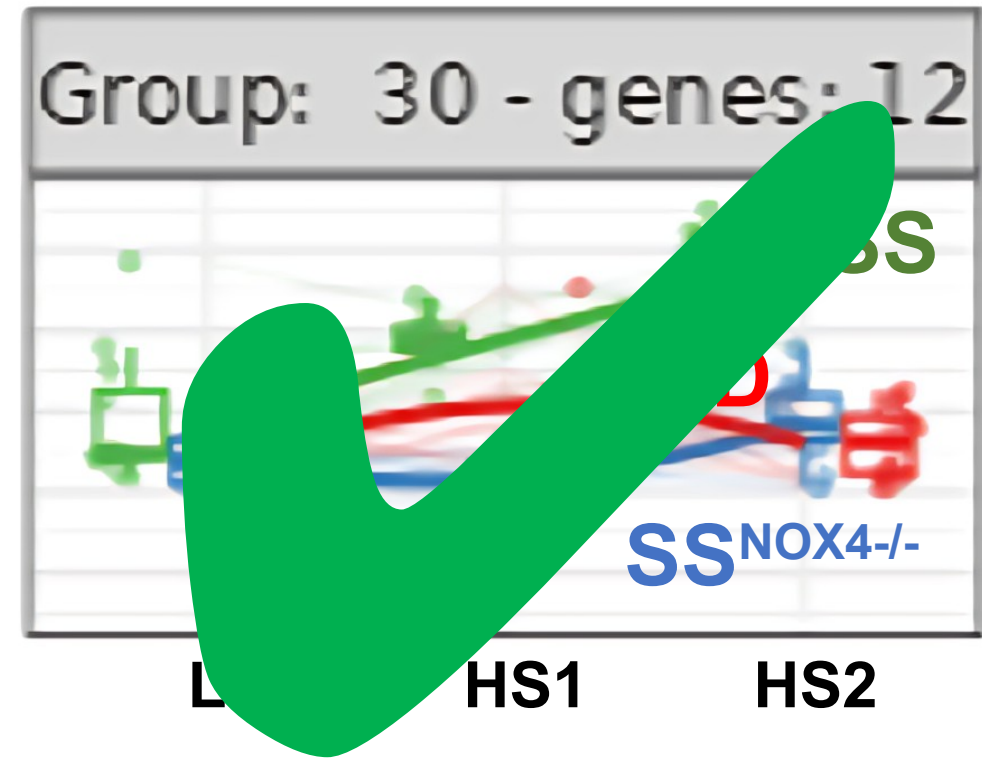
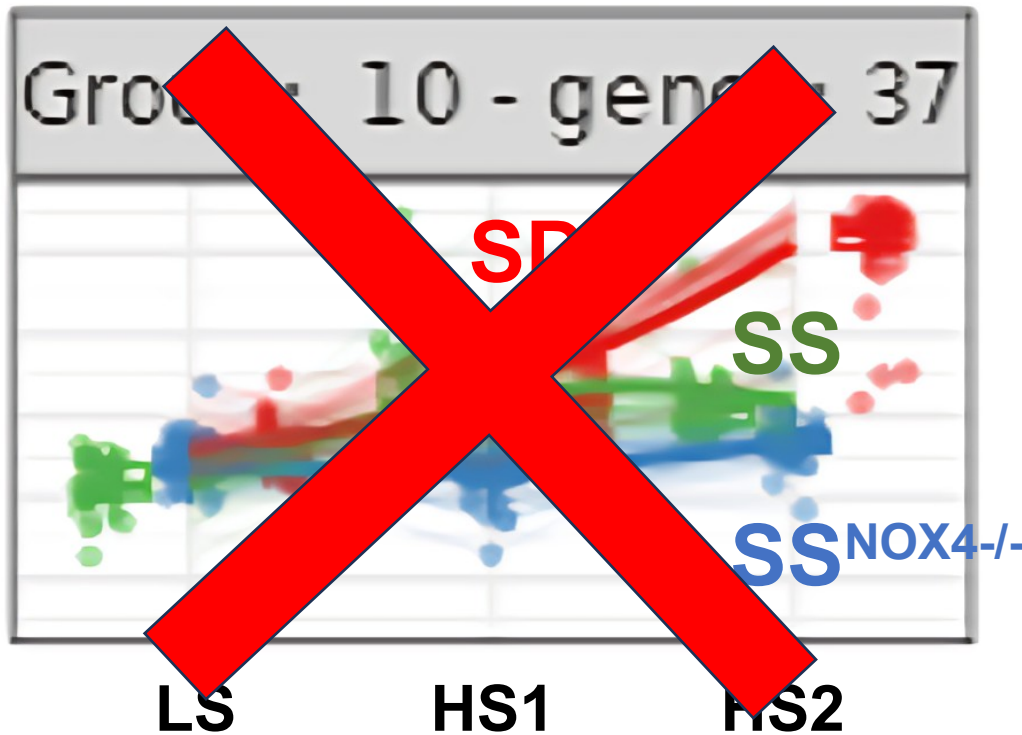
# The result of divisive clustering analysis



Filtration criteria ( $\text{fdr} < 0.05$ ,  $\text{basemean} > 0$ ,  $|\log_2(\text{HS2SS}/\text{HS2SD})| > 1$ ): 1729



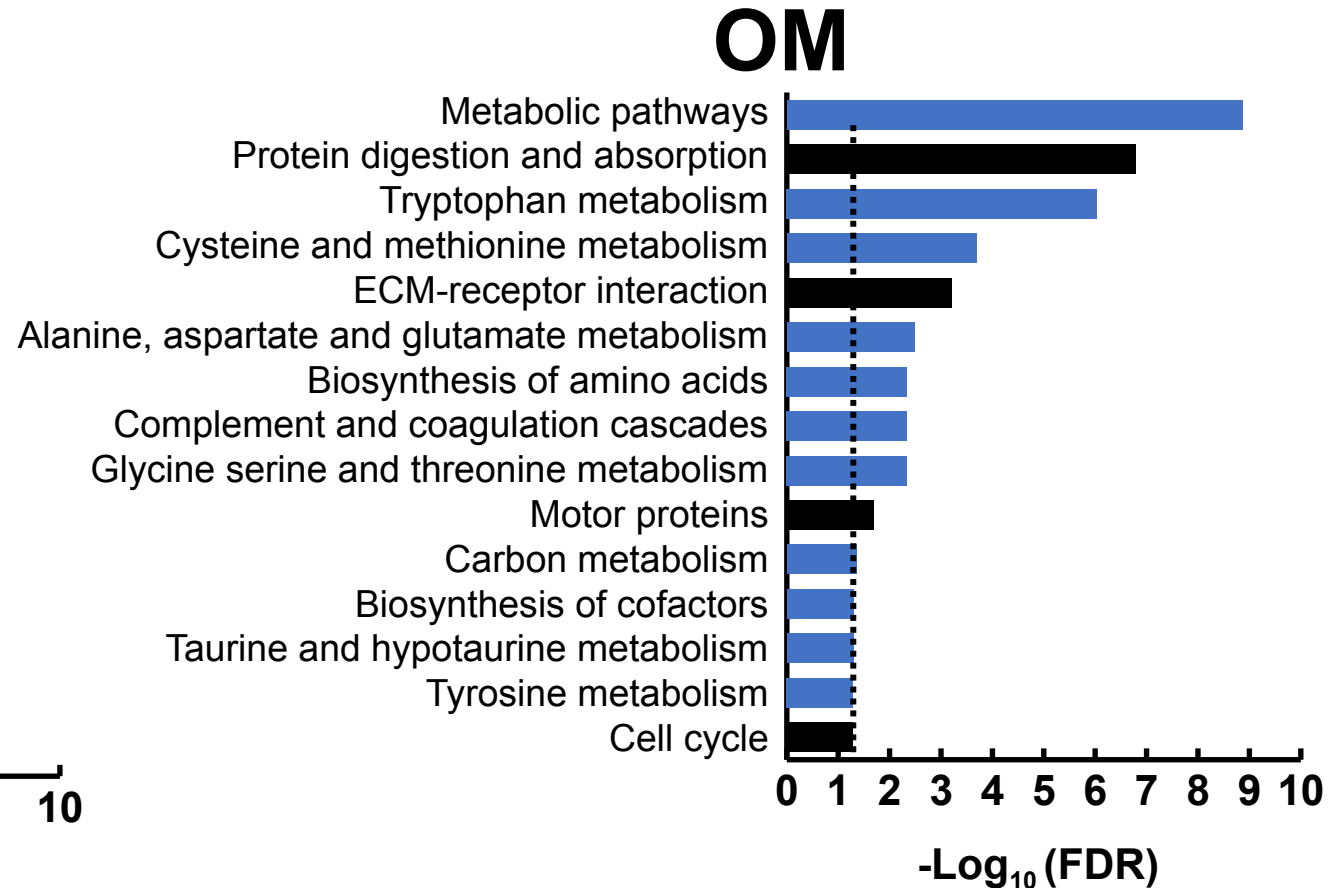
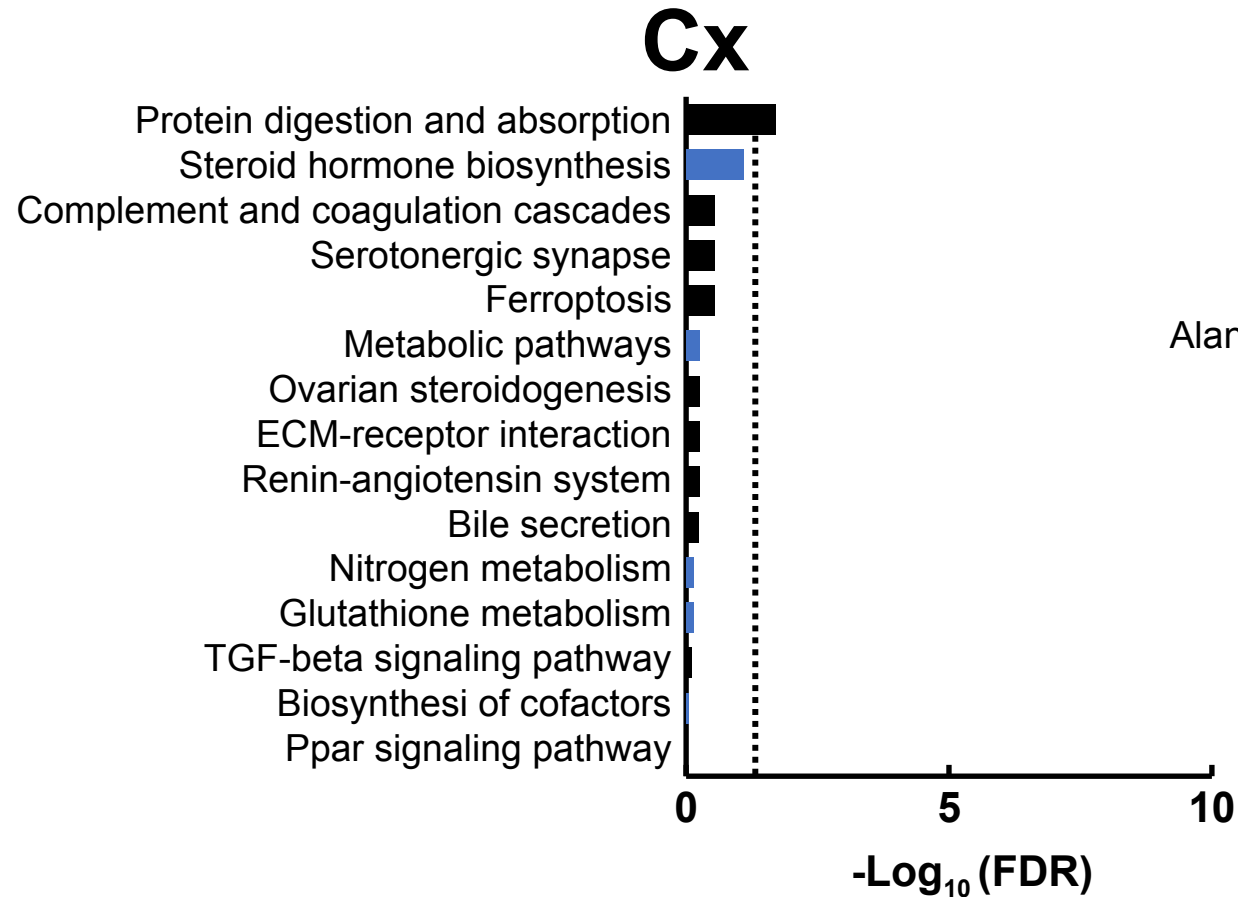
# Pick up genes that show distinct responses in SS only



Among the mRNAs analyzed, **446** (out of 1729) in Cx and **1,550** (out of 2775) in OM exhibited distinct responses in SS, setting them apart from the similar patterns observed in SD and SS<sup>Nox4-/-</sup>.

What those genes are?

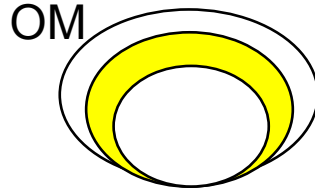
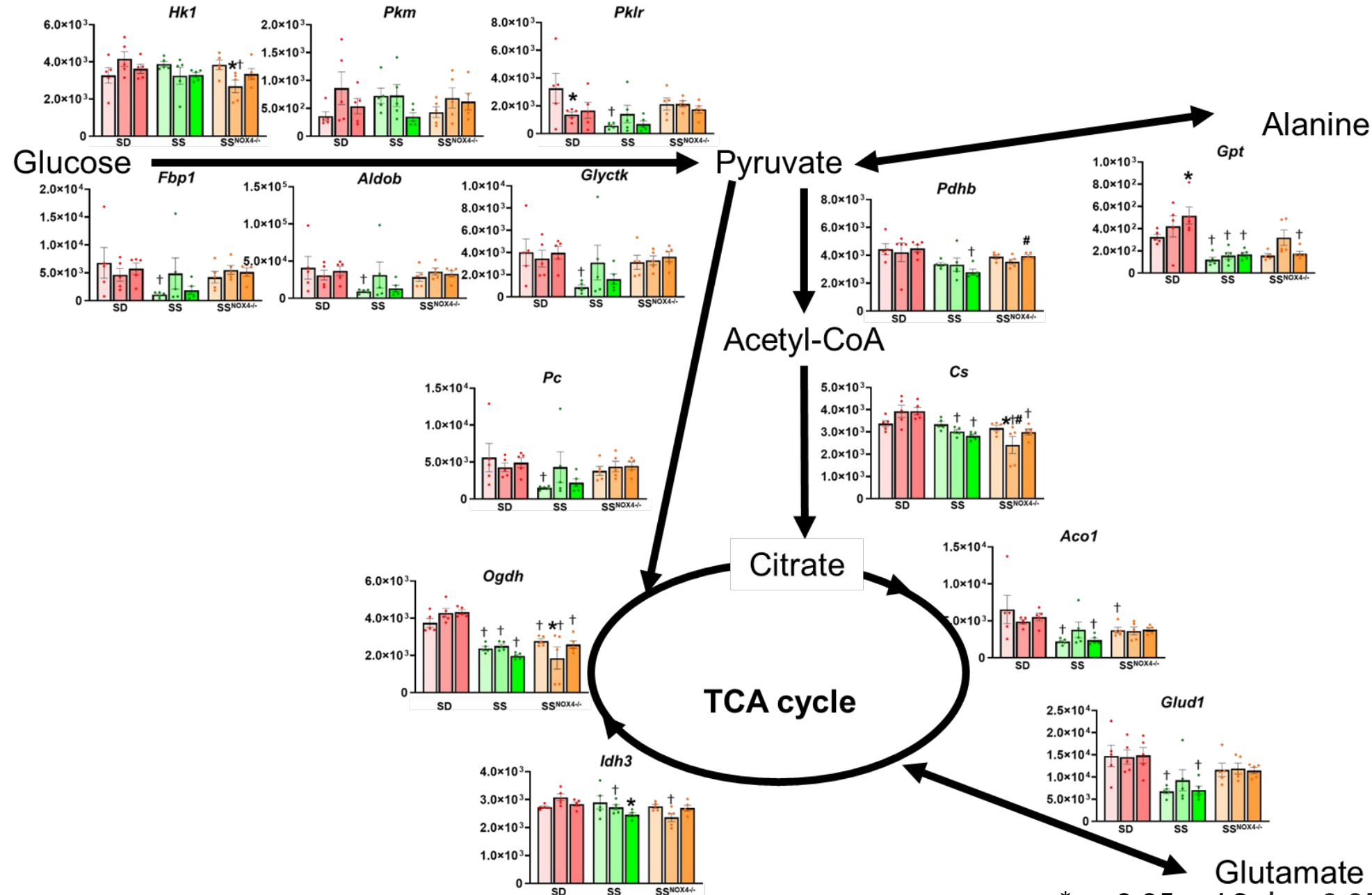
# Salt affects many pathways differently in SS in OM



Blue denotes metabolism pathways



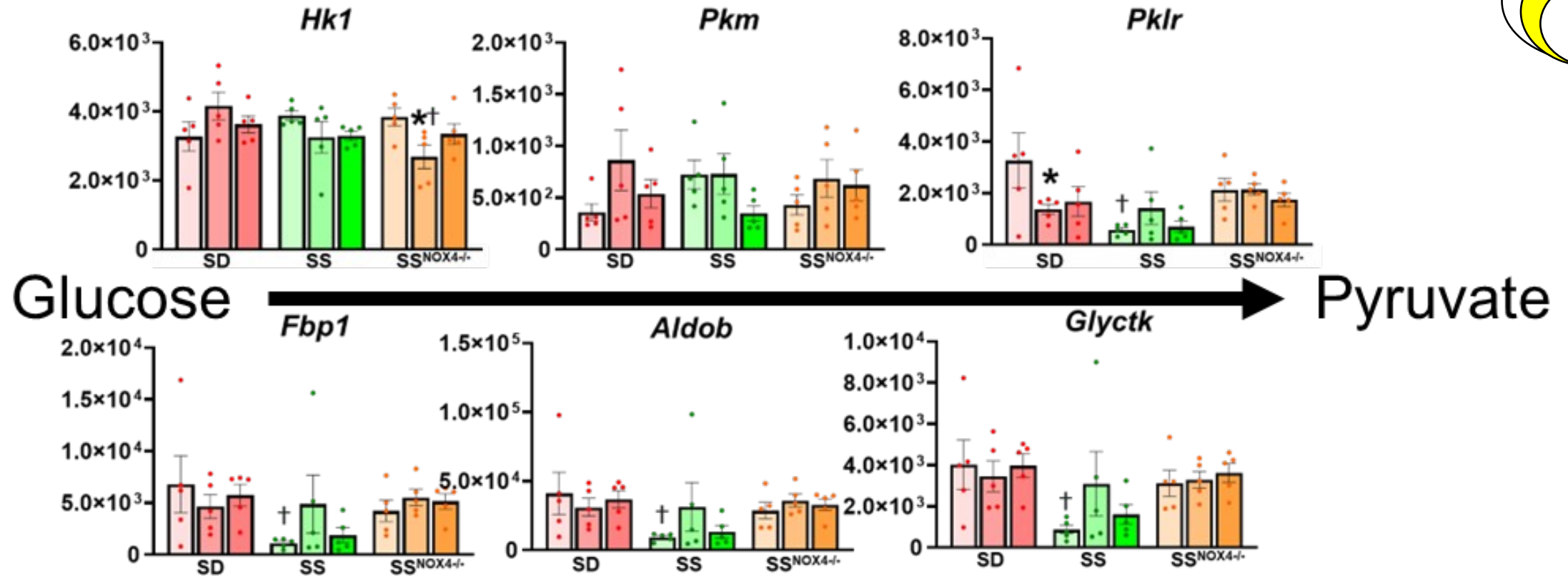
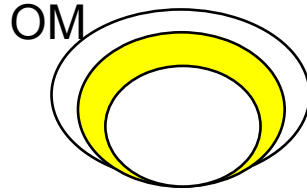
# Several genes were affected differently by salt in SS in OM



LS	HS14	HS21
LS	HS7	HS21
LS	HS7	HS21

\* p < 0.05 vs LS. † p < 0.05 vs SD. # p < 0.05 vs SS

# Several genes were affected differently by salt in SS in OM



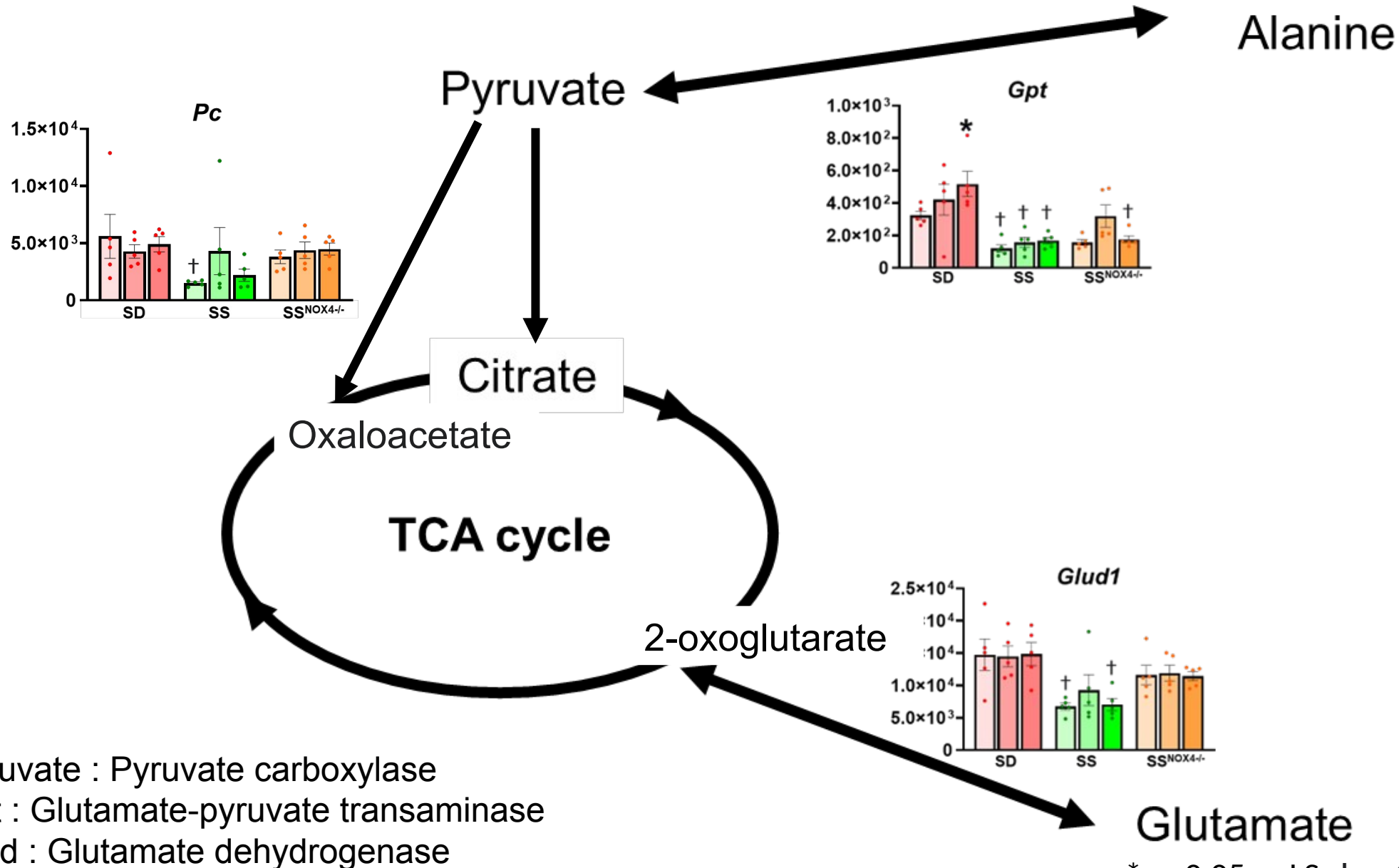
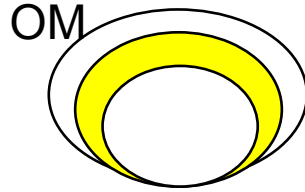
Hk : Hexokinase  
 Pk : Pyruvate kinase  
 Fbp : Fructose-Bisphosphatase

Aldo : Aldolase  
 Glyck: Glycerate Kinase

LS	HS14	HS21
LS	HS7	HS21
LS	HS7	HS21

\* p<0.05 vs LS, † p<0.05 vs SD, # p<0.05 vs SS

# Several genes were affected differently by salt in SS in OM



# Summary and conclusion of three group comparison

- Transcriptomic response of some genes differed when comparing kidneys of SS to SS<sup>Nox4<sup>-/-</sup></sup> and SD rats, which could potentially be related to salt sensitivities
- Carbon metabolism related genes including Fbp1, Pc and Gpt were suppressed in OM in SS which could functionally lead to lactate accumulation and eventually renal damage as energy demand increased with the HS.
- Oxidative stress appear to drive these changes given the absence of such changes in the SS<sup>Nox4<sup>-/-</sup></sup> and SD rats.

# Acknowledgement

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Thank you!  
Questions?