

# Cisplatin-induced nephrotoxicity: modulation of the expression of protein-coding and non-coding genes and transcripts

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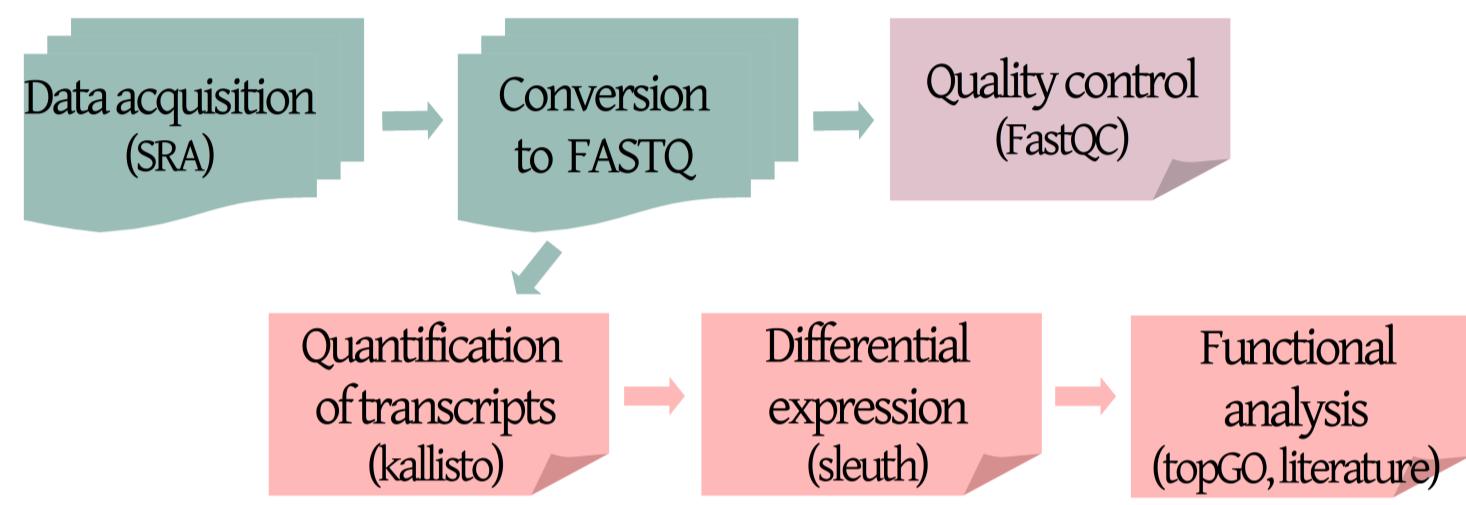
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## INTRODUCTION

Cisplatin is a chemotherapy drug used in the treatment of tumors, however, nephrotoxicity is the greatest limitation for its use. Despite efforts, the mechanisms of cisplatin toxicity are not yet completely elucidated. In this work, we evaluated the modulation of transcript expression in kidneys of mice treated with cisplatin (20 mg/kg) or saline (control) using publicly available data in the GEO under access numbers GSE69652 (Data A) and GSE106993 (Data B).

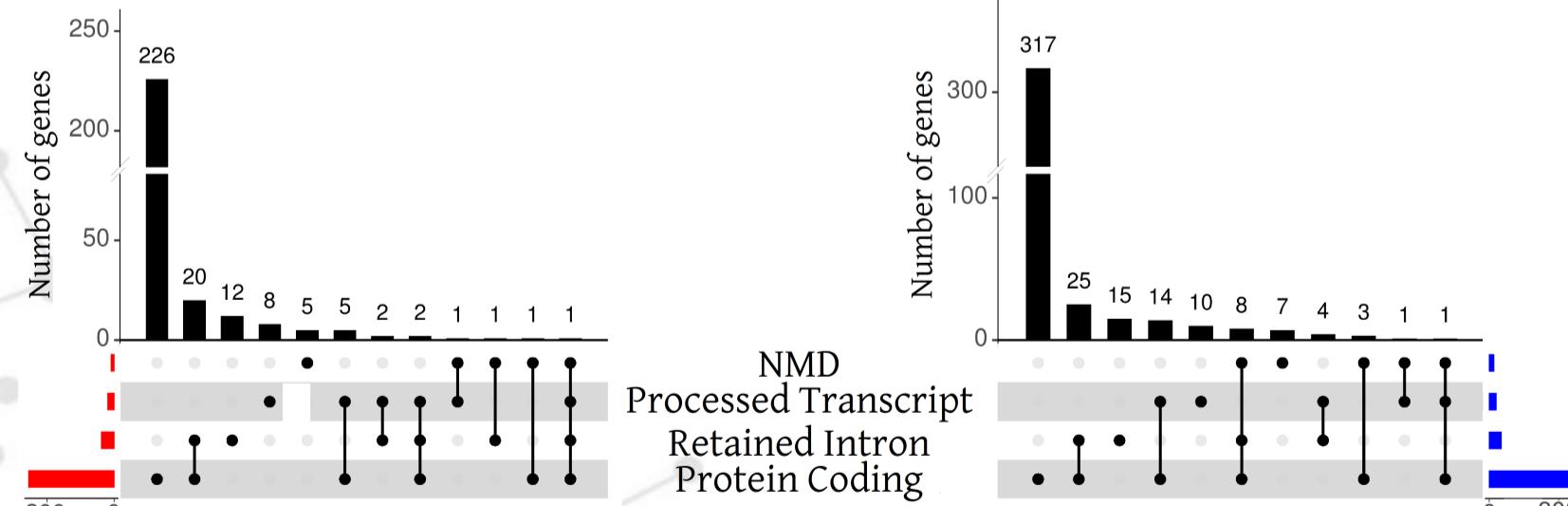
## METHODS



**Fig.1.** RNA-Seq reads from mice kidney were obtained from data available in GEO (GSE69652 and GSE106993). The raw reads quality was evaluated using FastQC and the transcripts were quantified with kallisto v0.43.1 using the reference mouse transcriptome release M20 (GRCm38). After, transcript differential expression analysis was conducted individually for Data A and Data B with sleuth v0.30.0. The GO enrichment terms for differentially expressed transcripts (DET), shared by Data A and Data B, were done with topGO v2.36.0.

## RESULTS

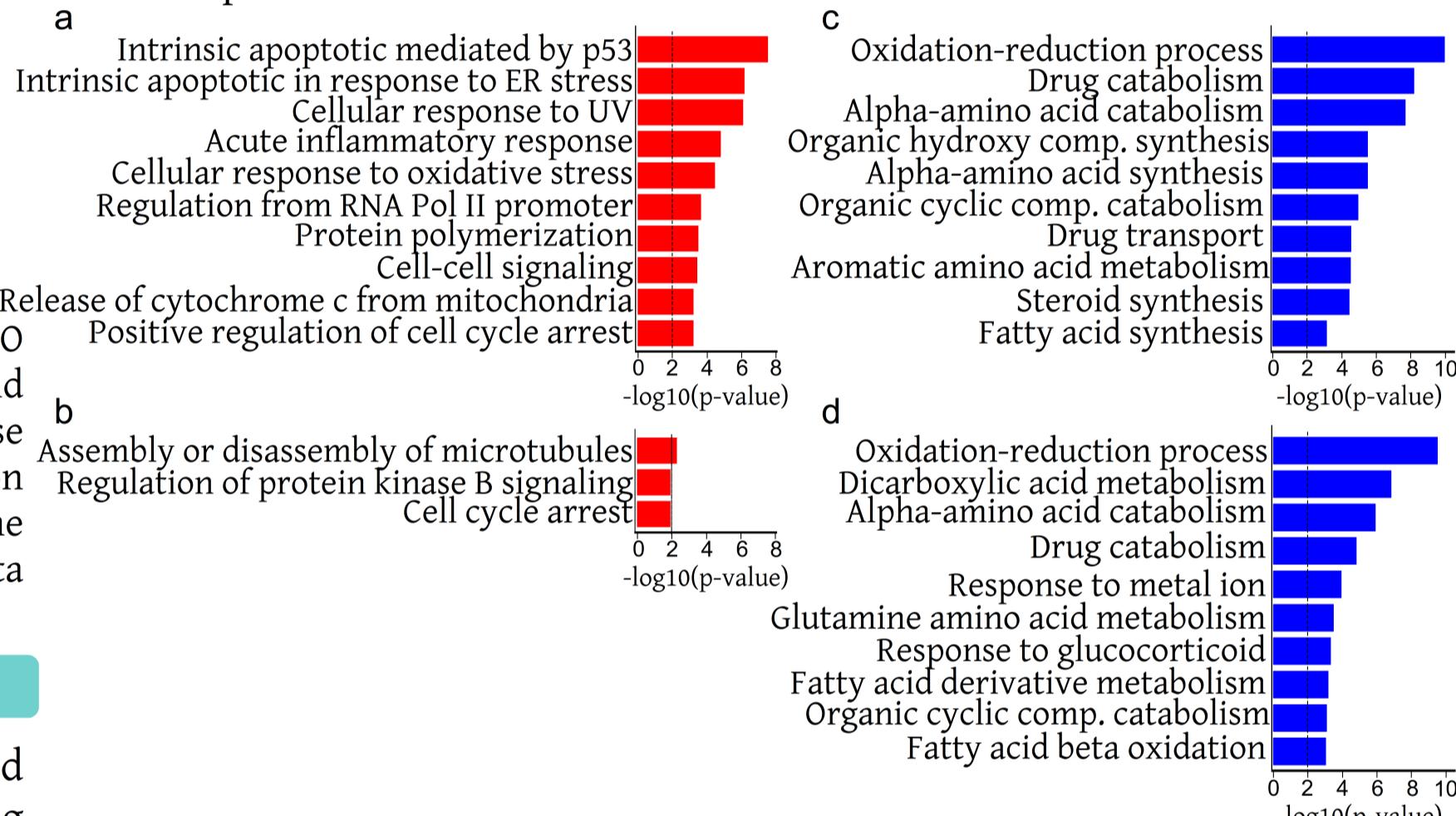
Data A and Data B showed 404 upregulated and 637 downregulated transcripts in common. After separate common DET into groups according to their coding protein potential, the protein-coding (PC) was revealed as the largest group of transcripts and the non-coding (NC) the smallest. Despite the greater number of PC transcripts, many PC genes are transcribed in their NC isoform (Fig.2).



**Fig.2.** Distribution of protein-coding genes in transcripts biotypes. Upregulated transcripts in left panel and downregulated transcripts in right panel. Values above the black bars represent the number of genes contained in the categories of transcripts marked by a black dot.

## ACKNOWLEDGMENT

For upregulated PC transcripts, we identified an enrichment in the process of cellular response to DNA damage, especially related to apoptosis by intrinsic pathways. For downregulated genes, enriched processes were related to cellular basal metabolism, such as amino acid and fatty acid metabolism (Fig 3). In addition to PC transcripts, the lncRNA-p21 and the NC transcripts isoforms from Mdm2 PC gene were upregulated and they seem to be involved in maintaining apoptosis. Among the downregulated genes that constitute the drug catabolic process are the genes of the cytochrome P450 subfamily CYP2J. As cisplatin is not metabolized by these enzymes and they are involved in arachidonic acid (AA) metabolism, our results indicate that the metabolism of this acid may be impaired in the kidneys due to treatment with cisplatin.



**Fig.3.** Enriched biological processes among genes that originated DET (a) upregulated PC transcripts, (b) upregulated NC isoforms from PC genes, (c) downregulated PC transcripts, (d) downregulated NC isoforms from PC genes. Black dotted line refers to  $p = 0.01$ .

## CONCLUSION

Cisplatin represses the negative control of apoptosis by favoring the expression of NC transcripts of the Mdm2 and to induce the expression of lncRNA-p21, which is capable of inhibiting the activity of the MDM2 protein. The epoxyeicosatrienoic acids (EET) are able to inhibit apoptosis and genes responsible for metabolizing AA in EET were downregulated by cisplatin. Then, re-establish the expression of these genes is a possible therapeutic target to attenuate cisplatin-induced nephrotoxicity.

## REFERENCES

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