Functional and transcriptomic characterization of cisplatin-resistant AGS and MKN-28 gastric cancer cell lines

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Gastric cancer (GC) is a significant cancer-related cause of death worldwide. The most used chemotherapeutic regimen in GC is based on platinum drugs such as cisplatin (CDDP). However, CDDP resistance reduces advanced GC survival. In vitro drug-resistant cell model would help in the understanding of molecular mechanisms underlying this drugresistance phenomenon. The aim of this study was to characterize new models of CDDPresistant GC cell lines (AGS R-CDDP and MKN-28 R-CDDP) obtained through a stepwise increasing drug doses method, in order to understand the molecular mechanisms underlying chemoresistance as well as identify new therapeutic targets for the treatment of GC. Cell viability assays, cell death assays and the expression of resistance molecular markers confirmed that AGS R-CDDP and MKN-28 R-CDDP are reliable CDDP-resistant models. RNAseq and bioinformatics analyses identified a total of 189 DEGs, including 178 up-regulated genes and 11 down-regulated genes, associated mainly to molecular functions involved in CDDP-resistance. DEGs were enriched in 23 metabolic pathways, among which the most enriched was the inflammation mediated by chemokine and cytokine signaling

pathway. Finally, the higher mRNA expression of SERPINA1, BTC and CCL5, three up-regulated DEGs associated to CDDP resistance found by RNA-seq analysis was confirmed. In summary, this study showed that AGS R-CDDP and MKN-28 R-CDDP are reliable models of CDDP resistance because resemble many of resistant phenotype in GC, being also useful to assess potential therapeutic targets for the treatment of gastric cancers resistant to CDDP. In addition, we identified several DEGs associated with molecular functions such as binding, catalytic activity, transcription regulator activity and transporter activity, as well as signaling pathways associated with inflammation process, which could be involved in the development of CDDP resistance in GC. Further studies are necessary to clarify the role of inflammatory processes in GC resistant to CDDP and these models could be useful for these purposes.