ID: 00960
Type: Poster
Topic: Tumor treatment

Resistance mechanisms to oxaliplatin in metastatic colorectal cancer and the importance of the molecular scenario.

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MOTIVATION: Metastatic colorectal cancer (mCRC) is diagnosed in the 25% of the patients and has a critical prognosis with a 5-year survival rate of less than 10%. One of the first-line treatment widely used in mCRC is based on the combination of oxaliplatin and fluoropyrimidines, but about 50% of patients show innate or acquired resistance[1]. Therefore, it is of capital importance to identify genes and mechanisms involved in this resistance that allow us to discriminate mCRC patients which could obtain a great benefit from these therapies. On the other hand, CRC is not only heterogeneous to the drug response, but also at molecular features. This heterogeneity has been collected inside the Consensus Molecular Subtypes (CMS). Colorectal tumors can be classified into four Consensus Molecular Subtypes (CMSs); Immune (CMS1), Canonical (CMS2), Metabolic (CMS3) and Mesenchymal (CMS4), which present different clinical, molecular, functional and immune patterns[2].

AIM: The aim of our study was to assess if the genes and molecular pathways that are differentially expressed between responders and non responders to oxaliplatin in mCRC depends on the CMSs.

METHODS: We analyzed gene-expression profile from 86 mCRC tumors using RNA-sequencing by Nextpresso RNA-seq pipeline[3]. The samples were classified into CMS groups by CMSclassifier R package. Genset enrichment analysis (GSEA) was performed with 0.05 FDR threshold.

RESULTS: We observed that 55 genes were differentially expressed (FDR < 0.05) between all responders and non responders. Only 3 of these genes appeared in the same analysis considered CMS3 tumors (62 genes), 4 in CMS4 tumors (14 genes) and not one in CMS2 tumors (80 genes). In addition to that, 6 genes were differentially expressed both in CMS2 and CMS3 tumors. We also applied a GSEA preranked analysis in order to obtain functional differences between both phenotypes. We saw that

oxidative phosphorylation, ribosome and adipogenesis gensets were enriched in all responder patients, while TNFα signaling via NFκ-B, inflammatory response, interferon gamma response, E2F targets, G2M checkpoint and EMT gensets were enriched in all no responder patients. Surprisingly, EMT genset appeared more enriched in CMS2 responders, while E2F targets and G2M checkpoints appeared more enriched in CMS2 and CMS3 non responders. Furthermore, Ribosome and Interferon gamma response gensets were enriched in CMS3 responders. In CMS4 oxidative phosphorylation genset was more enriched in responder patients and TNFα signaling via NFκ-B, inflammatory response, interferon gamma response and EMT gensets were enriched in non responders.

CONCLUSIONS: We have applied a bioinformatic approach to study differential expression and functional patterns between responders and non responders to oxaliplatin. We found that differences in genes expression and gensets enrichment are not the same in all CMSs. These findings show the relevance of molecular scenario in the resistance mechanisms to oxaliplatin in mCRC patients, that should be considered in future studies of predictive biomarker genes response.

References

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