TOPIC

INNOVATIVE THERAPIES

In Silico analysis to identify the core genes implicated in colorectal cancer radiation resistance

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Introduction

The knowledge of the core genes and protein biomarkers of resistance to radiotherapy can help radiation oncology professionals to carry out a more individualized approach and avoid the morbidity caused by irradiation in healthy tissues. New research is focused on the search for core genes/proteins with the purpose of finding new therapeutic targets, combating resistance to treatments and obtaining a better prognosis.

Objectives

The aim of this work is the identification of key genes implicated in radiation resistance of colorectal cancer to be used as biomarkers.

Methods

Genes implicated in radiation resistance were obtained after data mining in Pubmed. Then, an In-Silico analysis were preformed using the following bioinformatics tools: cluster identification analysis with Metascape, gene ontology (GO) enrichment and Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathways with GeneCodis, and the REACTOME study was made in the Reactome database. In addition, a protein-protein interaction study was made with the Search Tool for the Retrieval of Interacting Genes (STRING) and with the STITCH databases.

Results

Data mining performed found 21 genes involved in radiation resistance mechanisms in colorectal cancer. The in-Silico analysis allowed the identification of the core genes. The gene interaction analysis performed showed a network where 13 clusters were identified, ordered by their statistical significance (hypergeometric test). Among them, the highest statistical probability was to EGFR tyrosine kinase inhibitor resistance cluster ($p<1.91\times10^{-11}$), followed by extracellular vesicles in the crosstalk of cardiac cells ($p<1.26\times10^{-9}$), EGF/EGFR signaling pathway ($p<1.48\times10^{-9}$), androgen receptor network in prostate cancer ($p<1.45\times10^{-8}$) and regulation of mitotic cell cycle ($p<5.62\times10^{-8}$).

The GO enrichment analysis showed the involvement of 13 biological processes, 13 cellular components, 9 molecular functions and 25 KEGG pathways; all with a *p*-value <0.01 (hypergeometric test). The protein phosphorylation and negative regulation of apoptotic process stood out with greater statistical significance as biological processes; the cell nucleus as the cellular component; the identical protein binding as the most significant molecular function; and the KEGG pathways: FoxO signaling pathway, prostate cancer, and EGFR tyrosine kinase inhibitor resistance as the most enriched and significant pathways. The evaluation of the genes involved in this enrichment process showed that only 12 genes appear in the KEGG pathways analysis.

The REACTOME analysis showed that these genes were involved in developmental biology, immune system, cell cycle, programmed cell death, DNA repair, signal transduction, disease, metabolism of proteins, cellular responses to stimuli, and gene expression (transcription), $p<0.05$ (hypergeometric test).

The interaction analysis between the 12 proteins identified after GO enrichment showed the categorization in a single cluster related to gastric cancer (CL:4867) (false discovery rate: 0.0091). In this cluster only the BIRC5, AURKA and PLK1 proteins were found (Fig. 2E). The analysis of interactions with STITCH identified the BIRC5 protein in the colorectal cancer (ID 05210) KEGG pathway. The three proteins of the STRING cluster showed multiple interactions between them in the STITCH analysis. These proteins constitute the core proteins of all those previously described related to radiation resistance in colorectal cancer.

Conclusions

Twenty-one proteins have been identified that act with different molecular mechanisms and that, to a greater or lesser extent, induce radiation resistance in colorectal cancer cells that overexpress them. The in-silico study showed that AURKA, BIRC5 and PLK1 constitute the core proteins of that group.