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Deciphering pharmacological targets via computational analysis for drug repositioning in treating 5-FU-resistant colorectal cancer

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Abstract

Colorectal cancer (CRC) is a globally prevalent and deadly disease, with its treatment primarily relying on cytotoxic drugs, notably 5-fluorouracil (5-FU). However, the development of resistance to these treatments and tumor recurrence is a common phenomenon. Drug repositioning seeks to uncover new drug uses, both repurposing existing ones and considering new compounds. Employing genetic signatures, computational drug repositioning predicts drug interactions within disease pathways. Here, we employ public gene expression data to identify potential drugs for treating recurrent CRC post 5-FU-based chemotherapy. By analyzing two independent studies, common differentially expressed genes (FDR<0.05 and |logFC|>1) between recurrence-present and -absent patients were selected using non-parametric algorithms. These genes underwent functional enrichment analysis and were matched with a drug repositioning database to pinpoint drugs capable of countering the recurrence-associated expression pattern.

Additionally, through batch effect reduction methods, we constructed a merged gene expression matrix for patients subjected to 5-FU-based chemotherapies. Applying feature selection algorithms, we identified key genes associated with recurrent phenotype and carried out functional enrichment studies.

Both approaches indicated potential involvement of Rho GTPase protein pathway in upregulated instances during tumor recurrence. Immune response-related pathways showed significant downregulation (adjust p-value<0.05). Analyzing promoter regions revealed enrichment of binding sites for Serum Response Factor family and zinc finger proteins within overexpressed genes.

Guided by these insights and drug repositioning database results, we shortlisted compounds for in vitro testing on 5-FU-resistant CRC cells models. Two compounds showed promise and were validated in murine models, revealing reduced tumor growth, resensitization to 5-FU, and fewer lung micrometastases. Among the tested compounds, the RAC1 inhibitor 1A-116 yielded the most significant reversal of resistance.

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RAC1 as a therapeutic target in colorectal cancer

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Background: Colorectal cancer (CRC) is the third most commonly diagnosed type of cancer worldwide. Rac1 is a key member of the Rho GTPases family. It modulates cell adhesion and movement, and is highly expressed in tumors. Researchers are increasingly exploring Rac1 as a potential target for tumor therapy.

The aim of this work was to evaluate the impact of Rac1 in CRC. Given that approximately 30–40% of CRC patients carry a KRAS mutation, we began evaluating the relevance of RAC1 expression in KRAS wild-type/mutated CRCs. We first downloaded the TCGA-COAD dataset and separated patients according to RAC1 expression levels using the "Survminer" package. In turn, we added an additional filter further separating patients according to KRAS gene status. We extended this evaluation for Rac1 guanine nucleotide exchange factors (GEFs).

To continue characterizing the role of Rac1 in CRC, the study aimed to identify genes that exhibited differential expression between patients with high and low RAC1 expression. The analysis was refined by filtering patients based on their KRAS gene status. By identifying these differentially expressed genes, we created a genetic signature for each patient group. These signature genes were then subjected to overrepresentation analysis and gene set enrichment analysis, enabling the identification of key pathways associated with each phenotype.

Results: Differential genes obtained as a result of this study are strongly linked to cellular metabolism, proliferation, amyloid fiber formation and programmed cell death. Moreover, we found that high expression of RAC1 was associated with poor prognosis in patients where KRAS is mutated and that several RAC1 GEFs display different survival patterns depending on the presence of KRAS mutations in their genomes.

Conclusions: All our data allowed us to postulate that targeting Rac1 represents a promising approach for developing novel therapies for CRC patients, particularly those with mutated KRAS gene.

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A workflow integrating R/Bioconductor, GSEA, and TIMER 2.0 to explore the role of the Vav protein family in cutaneous melanoma

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Abstract

Vav proteins are RHO guanine nucleotide exchange factors (GEFs). This family consists of three members, which typically exhibit functional redundancy and are associated with proactive functions in cancer. However, their role in melanoma remains largely unexplored.

Our aim was to establish a systematic approach, utilizing bioinformatic techniques, to investigate the role of each member of the Vav family in melanoma.

Gene expression data from cutaneous melanoma patients were obtained from the 'Cancer Genome Atlas' database. Raw counts were subsequently normalized to counts per million (CPM) using the 'edgeR' package. The patient cohort (n=460) was stratified based on high or low expression levels of VAV1, VAV2, and VAV3. Survival plots were generated using the Kaplan-Meier estimator and 'survminer' package. The log-rank test revealed an association between high VAV2 expression and poorer prognosis, whereas elevated VAV1 and VAV3 expressions correlated with increased patient survival probability ($p<0.05$ in each case).

Gene set enrichment analysis was conducted for each comparison group using the GSEA software. To assess immune and stromal cell infiltration in tumor tissues, Immune Score and Microenvironment Score were calculated based on gene expression profiles of the tumor microenvironment, employing the ESTIMATE and xCell algorithms. Both Scores showed a strong and positive association with VAV1 and VAV3 expressions ($p<0.001$). Then, using eight different algorithms, with the 'estimate' package and the TIMER2.0 application, correlation with some cell types was evaluated. A robust positive correlation was identified between VAV1 expression and some types of immune cell signatures ($p<0.001$). Conversely, no significant correlation was observed between VAV2 or VAV3 expression and cell types.

Our findings suggest that a favorable prognosis in melanoma is linked to elevated expressions of VAV1 and VAV3, coupled with reduced VAV2 expression. This prognosis may arise from Vav1's impact on intercellular communication within the tumor microenvironment, while heightened VAV3 expression could regulate the activation of tumor cell signaling pathways, thereby promoting greater immunogenicity.

Our study presents a comprehensive pipeline that could serve to explore the implications of other proteins in diverse disease.