Background: Mouse syngeneic models are widely used to study tumor-immune interactions and evaluate the efficacy of immunotherapies. Multiomics biomarker analysis is a powerful approach that integrates different types of biological data, such as genomics, transcriptomics, proteomics, and metabolomics, to identify and validate biomarkers for a variety of diseases, such as cancer. By combining multiple layers of information, multiomics biomarker analysis can reveal more comprehensive and accurate insights into the molecular mechanisms and pathways underlying disease development and progression, as well as the response/resistance to treatment and prognosis. This poster presents the results of a multiomics biomarker analysis in 12 mouse syngeneic models. The aim of this analysis was to identify potential biomarkers and targets for immunotherapy.

Methods: The study involved a multiomics approach to identify potential biomarkers for immunotherapy response in 12 widely used mouse syngeneic models (e.g., CT26, MC38, EMT6, Pan02...). Transcriptomics, proteomics, and phosphoproteomics analyses were performed on these models, and their responses to three immune checkpoint inhibitors (ICI, including anti-PD-1, anti-PD-L1, and anti-CTLA4) were evaluated using two metrics: tumor growth inhibition (TGI) and median area under the curve ratio (median AUC ratio). A variety of statistical and computational methods were applied, such as correlation analysis, differential expression analysis, pathway analysis, co-expression network analysis, and integrative OMICs analysis, to explore the associations between molecular features and drug efficacy.

Results: The results showed that ICI treatments were more effective in hot tumors, which were characterized by high levels of antigen presentation, inflammation, and cytolytic T-cell activity in the tumor microenvironment (TME). Conversely, tumors with elevated oxidative phosphorylation activity or tumors with cold TME exhibited resistance to ICI treatment. Dnmt3a was identified as a resistance biomarker through multiomics analysis, which corroborated the role of Dnmt3a-mediated de novo DNA methylation in limiting the ICI treatment efficacy. Furthermore, multiomics factor analysis (MOFA) was applied and identified a common factor (Factor 1) that was associated with the responses to all three ICI treatments. The genes/proteins with high factor 1 scores were enriched in pathways related to interferon gamma/alpha response, JAK-STAT signaling, and complement activation.

Conclusions: Proteomics data is largely consistent with mRNA expression data, and for some genes, it can amplify the mRNA signal and therefore better correlate with drug efficacy. Multiomics analysis can integrate different types of data, such as gene expression, protein expression, mutation, and methylation, to identify more robust biomarkers that are consistent across multiple levels of biological information, potentially redefining precision medicine.

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