Abstract:
Targeted therapies specifically act by blocking the activity of genes that are critical for tumorigenesis. However, most cancers acquire resistance and long-term disease control is rarely observed. Knowing the timing of molecular changes responsible for the development of acquired resistance can enable optimization of alterations to patients treatments. Clinically, acquired therapeutic resistance can only be studied at a single time point in resistant tumors. To determine the dynamics of these molecular changes, we obtained high throughput omics data weekly during the development of cetuximab resistance in a head and neck cancer model. Results: An unsupervised algorithm, CoGAPS, quantified the evolving transcriptional and epigenetic changes. Further applying a PatternMarker statistic to the results from CoGAPS enabled novel heatmap-based visualization of the dynamics in these time-course omics data. We demonstrate that transcriptional changes resulted from immediate therapeutic response and resistance whereas epigenetic alterations only occurred with resistance. Integrated analysis demonstrated delayed onset of changes in DNA methylation relative to transcription, suggesting that resistance was stabilized epigenetically. Conclusions: Genes with epigenetic alterations associated with resistance that had concordant expression changes were hypothesized to stabilize resistance. These genes include FGFR1, which was associated with EGFR inhibitor resistance previously. Thus, integrated omics analysis distinguishes the timing of molecular drivers of resistance. Our findings are a relevant step into the better understanding of the time course progression of changes resulting in acquired resistance to targeted therapies. This is an important contribution to the development of alternative treatment strategies that would introduce new drugs before the resistant phenotype develops.