Landscape of alternative splicing characterizes the epithelial-mesenchymal transition subtype of gastric cancer

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Abstract

Alternative splicing (AS) has been known to play roles in the tumorigenesis, progression, and metastasis of gastric cancer. However, the landscape pattern of AS and its molecular characteristics in gastric cancer has not been comprehensively investigated yet. Using RNA-Seq data for paired gastric tumor and corresponding normal gastric mucosa of 83 gastric cancer patients, we observed 8 robust AS events that were differentially regulated between tumor and normal tissues and showed variable amount of differential AS across patients. Based on the differential exon usage of these 8 differential AS events, we then developed a patient classification scheme that divided patients into three groups. Molecular characterization using gene set enrichment analysis revealed roles of epithelial-mesenchymal transition (EMT) process in patient classification. Next, we investigated splicing regulators that had binding sites statistically enriched and were differentially expressed between epithelial and mesenchymal subgroups, which identified three RNA-binding proteins. Our patient stratification scheme was validated in independent cohorts of gastric cancer patients. The mesenchymal subtype was associated with the EMT subtype of the ACRG cohort and with the genomically stable (GS) subtype of the TCGA cohort, and the expression of three RBPs was significantly different with other subtypes in those data sets as well. Our study provides a novel patient classification scheme based on AS and highlights possible roles of AS on the EMT process in gastric cancer.

Keyword: Alternative splicing, Gastric cancer, Epithelial-mesenchymal transition, Patient classification