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Sex-specific differences in DNA methylation defining prognostically relevant subgroups in glioblastoma

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Abstract

Objective: Glioblastoma is an aggressive brain tumor that is more common and has a worse outcome in males. Recently, the observed sex differences have been linked to tumor biology, prominently highlighting fundamental differences in gene expression programs. Here, the authors advance this concept to epigenome-based DNA methylation patterns across primary and recurring glioblastoma.

Methods: The authors leveraged their 614 publicly available DNA methylation datasets comprising 252 female and 362 male patients with glioblastoma. They applied a joint and individual variation explained analysis to explore clusters among tumors in males and females in an unsupervised way. Their prognostic association was explored using Kaplan-Meier analysis and a Cox proportional hazards model. Their findings were validated using The Cancer Genome Atlas (TCGA) dataset.

Results: Clustering of the individual, sex-specific components yielded two distinct clusters in males and females, which were predictive of overall survival in males ($p = 0.0098$). Among differentially regulated genes in males, the 20 most consistently altered genes resulted in a targeted panel, which predicted overall survival in males and females at the first surgery ($p < 0.0001$ and $p = 0.013$) but not at recurrence ($p = 0.3$ and $p = 0.85$, respectively). These findings were validated in TCGA dataset. The authors translated the observed differences in survival to networked pathways prominently highlighting protein metabolism in males and oxidative phosphorylation in females.

Conclusions: In summary, the authors report sex-specific differences in DNA methylation patterns among male and female cases of glioblastoma that converge on a set of 20 genes that have a prognostic impact in both sexes at the first surgery. Sex-specific networks of pathways suggest prominent roles for protein processing and antigen presentation in males and metabolism in females. The study findings provide new insights in sex-specific tumor biology to further improve individual gender-based patient management and estimation of disease prognosis.

Keywords: DNA methylation; gene regulation; glioblastoma; prognosis; sex-specific differences; tumor.