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Sex differences in the molecular profile of adult diffuse glioma are shaped by IDH status and tumor microenvironment

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Abstract

Background: Sex differences in adult diffuse glioma (ADG) are well-established clinically, yet the underlying molecular mechanisms remain inadequately understood. Here, we aim to reveal molecular features and cellular compositions unique to each sex in ADG to comprehend the role of sex in disease etiology.

Methods: We quantified sex differences in transcriptome of ADG using multiple independent glioma patient datasets. Next, we delved into the single-cell landscape to examine sex differences in gene expression and cellular composition. To explore how sex influences disease progression, we analyzed paired samples from primary and recurrent ADG cases, aiming to identify sex-specific differences in molecular and cellular features.

Results: Our analysis revealed that mutations in isocitrate dehydrogenase (IDH) genes and the tumor microenvironment emerged as primary influencers of sex-differential molecular enrichments. In IDHwt tumors, genes in neuronal signaling pathway are found to be enriched in male tumors, while genes in hypoxia and inflammatory response pathways are enriched in female tumors. This pattern was reversed in IDHmut gliomas. We hypothesized that these distinctions could be attributed to heterogeneous cellular composition between sexes. Using single-cell data, we observed distinctive patterns of sex differences in cell states, cell composition and cell-cell interaction in IDHwt and IDHmut tumors separately. Further, by comparing molecular changes in paired primary and recurrent ADG samples, we identified sex-specific differences in molecular characteristics and cellular compositions of recurrent tumors.

Conclusion: Our results provide a comprehensive multi-level characterization of sex differences in ADG, such findings provide novel insights into glioma disease progression in each sex.

Keywords: Adult diffuse Glioma; Glioblastoma; Sex differences.