ABSTRACT

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## Unexplored functions of sex hormones in glioblastoma cancer stem cells.

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Biological sex impacts a wide array of molecular and cellular functions that impact organismal development and can influence disease trajectory in a variety of pathophysiological states. In non-reproductive cancers, epidemiological sex differences have been observed in a series of tumors, and recent work has identified previously unappreciated sex differences in molecular genetics and immune response. However, the extent of these sex differences in terms of drivers of tumor growth and therapeutic response is less clear. In glioblastoma, the most common primary malignant brain tumor, there is a male bias in incidence and outcome, and key genetic and epigenetic differences, as well as differences in immune response driven by immune-suppressive myeloid populations, have recently been revealed. Glioblastoma is a prototypic tumor in which cellular heterogeneity is driven by populations of therapeutically resistant cancer stem cells (CSCs) that underlie tumor growth and recurrence. There is emerging evidence that GBM CSCs may show a sex difference, with male tumor cells showing enhanced self-renewal, but how sex differences impact CSC function is not clear. In this mini-review, we focus on how sex hormones may impact CSCs in GBM and implications for other cancers with a pronounced CSC population. We also explore opportunities to leverage new models to better understand the contribution of sex hormones versus sex chromosomes to CSC function. With the rising interest in sex differences in cancer, there is an immediate need to understand the extent to which sex differences impact tumor growth, including effects on CSC function.



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