Abstract:

Glioblastoma (GBM) is characterized by extensive tumor cell invasion, angiogenesis, and proliferation. We previously established subclones of GBM cells with distinct invasive phenotypes and identified annexin A2 (ANXA2) as an activator of angiogenesis and perivascular invasion. Here, we further explored the role of ANXA2 in regulating phenotypic transition in GBM. We identified oncostatin M receptor (OSMR) as a key ANXA2 target gene in GBM utilizing microarray analysis and hierarchical clustering analysis of the Ivy Glioblastoma Atlas Project and The Cancer Genome Atlas datasets. Overexpression of ANXA2 in GBM cells increased the expression of OSMR and phosphorylated signal transducer and activator of transcription 3 (STAT3) and enhanced cell invasion, angiogenesis, proliferation, and mesenchymal transition. Silencing of OSMR reversed the ANXA2-induced phenotype, and STAT3 knockdown reduced OSMR protein expression. Exposure of GBM cells to hypoxic conditions activated the ANXA2–STAT3–OSMR signaling axis. Mice bearing ANXA2-overexpressing GBM exhibited shorter survival times compared with control tumor-bearing mice, whereas OSMR knockdown increased the survival time and diminished ANXA2-mediated tumor invasion, angiogenesis, and growth. Further, we uncovered a significant relationship between ANXA2 and OSMR expression in clinical

GBM specimens, and demonstrated their correlation with tumor histopathology and patient prognosis. Our results indicate that the ANXA2–STAT3–OSMR axis regulates malignant phenotypic changes and mesenchymal transition in GBM, suggesting that this axis is a promising therapeutic target to treat GBM aggressiveness.

Keywords:

ANXA2, OSMR, invasion, mesenchymal transition, glioblastoma