

## **INHIBITION OF SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3 ACTIVATION SUPPRESSES THE BRAIN METASTASES OF MDA-MB-231-BR CELLS IN NUDE MICE**

**Suyun Huang,<sup>1</sup> Feng-Ju Huang,<sup>2</sup> Ping-Chieh Chou,<sup>1</sup> Raymond Sawaya,<sup>1</sup> and Patricia Steeg<sup>3</sup>**

<sup>1</sup>M. D. Anderson Cancer Center, University of Texas, <sup>2</sup>Burnham Institute, and <sup>3</sup>National Cancer Institute

Brain metastasis is a major cause of morbidity and mortality in patients with breast cancer. The molecular changes that lead to brain metastasis remain poorly understood. In the present study, we found that the level of signal transducer and activator of transcription 3 (Stat3) activation was increased in human brain-metastatic breast cancer cells when compared with that in primary breast cancer cells. To investigate the role of Stat3 activation in brain metastases of breast cancer, we used SOCS-1 (suppressor of cytokine signaling-1) protein to inhibit Stat3 activation in MDA-MB-231BR brain metastatic cells. MDA-MB-231BR cells were transfected with low (2-fold) or high (6-fold) levels of SOCS-1. SOCS-1-overexpressing 231-BR cell lines have decreased levels of phospho-Stat3 but not total Stat3. In vitro, SOCS-1-overexpressing 231-BR cell lines have similar anchorage-dependent growth rates as control transfectants, but anchorage-independent growth of the cells was significantly decreased compared to control transfectants. In vivo, high SOCS-1-overexpressing 231-BR cell lines did not form subcutaneous tumors in nude mice whereas control transfectants formed aggressively growing subcutaneous tumors. Moreover, in a model of brain metastasis, high SOCS-1-overexpressing 231-BR cell lines failed to produce brain metastasis in nude mice, but control transfectants produced brain metastases in all of the mice injected. Mechanistically, overexpression of SOCS-1 significantly inhibited the expression of Stat3 target genes cyclin D1, survivin, and vascular endothelial growth factor genes. These data suggest that inhibition of Stat3 activation by SOCS-1 suppressed brain metastasis of breast cancer. Therefore, Stat3 activation might be a new potential target for therapy of human breast cancer brain metastases.

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