The heparin-related carbohydrate heparan sulphate regulates several cellular functions related to tumorigenesis, including cell proliferation, motility and angiogenesis. HS3ST2, an enzyme mediating 3-O sulfation to heparan sulfate is silenced by hypermethylation in breast cancer, suggesting a role in molecular pathogenesis. To uncover its molecular role, we used stably transfected a HS3ST2 expression plasmid into the human breast cancer cell lines MDA-MB-231 and MCF-7. In vitro, HS3ST2-transfected MCF-7 cells became less invasive while the triple-negative MDA-MB-231 cell line showed a highly significant increase in invasiveness and motility. Increased invasiveness was accompanied by significantly increased expression of several matrix metalloproteinases, cadherin 11 and E-cadherin. Also, increased basal and FGF-specific signalling through the p44/42 MAPK pathway is observed in MDA-MB-231 and this increased activation of MAPK was accompanied by a significantly increased expression of the transcription factor TCF4 (Tcf7-L2) and ß-catenin. Both cell lines became sensitive to chemotherapeutic drugs, due to dysregulated ion transporter expression. MAPK inhibition with a MEK1/2 inhibitor downregulated the expression of TCF-4 and also reduced invasion in MDA-MB-231 cells, providing a clue that increased MAPK signalling also plays a role in the invasion having a cross talk with Wnt pathway.

This study provides the first in vitro evidence of the involvement of HS3ST2 in breast cancer cell invasion. These results highlight that increased invasion of MDA-MB-231 cells is due to increased MAPK and Wnt signaling corresponding to increased expression of proteases upon HS3ST2 reexpression, thus marking as a future target for personalized therapy.