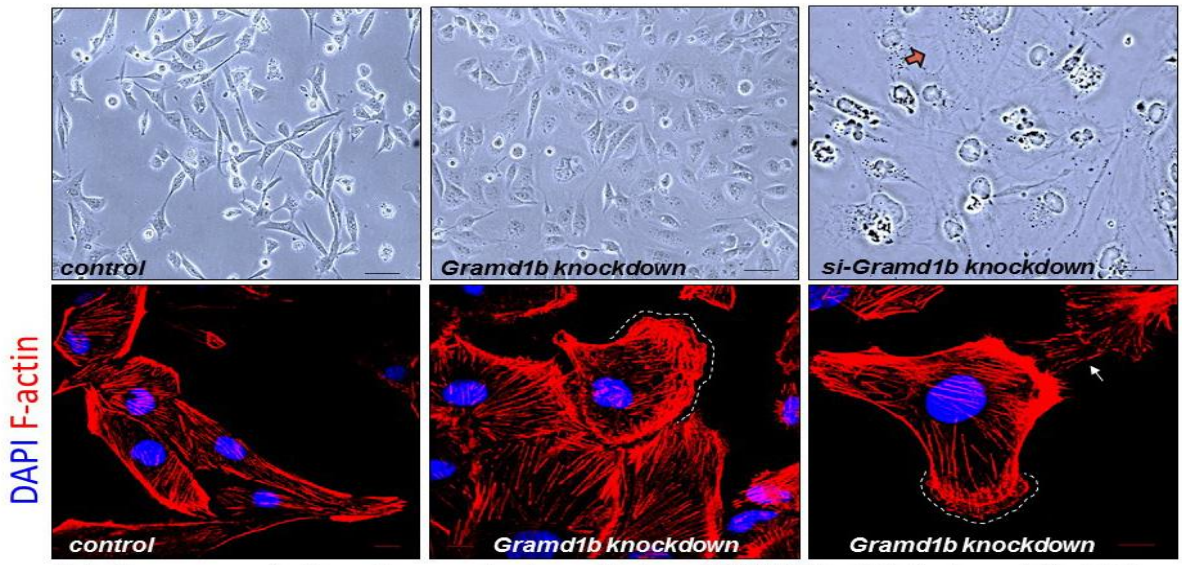
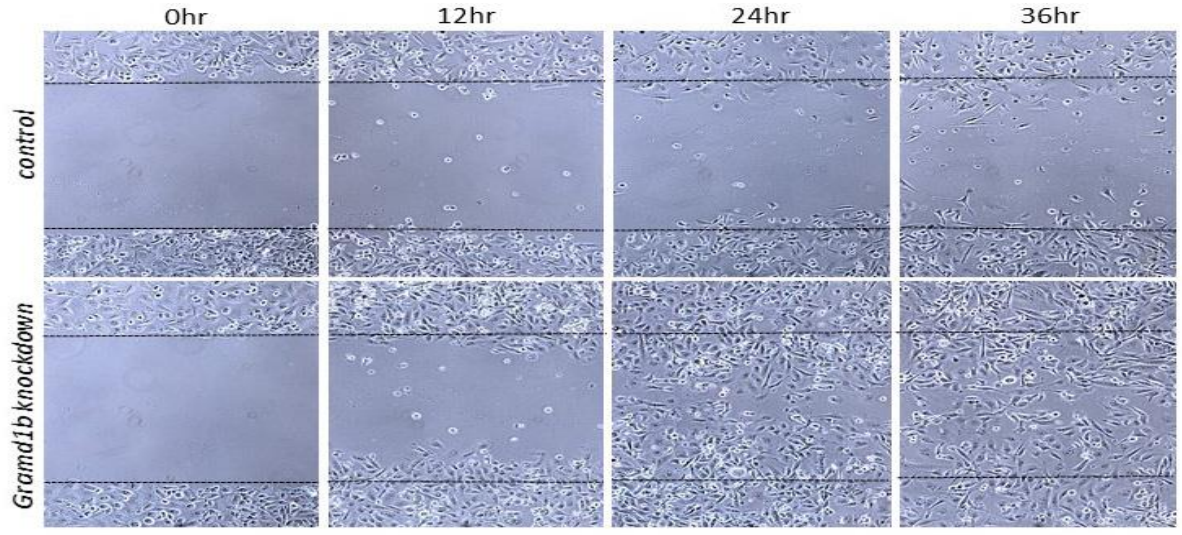
GRAMD1B regulates cell migration in breast cancer cells through JAK/STAT and Akt signaling

Khanna *et al*., 2018 Scientific Reports

Aberrant JAK/STAT signaling activation is implicated in breast cancer metastasis, which is associated with high relapse risks. However, mechanisms underlying JAK/STAT-mediated breast tumorigenesis are poorly understood. Here, we showed that GRAMD1B expression is upregulated on interleukin (IL)-6 but downregulated upon treatment with the JAK2 inhibitor AG490 in the breast cancer MDA-MB-231 cells. Notably, *Gramd1b* knockdown caused morphological changes of the cells, characterized by the formation of membrane ruffling and protrusions, implicating its role in cell migration. Consistently, GRAMD1B inhibition significantly enhanced cell migration, with an increase in the levels of the Rho family of GTPases. We also found that *Gramd1b* knockdown-mediated pro-migratory phenotype is associated with JAK2/STAT3 and Akt activation, and that JAK2 or Akt inhibition efficiently suppresses the phenotype. Interestingly, AG490 dose-dependently increased p-Akt levels, and our genetic analysis suggested that the effect of JAK/STAT inhibition on p-Akt is *via* the transcriptional regulation of *Gramd1b*. Taken together, our results implicate GRAMD1B as a key signaling molecule that functions to inhibit cell migration in breast cancer by negating both JAK/STAT and Akt signaling, providing the foundation for its development as a novel biomarker in breast cancer.



Note the presence of cell membrane protrusions on the loss of GRAMD1B activity (red arrow). Phalloidin staining of *si-Gramd1b* transfected cells reveals the presence of F-actin-rich membrane protrusions (white arrow), accompanied by membrane ruffle formation (white dashed lines). (Scale bar = 10µm).



Wound healing assay indicates the inhibitory effects of GRAMD1B on cell migration