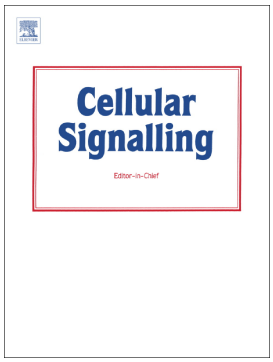

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KiSS1 gene as a novel mediator of TGFβ-mediated cell invasion in triple negative breast cancer

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Abstract

The invasive and metastatic phenotypes of breast cancer correlate with high recurrence rates and poor survival outcomes. Transforming growth factor-β (TGFβ) promotes tumor progression and metastasis in aggressive breast cancer. Here, we identified the kisspeptin KiSS1 as a downstream target of canonical TGFβ/Smad2 pathway in triple negative breast cancer cells. We also found KiSS1 expression to be required for TGFβ-induced cancer cell invasion. Indeed, knockdown expression of KiSS1 blocked TGFβ-mediated cancer cell invasion as well as metalloproteinase (MMP9) expression and activity. Interestingly, Kisspeptin-10 (KP-10), the smallest active form of kisspeptin also stimulates cancer cell invasive behavior through activation of MAPK/Erk pathway. We described a positive feedback loop between KiSS1 and p21 downstream of TGFβ, further contributing to TGFβ-induced cancer cell invasion. Lastly, we explored both the clinical utility of KiSS1 as a lymph node involvement predictive tool and its potential as a therapeutic target. We found KiSS1 high expression to correlate with lymph node positive status. Furthermore, blocking KiSS1 using a specific small peptide antagonist (p234) impaired TGFβ-mediated cell invasion and MMP9 induction. Together, our results define an essential role of KiSS1 in regulating TGFβ pro-invasive effects and define KiSS1 as a therapeutic new target for triple negative breast cancer.

Highlights

1. KiSS1 is a downstream target of the canonical TGFβ/Smad2 pathway in triple negative breast cancer cells.
2. KiSS1 is required for TGFβ-induced cancer cell invasion as well as MMP9 expression and activity.
3. The p234 KiSS1 antagonist blocks TGFβ-dependent invasiveness.
4. High KiSS1 expression is correlated with lymph node positivity.

Key words: triple negative breast cancer, TGFβ, KiSS1, cancer cell invasion, MMP9, lymph node positive, p234 kisspeptin antagonist