Abstract

Background: Triple-negative breast cancer (TNBC) cells are a highly formidable cancer to treat. Nonetheless, by continued investigation into the molecular biology underlying the complex regulation of TNBC cell activity, vulnerabilities can be exposed as potential therapeutic targets at the molecular level. We previously revealed that lysyl oxidase-like 4 (LOXL4) promotes the invasiveness of TNBC cells via cell surface annexin A2 as a novel binding substrate of LOXL4, which promotes the abundant localization of integrin-β1 at the cancer plasma membrane. However, it has yet to be uncovered how the LOXL4-mediated abundance of integrin-β1 hastens the invasive outgrowth of TNBC cells at the molecular level.

Methods: LOXL4-overexpressing stable clones were established from MDA-MB-231 cells and subjected to molecular analyses, real-time qPCR and zymography to clarify their invasiveness, signal transduction, and matrix metalloprotease (MMP) activity, respectively.

Results: Our results show that LOXL4 potently promotes the induction of matrix metalloprotease 9 (MMP9) via activation of nuclear factor-κB (NF-κB). Our molecular analysis revealed that TNF receptor-associated factor 4 (TRAF4) and TGF-β activated kinase 1 (TAK1) were required for the activation of NF-κB through Iκβ kinase kinase (IKKα/β) phosphorylation.

Conclusions: Our results demonstrate that the newly identified LOXL4-mediated axis, integrin-β1-TRAF4-TAK1-IKKα/β-Iκβα-NF-κB-MMP9, is crucial for TNBC cell invasiveness.