Targeting of TGF-β-activated protein kinase 1 inhibits chemokine (C-C motif) receptor 7 expression, tumor growth and metastasis in breast cancer

Hui-Ling Huang[1,*], Chi-Hsiang Chiang[2,*], Wen-Chun Hung[1,2,5], Ming-Feng Hou[3,4,5]

[1]Institute of Biomedical Sciences, National Sun Yat-Sen University, Kaohsiung 804, Taiwan, Republic of China

[2]National Institute of Cancer Research, National Health Research Institutes, Tainan 704, Taiwan, Republic of China

[3]Department of Surgery, College of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan, Republic of China

[4]Department of Surgery, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung 801, Taiwan, Republic of China

[5]Cancer Center, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan, Republic of China

[*]These authors have contributed equally to this work

Correspondence to:
Ming-Feng Hou, **e-mail:** mifeho@kmu.edu.tw
Wen-Chun Hung, **e-mail:** hung1228@nhri.org.tw

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ABSTRACT

TGF-β-activated protein kinase 1 (TAK1) is a critical mediator in inflammation, immune response and cancer development. Our previous study demonstrated that activation of TAK1 increases the expression of chemokine (C-C motif) receptor 7 (CCR7) and promotes lymphatic invasion ability of breast cancer cells. However, the expression and association of activated TAK1 and CCR7 in breast tumor tissues is unknown and the therapeutic effect by targeting TAK1 is also unclear. We showed that activated TAK1 (as indicated by phospho-TAK1) and its binding protein TAB1 are strongly expressed in breast tumor tissues (77% and 74% respectively). In addition, increase of phospho-TAK1 or TAB1 is strongly associated with over-expression of CCR7. TAK1 inhibitor 5Z-7-Oxozeaenol (5Z-O) inhibited TAK1 activity, suppressed downstream signaling pathways including p38, IκB kinase (IKK) and c-Jun N-terminal kinase (JNK) and reduced CCR7 expression in metastatic MDA-MB-231 cells. In addition, 5Z-O repressed NF-κB- and c-JUN-mediated transcription of CCR7 gene. Knockdown of TAB1 attenuated CCR7 expression and tumor growth in an orthotopic animal study. More importantly, lymphatic invasion and lung metastasis were suppressed. Collectively, our results demonstrate that constitutive activation of TAK1 is frequently found in human breast cancer and this kinase is a potential therapeutic target for this cancer.

INTRODUCTION

TGF-β-activated protein kinase 1 (TAK1) was originally identified as a protein kinase which activity is stimulated by TGF-β and bone morphogenetic proteins in a complementation screen [1]. Subsequent studies demonstrated that TAK1 is a key mediator in inflammation and can be activated by many pro-inflammatory cytokines like interleukin-1, tumor necrosis factor-α and Toll-like receptor ligands [2–5]. In addition, TAK1 has been shown to involve in the regulation of innate immunity, kidney fibrosis, cardiac remodeling and tumor pathogenesis [6–11].

In cells, TAK1 forms a multiple protein complex and is bound with its binding partners TAB1, TAB2 and TAB3 [12]. Knockout of TAK1, TAB1 or TAB2 in mice all leads to embryonic lethality indicating its activity is critical for development [13, 14]. TAK1 activity is mainly controlled by post-translation modifications. Phosphorylation of the activation loop of TAK1 induced