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A Key Axis Of The NWASP Signaling Pathway That Plays An Important Role In Distant Metastasis Of Pancreatic Cancer: LOXL2–FAK–NWASP

Hyung Sun KIM[1], Joon Seong PARK*[1], Yun Sun LEE[1]

[1]*SURGERY, Gangnam Severance Hospital, REPUBLIC OF KOREA*

Background : Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive solid malignancies, with median survival of less than one year and overall 5–year overall survival rate of less than 5%. However, specific regulator of PDAC has yet to be established. In the present study, we investigated whether Neural Wiskott–Aldrich Syndrome Protein (N–WASP) plays a role in distant metastasis of PDAC.

Methods : Between June 2002 and December 2012, 81 patients underwent radical curative resection for pancreatic cancer at Gangnam Severance Hospital. Pancreatic cancer cell lines MIA PaCa–2, PANC–1 were used for in vitro and in vivo study. To evaluate the endogenous expression level of N–WASP, we purified the whole RNA and protein to perform the qPCR, RT–PCR and Western blot. And we confirmed the motility and invasiveness of MIA PaCa–2 and PANC–1. By using of pancreatic cancer cell lines, orthotopic mouse model of pancreatic cancer was established.

Results : We found that N–WASP was markedly expressed in PDAC patients. Knockdown of N–WASP in pancreatic cancer cell significantly decreased cell invasion and migration. Using gene expression profile studies, we found that N–WASP is a novel mediator of epithelial–mesenchymal transition (EMT). Knockdown of N–WASP expression with siRNA inhibited cell migration and EMT. We also observed that the lysyl oxidase–like 2 (LOXL2) and focal adhesion kinase (FAK) is associated with the N–WASP–mediated response, thereby modulating EMT and invadopodia. Finally, N–WASP depletion significantly reduced the incidence of liver and lung metastatic lesions in orthotopic mouse models of pancreatic cancer.

Conclusions : These results identify a new role for N–WASP signaling in EMT and invadopodia that regulate their intercellular communication with tumor cells to inhibits pancreatic cancer metastasis.

Corresponding Author : **Joon Seong PARK** (jspark330@yuhs.ac)