Farnesoid X Receptor Promotes Metastasis of Non-Small Cell Lung Cancer by Transcriptionally Activating *MMP-9*

PURPOSE: Non-small cell lung cancer (NSCLC) is a tumor with highly metastasic potential in later stage. Farnesoid X receptor (FXR) has previously been reported to be expressed in human NSCLC specimens. We investigated the functional role of FXR in NSCLC metastasis and its underlying mechanism of action.

METHODS: The expression of FXR in human NSCLC cell lines was evaluated by immunoblotting. The role of FXR in NSCLC motility was examined by using transwell migration and invasion assays *in vitro,* and the promoting effect of FXR on matrix metalloproteinase (MMP)-9 transcription was assessed by using promoter-luciferase reporter analysis.

RESULTS: FXR was relatively highly expressed in human NSCLC H1975 cells, moderately expressed in HCC827 and A549 cells, and lowly expressed in PC9, HCC4006 and H460 cells. Z-guggulsterone-mediated FXR inhibition and small interfering RNA-mediated downregulation of FXR in H1975 resulted in a significantly reduction in cell migration and invasion, whereas overexpression of FXR promoted A549 migration and invasion *in vitro*. ELISA and zymography assays revealed decreased expression and activity of MMP-9 in conditioned medium from Z-guggulsterone-treated or FXR siRNA-tranfected H1975 cells, whereas overexpression of FXR in A549 cells showed the opposite effects. Moreover, the decreased cell motility in Z-guggulsterone-treated or FXR siRNA-tranfected H1975 cells was

attenuated by pretreatment with MMP-9 siRNA. Mechanistically, we identified three seperate FXR response elements in the promoter of *MMP-9* gene and demonstrated a direct promoting effect of FXR in MMP-9 transcription in FXR siRNA-tranfected H1975 and FXR-overexpressed A549 cells.

CONCLUSION: Our results have demonstrated a pivotal role for FXR in NSCLC metastasis and have revealed MMP-9 as the direct FXR target gene contributing to this process. These findings highlight FXR as a novel target for developing antimetastatic agent.