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100%; in the high-dose HNK treatment group, only 2 of 6 mice had lymphatic metastasis. The high-dose HNK also significantly decreased the weight of mediastinal lymph nodes over 80% compared with control group (Fig. 2C).

HNK inhibits metastasis of lung cancer cells to the brain *in vivo*

In this assay, we used an ultrasound-guided procedure to insure the injection of brain-seeking H2030-BrM3 lung cancer cells into the LV of NOD/SCID mice (Fig. 3A). One day after cell inoculation, the mice were randomly grouped to vehicle control and HNK low- (2 mg/kg b.w.) and high-dose (10 mg/kg b.w.) groups. High-dose HNK significantly decreased brain metastasis over 70% when compared with the vehicle control group (Fig. 3B). At necropsy (28 days post-LV injection), the extent of brain metastases was also quantified by *ex vivo* bioluminescence and GFP imaging as shown in Fig. 3C. HNK treatment decreased brain metastasis to approximately one third of that observed in control mice. Lung tumor cell migration to brain was confirmed by H&E staining, as well as GFP staining (Fig. 3D and E). Collectively, our data suggest that HNK could be effective in preventing the metastasis of lung cancer cells to the brain.

STAT3 as a potential target of HNK in the inhibition of lung cancer brain metastasis

Potential mechanisms of action of HNK in the inhibition of lung cancer cell brain metastasis were examined via RTK assays (Fig. 4A). H2030-BrM3 cells were treated with 10 and 20 μmol/L HNK for 6 hours. PathScan RTK signaling array revealed that HNK treatment dramatically decreased STAT3 phosphorylation (Fig. 4B and C), suggesting that STAT3 is at least one molecular target of HNK. The effects of HNK on STAT3 phosphorylation in PC9-BrM3 and H2030-BrM3 cells were confirmed by Western blot analysis (Fig. 4D). Previously, HNK was found to be effective in the treatment of head and neck squamous cell carcinoma (HNSCC) via targeting the EGFR signaling pathway (32). In the current study, we also observed that HNK targets the EGFR–AKT

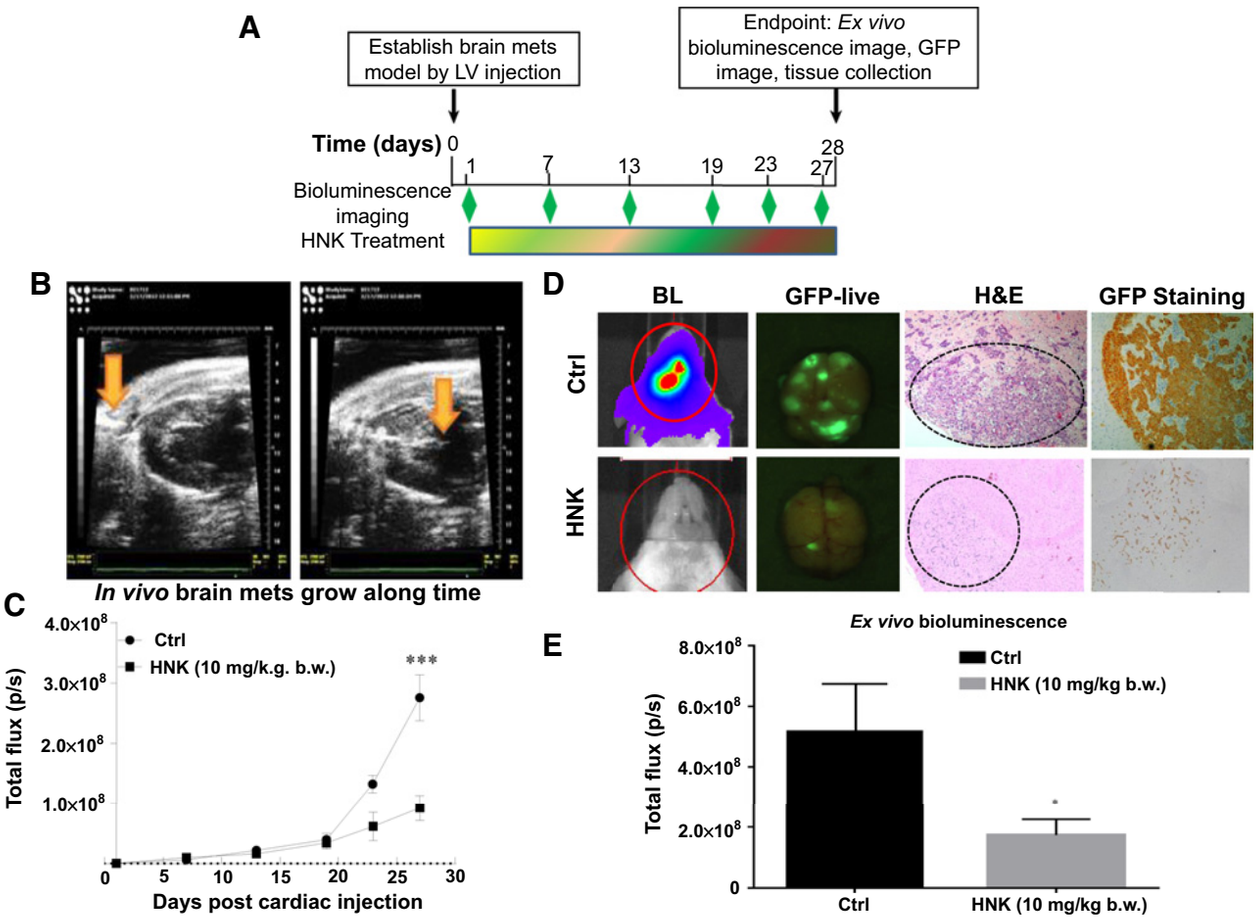

Figure 3.

HNK inhibits lung cancer brain metastasis. **A,** H2030-BrM3 cells expressing GFP and luciferase were engrafted in the arterial circulation by an ultrasound-guided LV injection. Brain metastasis was detected by bioluminescence at different time points with an IVIS 200 Xenogen monitor (Xenogen; exposure time, 1 minute; binning 8; no filter; f/stop16; field of view 12.5 cm). **B,** Corresponding grayscale photographs and color luciferase images are superimposed and analyzed with LivingImage (Xenogen). Mets, metastases. Data are expressed as normalized photon flux (photons/s/cm^2). After final IVIS scan, mouse brain was dissected and imaged using Maestro Multi-Spectral Imaging System for GFP signal. **C,** Quantification of bioluminescence imaging signal intensity in the control (Ctrl) and HNK-treated group at different time points after the injection of H2030-BrM3 cells. Quantified values are shown in total flux. **D,** Representative luciferase, GFP, and H&E IHC images from mice treated with either gavage control (Ctrl) or HNK. **E,** Quantification of bioluminescence imaging signal intensity in the control (Ctrl) and HNK-treated group at the end of study via ex vivo Live Imaging. *, $P < 0.05$; ***, $P < 0.001$.

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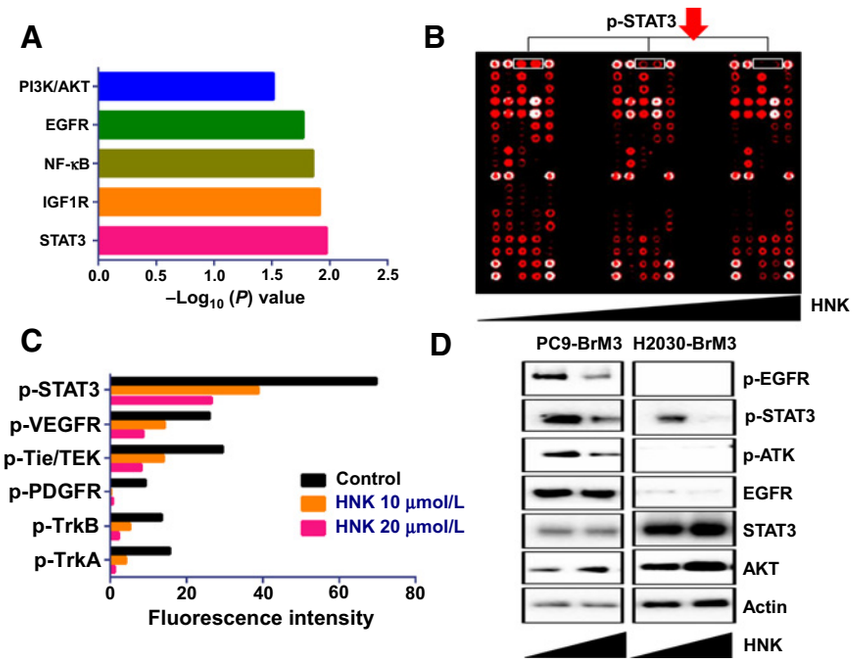

Figure 4.
HNK targets STAT3 phosphorylation via inhibition of multiple RTKs. **A,** Pathway analysis based on RNA-seq revealed that HNK inhibits multiple RTK pathways, including EGFR, as well as the IGF1R and NF-κB, PI3K/AKT, and STAT3 signaling pathway. Notably, STAT3 signaling pathway was the most significantly affected pathway by HNK. **B,** H2030-BrM3 cells were treated with HNK, and cell lysates were examined using RTK signaling arrays. STAT3 phosphorylation is downregulated by HNK in a dose-dependent manner. **C,** Effects of HNK on the phosphorylation of STAT3, as well as other signaling pathways, such as TrkA/B, PDGFR, Tie/TEK, and VEGFR signaling pathways. **D,** The phosphorylation of EGFR and AKT is downregulated by HNK only in the EGFR-mutant PC9-BrM3 cell line, but not in the Kras-mutant H2030-BrM3 cell line. STAT3 phosphorylation is downregulated by HNK in both cell lines.

signaling pathway in PC9-BrM3 cells, which harbor an EGFR mutation, but not in H2030-BrM3 cells, which harbor Kras mutations. In addition, we examined the interaction between HNK and multiple RTKs via the KINOMEScan binding assay. As shown in Supplementary Fig. S1, HNK did not bind directly to any of the RTKs tested.

STAT3 knockdown decreases the anticancer effects of HNK in lung cancer

shRNA knockdown was used to demonstrate the role of STAT3 in mediating the effects of HNK in lung cancer. Knockdown of STAT3 in PC9-BrM3 and H2030-BrM3 cells was validated by Western blot analysis (Fig. 5A). STAT3 knockdown decreases the antiproliferative (Fig. 5B) and antiinvasive (Fig. 5C and D) effects of HNK in both PC9-BrM3 and H2030-BrM3 cell lines. HNK treatment (20 μmol/L) for 48 hours inhibited the proliferation of PC9-BrM3 vector control cells by 30% and H2030-BrM3 vector control cells by 20% but had no significant effect on the proliferation of STAT3 knockdown PC9-BrM3 or H2030-BrM3 cells (Fig. 5B). In addition, HNK treatment (10 μmol/L) significantly inhibited the invasion of both PC9-BrM3 and H2030-BrM3 vector control cells but had no effect on the invasion of STAT3 knockdown PC9-BrM3 or H2030-BrM3 cells (Fig. 5C and D). Finally, we examined the effects of STAT3 on mitochondrial respiratory function in PC9-BrM3 and H2030-BrM3 cells. As shown in Fig. 5E, STAT3 knockdown significantly decreased mitochondrial respiratory function in both PC9-BrM3 and H2030-BrM3 cell lines. The anticancer effects of HNK, therefore, could be through inhibition of STAT3-mediated mitochondrial functions in lung cancer cells that have metastasized to the brain.

RNA-seq analysis showed that the expressions of key genes important to the activation of STAT3 pathway were downregulated in the metastatic lung tumors by HNK treatment

The differentially expressed genes identified by RNA-seq analysis software were subjected to IPA analysis (Ingenuity Pathway Analysis; http://www.ingenuity.com/products/ipa) to identify the most significant oncogenic pathways in metastatic lung tumors changed by HNK treatment. Our genome-wide RNA-seq scan showed that STAT3 pathway is the top downregulated one among the oncogenic pathways that were significantly downregulated in the HNK-treated human lung tumor metastases in mouse brains (Fig. 4A). In addition, RNA-seq analyses identified that six key genes involved in the activation of STAT3 pathways were significantly downregulated in metastatic lung tumors *in vivo* upon HNK treatment (Table 1). They were FGFR4, IGF1R, IGF2R, MAP2K1, MAP3K11, and SRC. These matched the findings from our functional studies and supported that the anti–lung cancer role of HNK was mediated via the STAT3 signaling pathway.

Discussion

One of the common sites for metastases of lung cancers is the brain. Currently available therapies to address CNS metastases include whole brain/CNS irradiation or surgical resection in eligible patients, treatment with anti-EGFR agents in patients whose tumors contain EGFR mutations, as well as using next-generation ALK TKI that is brain-penetrable such as PF-06463922, to control CNS metastases in lung cancer patients (2, 33). However, these treatment options are available only after the diagnoses of brain metastases, and in many cases, metastatic lesions remain undiagnosed for long periods or they are not amenable to treatment with chemo/radiotherapy or surgery. Therefore, it is necessary to develop prevention strategies to inhibit metastases from primary tumors. Recently, we demonstrated the ability of HNK to potently inhibit the development of lung tumors in mice (5). Analysis of HNK's mechanism of action suggests that its effect is primarily mediated by inducing apoptosis through a mitochondria-dependent mechanism (5, 7, 34). Here, through the use of the well-characterized brain metastases murine model, we report that HNK exerts inhibitory effects on the metastasis of lung cancer

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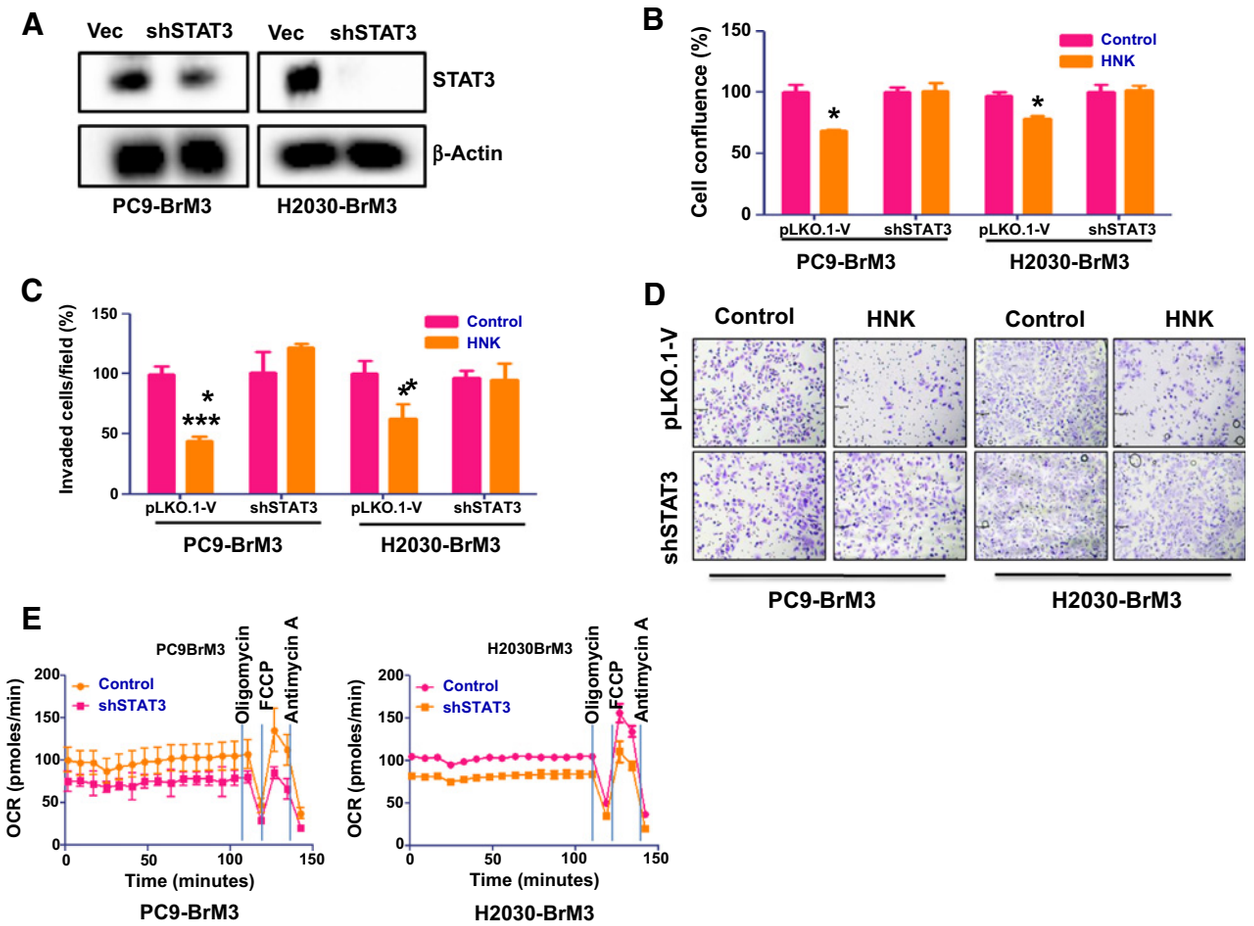

Figure 5.

STAT3 knockdown abrogates the antiproliferative, antimigratory, and anti-invasive effects of HNK. **A,** Efficiency of STAT3 knockdown via shRNA approach in PC9-BrM3 and H2030-BrM3 was determined via Western blot analysis. The role of STAT3 in mediating the antiproliferative and anti-invasive effects was determined as indicated in Material and Methods. STAT3 knockdown abrogates the antiproliferative **(B)** and anti-invasive **(C)** effects of HNK in PC9-BrM3 and H2030-BrM3 cell lines. **D,** Effects of STAT3 in mitochondria respiratory function were examined via Seahorse experiment. STAT3 knockdown decreases the mitochondria respiratory function in both PC9-BrM3 and H2030-BrM3 cells. **E,** Representative images of PC9-BrM3 and H2030-BrM3 control vector–transfected and STAT3 knockdown cells with/without treatment of HNK from invasion assay.

cells to the brain, indicating that the compound has chemopreventive potential against both primary lung tumors and on metastasis of lung cancer to the brain.

Direct injection of tumor cells into the LV is the most widely used brain metastasis model in rodents because it bypasses the precolonization steps of dissemination of cancer cells through the bloodstream, homing, and extravasation, and recapitulates the process of cancer cells crossing the BBB and growing within the brain microenvironment. Metastatic brain lesions in mice vary from round, circumscribed lesions typical of that seen on human scans, to infiltrative tumor cells, which over time form typical round lesions that are ideal for evaluating the preventative effect of HNK on lung cancer metastasis. The brain homing H2030 and PC9 lung cancer cell lines were developed to have 100% brain metastatic potential (5–7, 29–31), H2030 cells with a $KRAS^{G12C}$ mutation (35) and PC9 cell with an $EGFR^{\Delta exon19}$ mutation (36). These cell lines were engineered to stably express GFP–luciferase fusion for real-time monitoring of metastatic tumor growth. In the current study, we monitored metastatic tumor growth using both live animal imaging and endpoint *ex vivo* imaging. We also validated tumor growth by staining the brain tissues with H&E and GFP, and both stains consistently demonstrated about a 70% inhibition of brain metastases by HNK.

At least one of the mechanisms through which HNK inhibited lung cancer cell metastasis to the brain was through the inhibition of STAT3 phosphorylation. HNK is known to target multiple signaling pathways, including EGFR, MAPK, and PI3K/AKT (10–13). Recently, Sirt3 and GRP78 were also suggested as potential binding targets of HNK in different tissue types (34, 37). Interestingly, STAT3 is a major downstream mediator of multiple RTK pathways (14–17). Our data suggest that STAT3 could be a universal downstream target of HNK treatment. As indicated before, HNK was effective in the treatment of HNSCC via targeting the EGFR signaling pathway (38). The brain homing H2030 and PC9 lung cancer cell lines carry different driver mutations, H2030 with a $KRAS^{G12C}$ mutation (35) and PC9 with

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Table 1. Characteristics of the six key genes in the STAT3 pathway that was downregulated in the HNK-treated human lung tumor metastases in mouse brains

Symbol	Entrez gene name	Fold change (HNK vs. non-HNK Mets)	FDR	Location	Type(s)
FGFR4	Fibroblast growth factor receptor 4	−18.5	0.040	Plasma membrane	Kinase
IGF1R	Insulin-like growth factor 1 receptor	−2.3	0.022	Plasma membrane	Transmembrane receptor
IGF2R	Insulin-like growth factor 2 receptor	−1.6	0.012	Plasma membrane	Transmembrane receptor
MAP2K1	Mitogen-activated protein kinase kinase 1	−1.7	0.011	Cytoplasm	Kinase
MAP3K1	Mitogen-activated protein kinase kinase kinase 11	−1.8	0.011	Cytoplasm	Kinase
SRC	SRC proto-oncogene, non-receptor tyrosine kinase	−2.0	0.003	Cytoplasm	Kinase

Abbreviation: Mets, metastases.

an $EGFR^{\Delta exon19}$ mutation (36). In PC9-BrM3 cells, we observed downregulation of phosphorylated EGFR by HNK, but not in H2030-BrM3 cells, which do not carry an EGFR mutation. Therefore, the effects of HNK on the EGFR–AKT signaling pathway could be cell type- or tissue-specific. RNA-seq data suggest that FGFR4 is the most significant gene that was affected by HNK treatment, and FGFR4 is known to mediate STAT3 signaling pathway (39). Therefore, it will be interesting to investigate the role of FGFR4–STAT3 signaling pathway in mediating the anticancer effects of HNK. STAT3 phosphorylation was reduced in both PC9-BrM3 and H2030BrM lung cancer cell lines by HNK, and knockdown of endogenous STAT3 in these cell lines abrogated the antiproliferative, antimigratory, and anti-invasive effects of HNK, further supporting the concept that STAT3 could be a universal downstream target of HNK regardless of EGFR mutation status of lung cancer cells. Although, with prolonged treatment (over 48 h), HNK will eventually inhibit proliferation of STAT3 knockdown cells (data not shown), which most likely would be due to the off-target effects of HNK, considering it is a polyphenol compound, once its main target has been blocked, it may target other pathways to inhibit tumor growth. STAT3 knocked down PC9-BrM3 and H2030-BrM3 cells exhibit significantly less mitochondrial respiratory function than normal lung cells. HNK inhibition of lung cancer progression via inhibition of mitochondrial respiratory function could, therefore, be due to inhibition of STAT3 phosphorylation which, in turn, leads to inhibition of the metastases of lung cancer cells to the brain.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Y. Lee, M. You
Development of methodology: J. Pan, Q. Zhang, T.C. Wan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Pan, Y. Lee, Q. Zhang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Pan, Y. Lee, Q. Zhang, D. Xiong
Writing, review, and/or revision of the manuscript: J. Pan, Y. Lee, Q. Zhang, D. Xiong, Y. Wang, M. You
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Lee, Y. Wang
Study supervision: M. You

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Cancer Prevention Research

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Jing Pan, Yongik Lee, Qi Zhang, et al.

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