

Src acts as the target of matrine to inhibit the proliferation of cancer cells by regulating phosphorylation signaling pathways

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Abstract

Background and Purpose: Identification of accurate targets is essential for a successful development of targeted therapy in cancer. Studies have shown that matrine has antitumor activity against many types of cancers. However, the direct target in cancer cells of its anticancer effect has not been identified. The purpose of this study was to find the molecular target of matrine to inhibit the proliferation of cancer cells and explore its mechanism of action. **Experimental Approach:** The effect of matrine on the proliferation of cancer cells were examined by MTT assay. Pull-down assay and liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) were performed to explore the target of matrine. A series of in vitro and in vivo experiments were conducted to reveal the mechanisms by which matrine targeted Src to regulate the downstream signaling pathways of Src in cancer cells. **Key Results:** Herein we showed that matrine inhibited the proliferation of cancer in vitro and in vivo. Pull-down assay with matrine-amino coupling resins (MA beads) and LC-MS/MS identified Src as the target of matrine. Src kinase domain is required for its interaction with matrine and Ala392 in the kinase domain participated in matrine-Src interaction. Intriguingly, matrine was proven to inhibit Src kinase activity in a non-ATP-competitive manner by blocking the autophosphorylation of Tyr419. Matrine down-regulated the phosphorylation levels of MAPK/ERK, JAK2/STAT3 and PI3K/Akt signaling pathways. **Conclusions and Implications:** Collectively, matrine targeted Src, inhibited kinase activity and down-regulated its downstream MAPK/ERK, JAK2/STAT3 and PI3K/Akt phosphorylation signaling pathways to inhibit the proliferation of cancer cells.

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Fig.1

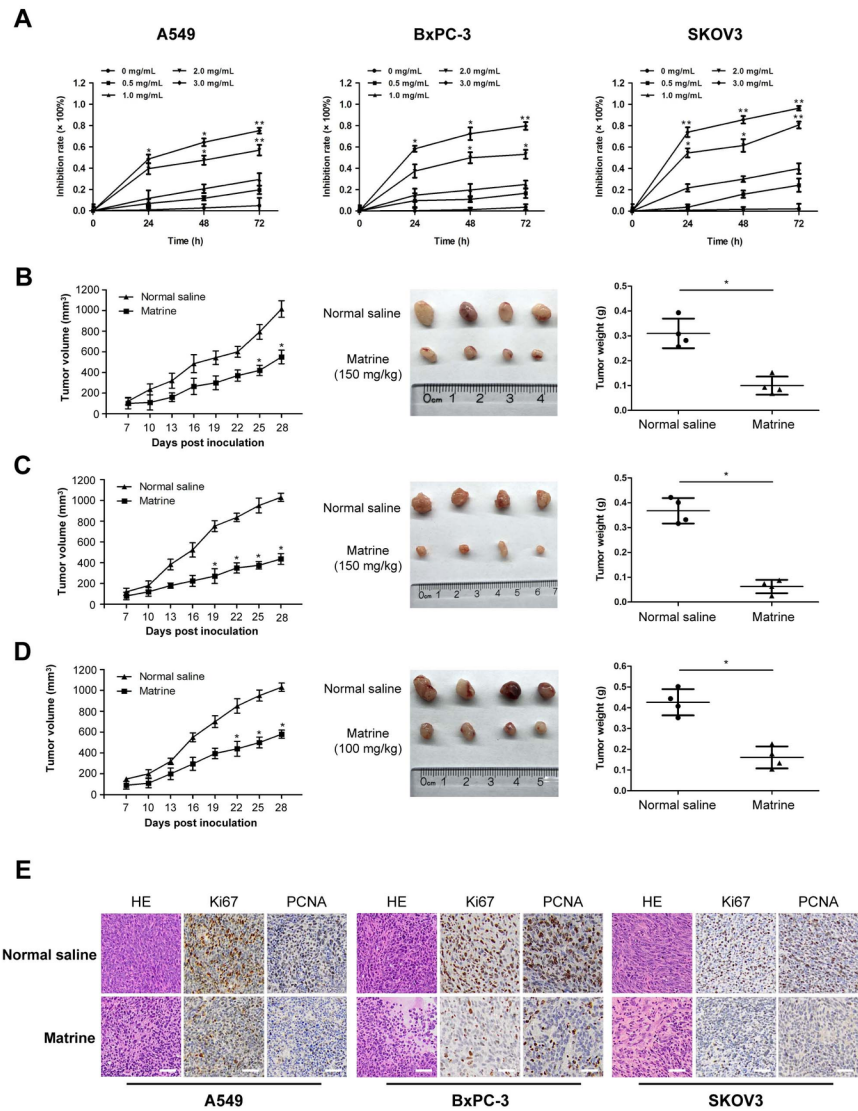
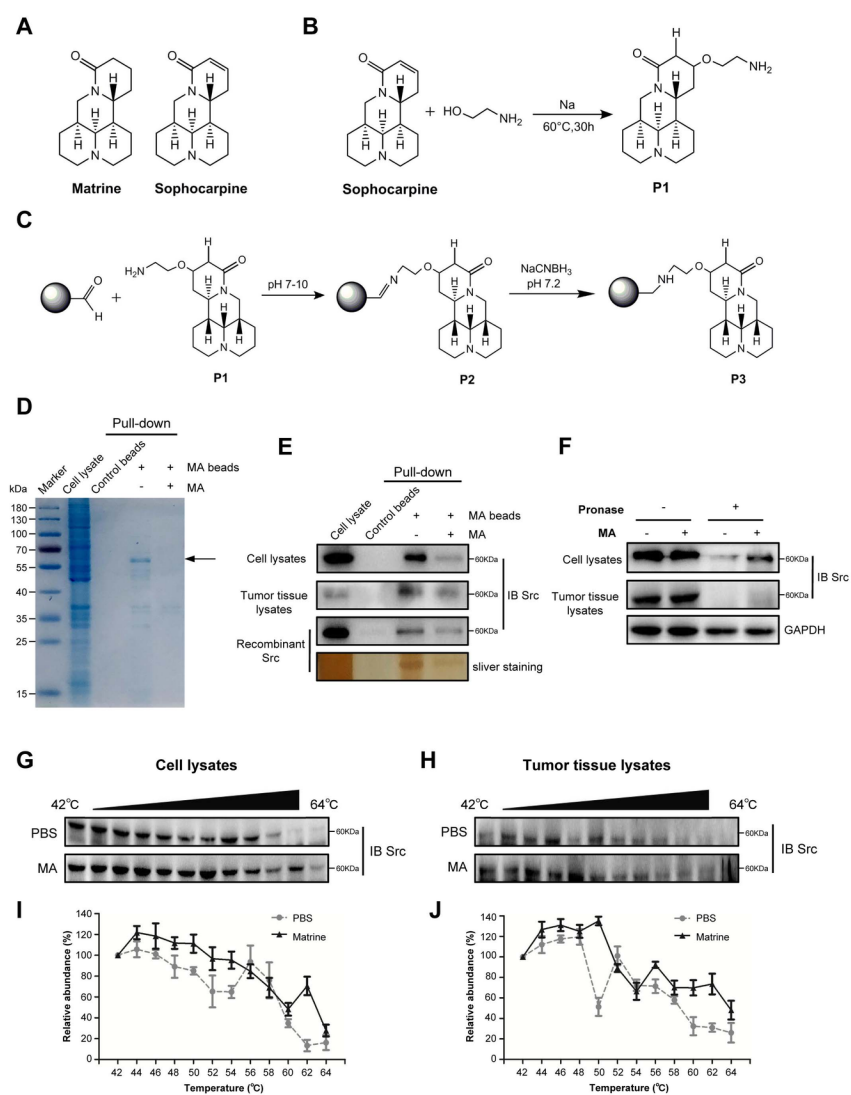
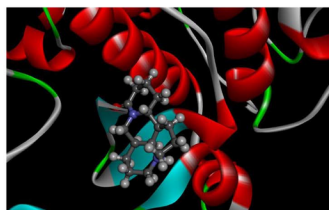


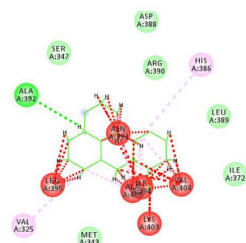
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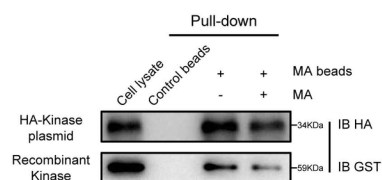
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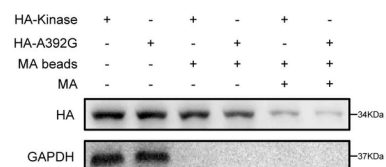
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C



F



G

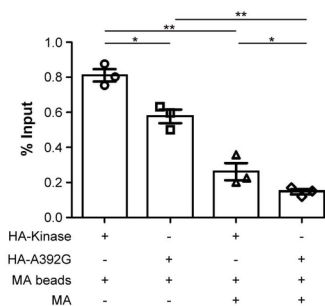


Fig.4

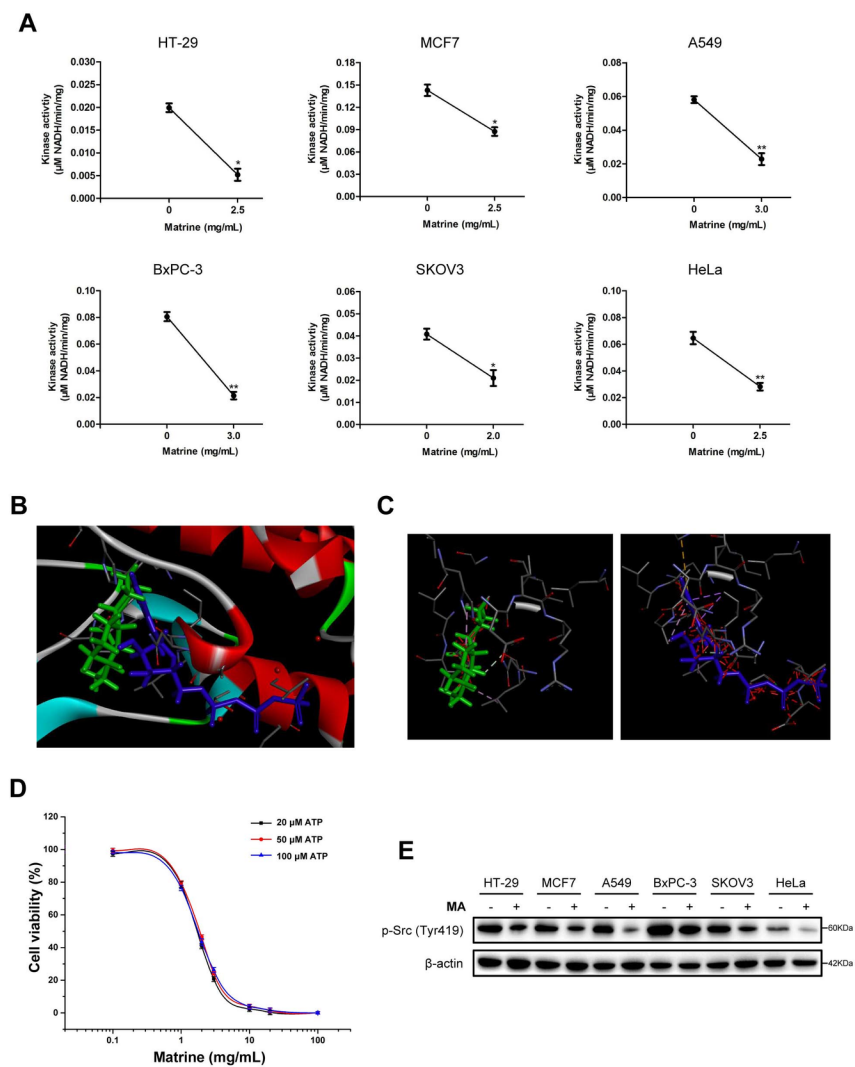


Fig.5

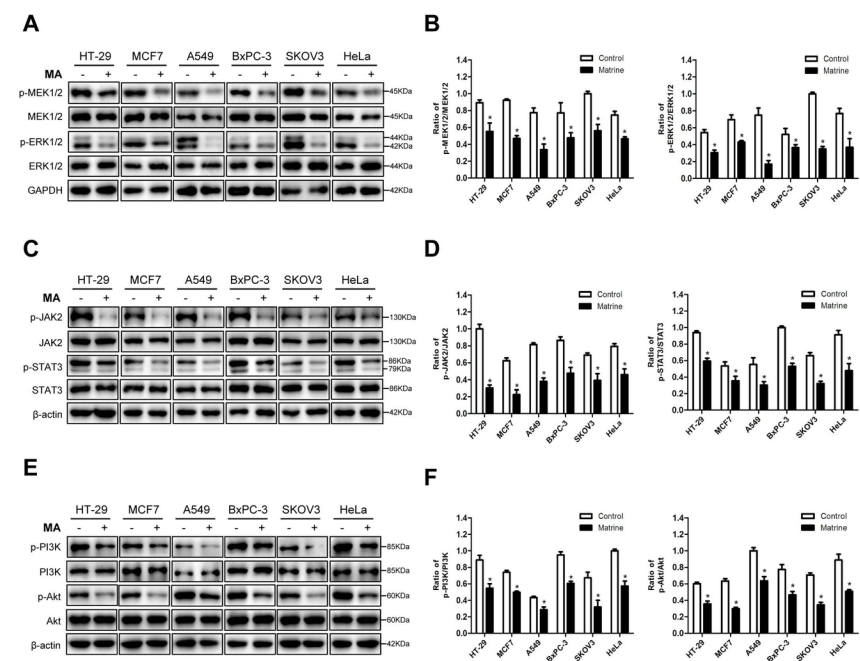


Fig.6

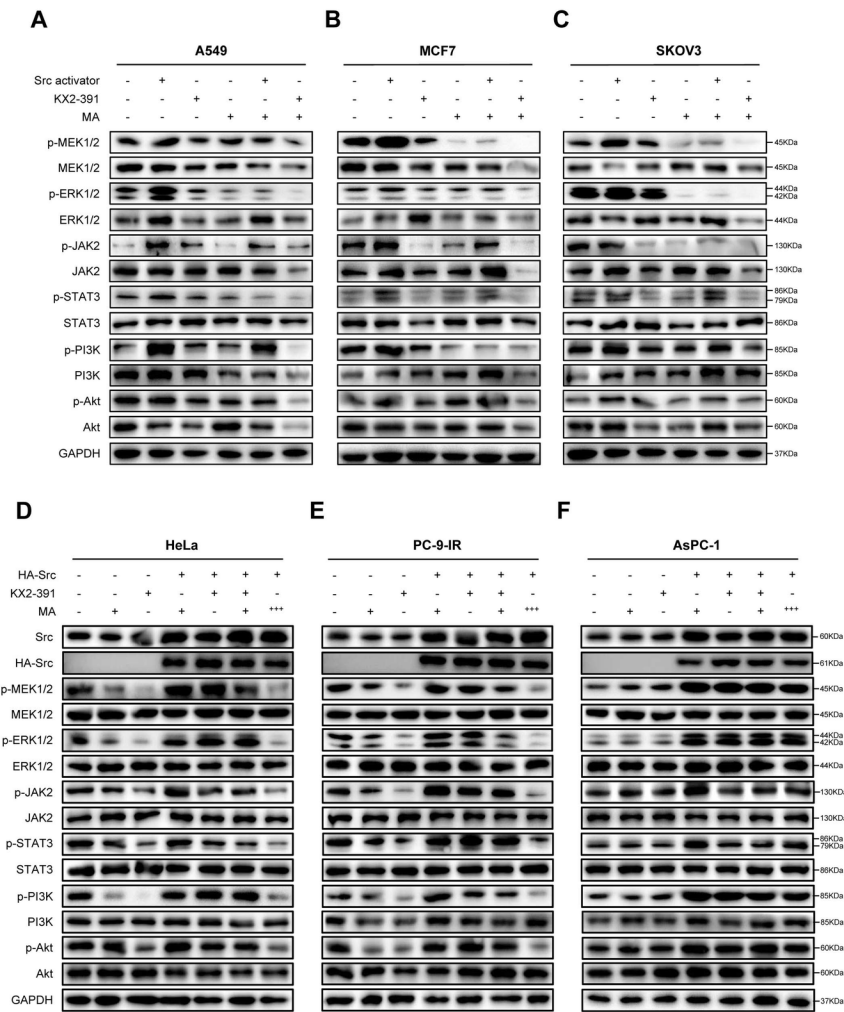


Fig.7

