ARHI re-expression inhibits subcutaneous xenograft growth and the lung/liver metastases of human gastric cancer cells (BGC823) in nude mice

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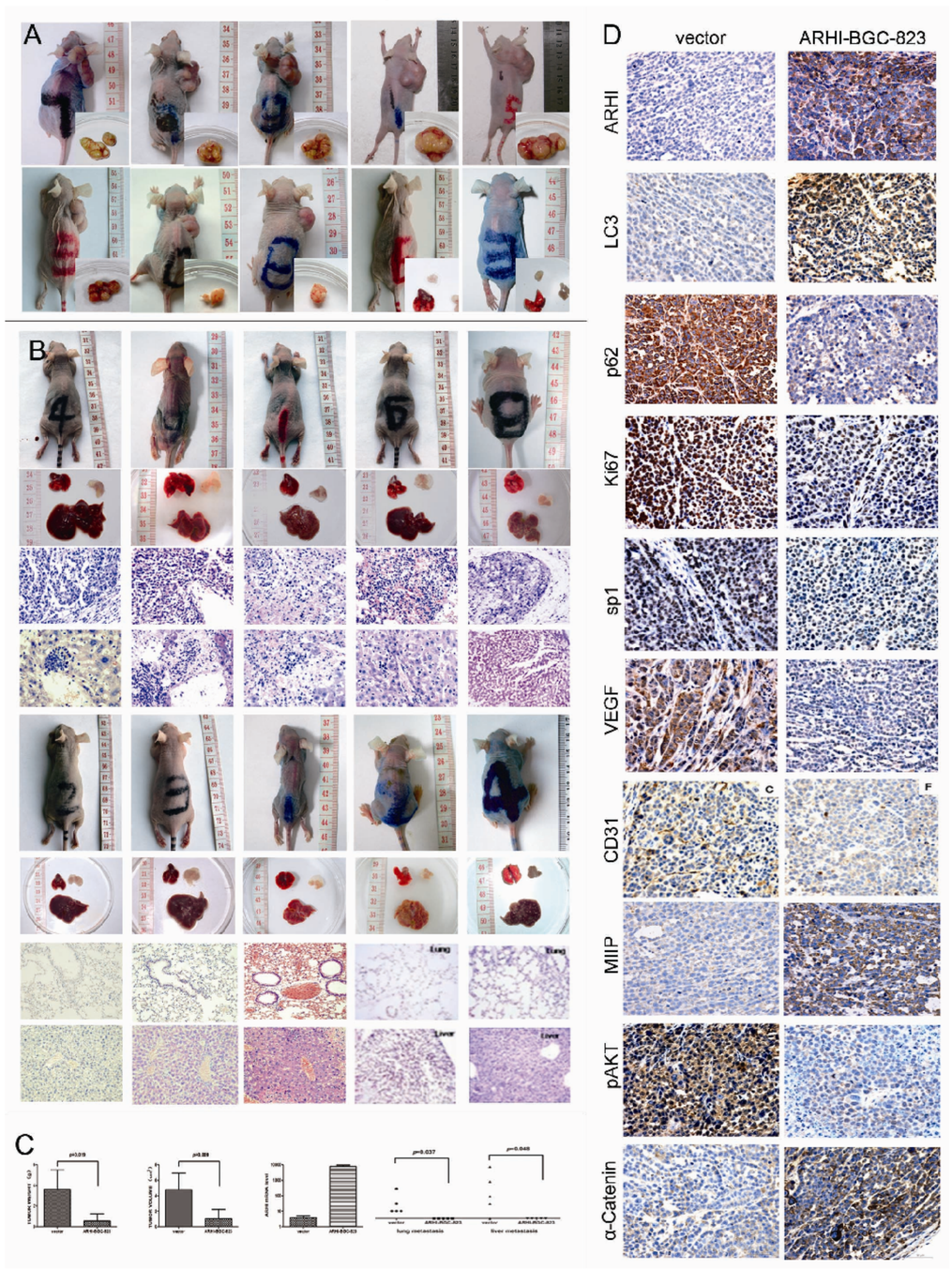
OBJECTIVES

Gastric cancer is a common malignancy, and distant metastasis of gastric cancer is the primary mode of treatment failure. ARHI is a maternally imprinted gene which inhibits proliferation and migration in breast and ovarian cancer[1-3]. Our previous study found that autophagy-related tumor suppressor gene ARHI can inhibit the proliferation invasion and migration of gastric cancer cells in vitro. This study aimed to investigate the effects of ARHI gene on tumor growth and metastasis in vivo, and to explore the mechanism.

METHODS

In this study, ARHI stably transfected BGC-823 gastric cancer cell line was used. In BALC/C Nu/Nu nude mice subcutaneous xenograft model, we evaluated the impact on the growth of subcutaneous xenografts of ARHI gene. Immunohistochemical staining was used to evaluate the level of LC3, P62, Ki67, SP1, VEGF, CD31, MIIP, p-AKT, α-Catenin proteins. In hematogenous metastasis model by tail vein injection, we evaluated the impact on lung and liver metastases tumorigenicity of ARHI gene.

Graphs and tables



RESULTS

Subcutaneous xenograft experiment showed that, re-expression of ARHI gene in gastric cancer cells inhibited the growth of subcutaneous xenograft, reduced autophagy level of subcutaneous tumor, inhibited the proliferation activity, reduced angiogenesis, and inhibited the level of p-AKT signaling pathway. hematogenous metastasis study showed that, re-expression of ARHI gene inhibited hematogenous liver metastasis of gastric cancer cells.

Figure (A) The BALB/c-nu mice and subcutaneous xenografts. The volume of xenograft(below) was less than that of vector-BGC-823(up). (B) The BALB/c-nu mice hematogenous metastasis model. In the vector-BGC-823 group (up), lung metastatic foci was found by naked eyes in 3 mice, decentralized lung metastatic foci was found in 2 mice, and micro liver metastatic foci was found in 4 mice, no liver metastatic foci was found in 1 mice. HE ×400For the ARHI-BGC-823 group no lung or liver metastatic foci was found in all 5 mice after careful observation by microscope. HE ×200 (C) Compared with vector-BGC823 group the volume and weight of subcutaneous xenografts reduced in ARHI-BGC-823 group, and the ARHI mRNA level of subcutaneous xenografts was higher detected by qRT-PCR, the number of lung and liver metastatic foci was higher in hematogenous metastasis model. (D) Compared with vector-BGC823 group (left), the subcutaneous xenografts of ARHI-BGC823 group(right) showed higher level of ARHI and LC3B protein level, lower level of p62 protein, and the Ki67-positive cell proportion was higher. The expression of SP1 and VEGF was down-regulated, and CD31-positive microvessel number was less in ARHI-BGC823. The level of MIIP and α-Catenin was higher and the level of p-AKT was lower. IHC ×400

CONCLUSIONS

Re-expression of ARHI gene inhibited the growth of subcutaneous xenograft, and inhibited the liver hematogenous metastases of gastric cancer cells probably by inducing autophagy in vivo.

References

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