

Function of Rho GTPase Activating Protein 11A in Tumors

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To the Editor: Rho GTPase Activating Protein 11A (*ArhGAP11A*) is a member of the Rho GTPase-activating proteins (*Rho GAPs*) gene family and is located on the long arm of 15 chromosome region 1 band 3 subband 2 (15q13.3). The full-length cDNA of *ArhGAP11A* is 24,806 bp with a single open-reading frame. *ArhGAP11A* is encoded by 13 exons and the encoded protein has three domains: a RhoGAP domain near the N terminus (amino acids 46–246), and two uncharacterized domains respectively located in the center (387–516) and C terminus (590–997) of the protein.^[1] Kagawa *et al.*^[2] compared the expression of *ArhGAP11A* in 74 colorectal cancer tissue specimens and five noncancerous mucosal tissue specimens with cDNA microarray-based comparative analyses. The results showed that *ArhGAP11A* expression was significantly higher in colorectal cancer tissue than that in noncancerous tissue, indicating that the upregulation of *ArhGAP11A* expression is beneficial to colorectal cancer cells *in vivo* migration and invasion activity. Ciriello *et al.*^[3] analyzed the RNA sequential data of 1201 patients with invasive breast lobular cancer, but only a few of the 64 *Rho GAPs* were found to be highly expressed in the basal-like breast cancer. Further study^[4] showed that the expression of *ArhGAP11A* in basal-like breast cancer was generally higher than other types of breast cancer, and *in vitro* experiments showed that *ArhGAP11A* overexpression could stimulate normal breast cancer cell proliferation. *ArhGAP11A* expression was also found to be upregulated in glioblastoma, hepatocellular, and pancreatic cancers. Based on these findings, the abnormal expression of *ArhGAP11A* might be closely related to the occurrence and development of tumors.

The cell cycle progression depends on the E2F transcription factor family. The role of E2F1 is regulated by the Rb protein, as dephosphorylated Rb protein is able to bind to E2F1 and inhibit the binding of E2F1 to specific DNA sequences. After phosphorylation of Rb protein by cyclin-dependent kinases (CDKs), E2F1 is released from the inhibitory complex of Rb/E2F1; it then binds to its dimerization partner (DP), either DP1 or DP2. This forms a heterodimeric E2F1/DP1 structure that combines with the target gene's promoter sequence (TTTSSCGCS, S = G or C) to initiate transcriptional activity of the gene. Kagawa *et al.*^[2] found that the binding of Rb protein to E2F1 hindered the transcriptional activity of the *ArhGAP11A* promoter, indicating that the Rb/E2F1 signaling pathway might be related to the transcriptional activity of *ArhGAP11A*. These authors suggested that the phosphorylation inactivation of tumor-inhibiting factor Rb protein might lead to abnormal activity of E2Fs causing in an increased *ArhGAP11A* expression. However, Lawson *et al.*^[4] found that when *ArhGAP11A* expression was inhibited, the expression of

p27 and the CDKs inhibitor CDKN2A/p27 was increased. This led to the breakdown of the complex formed between CDKs and cyclin D1 and E and decreased phosphorylation inactivation of tumor suppressor protein Rb1. Ultimately, this reduced the release of E2F inhibitor, inhibited cells from the G1 phase to S phase transition, and eventually caused cell cycle arrest. Both of these studies showed that Rb/E2F1 pathway can regulate *ArhGAP11A* expression; however, the role of E2Fs remains controversial. Therefore, the CDKN2A/p27/Rb/E2F1 pathway might be a molecular signaling pathway for *ArhGAP11A* expression.

Several studies have shown that *ArhGAP11A* can regulate the biological activity of Rho A, which is involved in tumor cell invasion and metastasis.^[1,2,4,5] The GTP structure of Rho A can stimulate the formation of focal adhesions and stress fibers by activating Rho-associated protein kinase (ROCK) or mammalian diaphanous protein. *In vitro* experiments showed that ROCK inhibitor could inhibit Rho-mediated signal pathway and cause cell morphology change similar to that of *ArhGAP11A* overexpression. A recent study^[6] also showed that Skp1-Cul1-F-box FBXL19 mediates Rho A ubiquitination and degradation. Therefore, we believe that inhibiting *ArhGAP11A* expression might reduce Rho A ubiquitination and degradation but increase its activity. This would continue to activate ROCK as well as the phosphorylation of ROCK downstream substrates, which is involved in the regulation of the cytoskeleton. Phosphorylation of ROCK downstream substrates also promotes the formation of tension fibers and focal adhesions, thus inhibiting the invasion and metastasis of tumors. Although the biological function of the Rho A pathway is obviously controversial and needs further study, the *ArhGAP11A*/Rho A/ROCK pathway might be an important signaling pathway for regulating the biological functions of *ArhGAP11A* in tumor cell proliferation, invasion, and metastasis.

ArhGAP11A is overexpressed in a variety of tumors; it plays an important role in the proliferation, invasion, metastasis, and cell cycle regulation of tumor cells. *ArhGAP11A* expression is significantly increased in highly aggressive tumors (e.g., glioblastoma and pancreatic cancer), and inhibition of *ArhGAP11A* could

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Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.232795

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Received: 01-03-2018 **Edited by:** Peng Lyu

How to cite this article: Zhou HN, Ren YX, Li L, Wang KS, Jiao ZY. Function of Rho GTPase Activating Protein 11A in Tumors. Chin Med J 2018;131:1365-6.

significantly reduce the possibility of tumor invasion and metastasis. In summary, *ArhGAP11A* might be a new marker for tumor diagnosis or as a new target for tumor therapy.

Financial support and sponsorship

This work was supported by grants from the Health Industry Scientific Research Program of Gansu province (No. GSWSKY2016-03), and the Key Research and Development Program of Gansu province (No. 17YF1FA127).

Conflicts of interest

There are no conflicts of interest.

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