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[Medicine] ZBRK1 Acts as a Metastatic Suppressor by Directly Regulating MMP9 in Cervical Cancer

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NCKU Research Express (2012/01/09) Cancer metastasis is the most common cause of death among cancer patients. It results from several highly organized sequential steps involving interactions between cancer cells and the host. However, details of candidate genes involved in other aspects of cancer metastasis/invasion processes remain less investigated. Precisely how tumor cells become metastatic is still largely unknown, especially in terms of a transcriptional factor that serves as a repressor in metastasis/invasion.

Zinc finger and BRCA1-interacting protein with KRAB domain-1 (ZBRK1), which was first identified in a yeast two-hybrid screening for proteins associated with BRCA1. Two corepressors of RING members, BRCA1 and KAP1, were shown to interact with ZBRK1 in coordinating transcriptional regulation of diverse DNA damage response genes. Recently, ZBRK1 has been identified as cooperating with the CtIP/BRCA1 to repress angiopoietin-1 (ANG1) gene activation and may play a role in tumor angiogenesis, implying that it may act as a potential tumor suppressor. However, whether ZBRK1 plays a direct role in tumor progression, especially in metastasis, has yet to be shown.

A research team from the Institute of Biosignal transduction, College of Bioscience and Biotechnology, National Cheng Kung University, found that reduction of ZBRK1 expression was observed in highly malignant cervical cancer cells compared with the counterpart normal tissue. Increase of ZBRK1 expression in HeLa cells significantly inhibits its neoplastic phenotypes. It is first to report on this significant discovery in cervical cancer cells. The findings suggest that a reduction of ZBRK1 allows the growth of cancer cells, whereas an increase of ZBRK1 has been shown to inhibit cell growth both in vitro and in vivo, suggesting that ZBRK1 can act as a tumor suppressor. Interestingly, analyses of gene expression patterns of these cells revealed groups of genes not only critical for cell proliferation but also for cell motility being downregulated. Furthermore, exogenous expression of ZBRK1 inhibits HeLa cell migration, in part by directly repressing transcription of the MMP9 metastatic gene. This result also presents the first demonstration of the direct negative repression of the transcriptional regulation of the MMP9 gene. This molecular evidence was validated in cervical cancer specimens, in which loss of ZBRK1 expression is inversely correlated with the elevated expression of MMP9. Taken together, these results suggest that ZBRK1 plays a critical role in tumor progression, especially in metastasis, by directly modulating metastatic genes.

Significant discoveries: （A） an increase in ZBRK1 inhibited the growth of cancer cells in vitro and in vivo, which suggests that ZBRK1 can act as a tumor suppressor. （B） This paper is the first work linking ZBRK1 and cancer metastasis/invasion. ZBRK1 acts as a metastasis/invasion suppressor through regulating cellular movement-related genes. （C） ZBRK1 can bind to the promoter regions of the MMP9 gene, according to in vivo and in vitro DNA binding assays. This molecular evidence is further confirmed by revealing the expression patterns of ZBRK1 and MMP9 in cervical cancer samples. Therefore, the findings of the NCKU research team also first demonstrate the direct negative repression of transcriptional regulation of the MMP9 gene.

Reference:
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