Effects of LYR71, a benzoxanthiol compound on activation of matrix metalloprotease-9 in MDA-MB-231 cancer cell line and on its growth in vivo

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INTRODUCTION The incidence of breast cancer – the second leading cause of cancer death in women in the world – is increasing, and current therapy is unable to achieve clinical responses in patients with highly invasive metastatic disease. Thus, developing drugs which target tumor growth and finding their underlying mechanism are valuable. Metalloproteinases are involved in breast cancer and Metalloproteinases9 involves STAT3. (1,2)

METHODS In vitro, cell lysate was collected after treatment for detecting the expression of phosphorylated STAT3 (Signal transducer and activator of transcription 3) by western blot, and the supernatant was collected to measure the activity of Matrix metalloproteinase9 (MMP 9) by gelatin zymography and the expression of MMP9 by Western blot. The level of MMP9 mRNA was detected by RT-PCR. Invasion assay was performed to quantify cell invasiveness. The effect of LYR71 on the MMP9 dependent gene was examined by Luciferase reporter assay. Chromatin immunoprecipitation (ChIP) was used to identify that STAT3 is associated with a region of MMP9 promoter. The in vitro results of MDA-MB 231 cells were further confirmed in vivo in nude mice (BALB/c- nu).

RESULTS LYR71 downregulated STAT3 activation and suppressed MMP9 expression in RANTES- induced MDA-MB-231 cells. It was shown in zymography that LYR71 inhibited RANTES - enhanced MMP9 activity and it consequently led to suppression of tumor invasion both in vitro and in vivo.

CONCLUSIONS We have found that LYR71 inhibits RANTES - induced STAT3 activation and the expression of its downstream target gene MMP9, therefore growth in breast cancer could be minimized. (Fig. 1)

REFERENCES


Fig. 1. Scheme of the signaling pathways involved in RANTES-induced MMP9 expression in human breast cancer. (A) RANTES-induced STAT3 upregulates MMP9 expression which lead invasion. (B) LYR71 suppresses RANTES–induced STAT3, which downregulates MMP9 expression. This MMP9 reduction decreases the cell invasion of breast cancer.