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Ascochlorin inhibits matrix metalloproteinase-9 expression by suppressing activator protein-1-mediated gene expression through the ERK1/2 signaling pathway

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The expression of matrix metalloproteinases (MMPs) has been implicated in the invasion and metastasis of cancer cells. Here we examined the effect of ascochlorin, a prenyl-phenol anti-tumor compound from the fungus Ascochyta viciae, on the regulation of signaling pathways that control MMP-9 expression in human renal carcinoma (Caki-1) cells. Ascochlorin reduced the invasive activity of Caki-1 cells and inhibited phorbol 12-myristate 13-acetate-induced increases in MMP-9 expression and activity in a dose-dependent manner. Reporter gene, electrophoretic mobility shift, kinase inhibitor assays, and in vitro kinase assay showed that ascochlorin inhibits MMP-9 gene expression by suppressing activation of the nuclear transcription factor activator protein-1 (AP-1) via the extracellular signal-regulated kinase 1 and 2 pathway. The AP-1 family member most specifically affected by ascochlorin was Fra-1. Ascochlorin did not affect the activation of the c-Jun N-terminal or p38 kinase pathways. Moreover, transfection of Caki-1 cells with AP-1 decoy oligodeoxynucleotides resulted in the suppression of phorbol 12-myristate 13-acetate-induced MMP-9 expression and invasion. In conclusion, ascochlorin represents a unique natural anti-tumor compound that specifically inhibits MMP-9 activity through suppression of AP-1-dependent induction of MMP-9 gene expression.

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ATF2 mediates p38 MAPK-induced MMP-2 upregulation in human breast epithelial cells

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We previously showed that H-Ras-specific activation of Rac-MKK3/6-p38 MAPK pathway resulted in MMP-2 up-regulation in MCF10A human breast epithelial cells. In this study, we aimed to elucidate the transcriptional regulation of MMP-2 by p38 MAPK pathway leading to the invasive and migrative phenotypes of MCF10A cells. By using 5' deletion mutant constructs of MMP-2 promoter, we showed that the AP-1 binding site is critical for the MMP-2 promoter activation in MKK6- and H-Ras-activated MCF10A cells. DNA binding and transcriptional activities of AP-1 were increased by MKK6 or H-Ras. We revealed the ATF2 as a transcription factor for MMP-2 gene expression through binding to the functional AP-1 site. Activation of ATF2 by MKK6 or H-Ras was crucial to MMP-2 promoter activity as well as induction of invasive and migrative phenotypes in MCF10A cells. This is the first report revealing ATF2 as an essential transcription factor linking MKK3/6-p38 MAPK signaling pathway to MMP-2 up-regulation, providing evidence for a direct role of ATF2 activation in malignant phenotypic changes of human breast epithelial cells. [Supported by a grant (R01-2005-000-10596-0) from Korea Science & Engineering Foundation and by the MOE, MOCIE and MOLAB through the fostering project of the Lab of Excellency]

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ATM associated NF-kB activation play a critical role in DNA damage induced apoptosis

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NF-kB is a DNA-damage responsive factor. It is activated by various stress situations, including oxidative stress, and DNA-damaging agents such as topoisomerase poisons. It was found that cells from Ataxia Telangiectasia (A-T) patients exhibit a defect in NF-kB activation in response to treatment with camptothecin, a topoisomerase I poison, or ionizing radiation(IR). Here we investigated whether CPT- or IR- induced cell apoptosis is associated with NF-kB activation. We found that CPT or IR caused caspase 3 activation but no NF-kB activation in A-T cells, however,conversely, MRC5 cells showed NF-kB activation without any caspase 3 induction. ProI itself,however,increased ATM-dependent apoptosis as evidenced by DNA fragmentation and caspase 3 activation.All the subsequent data suggest that DNA damage induced apoptosis be critically mediated by NF-kB activation is a ATM-dependent manner.

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Bcl-w promotes gastric cancer cell invasion by inducing matrix metalloprotenase-2 expression via phosphoinositide 3-kinase, Akt, and Sp1

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Given a previous report that Bcl-w is expressed in gastric cancer cells, particularly in those of an infiltrative morphology (Lee et al, Cancer Res 63:1093-1100, 2003), we investigated whether Bcl-w expression influences the invasiveness of gastric cancer cells. To accomplish this, Bcl-w was overexpressed in gastric adenocarcinoma cell lines, and this was found to result in an increase in their migratory and invasive potentials. These effects were not induced when Bcl-2 was overexpressed in the same cell types. Consistently, Bcl-w, but not Bcl-2, overexpression increased matrix metalloproteinase-2 (MMP-2) expression, and synthetic or natural inhibitors of MMP-2 abolished Bcl-w-induced cell invasion. Bcl-w overexpression also activated phosphoinositide 3-kinase (PI3K), Akt, and Sp1, and the blocking effects of each of these components using pharmacological inhibitors, dominant negative mutants, or siRNA abolished the ability of Bcl-w to induce MMP-2 and cell invasion. The inhibition of PI3K/Akt signaling also prevented Sp1 activation. Overall, our data suggest that Bcl-w, which was previously shown to enhance gastric cancer cell survivability, also promotes their invasiveness by inducing MMP-2 expression via the sequential actions of PI3K, Akt, and Sp1.