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Compound K of Ginseng radix inhibits basic fibroblast growth factor-induced angiogenesis in human umbilical vein endothelial cells via Akt dependent pathway

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The effect of compound K (20-O-(beta-D-glucopyranosyl)-20(S)-protopanaxadiol), a ginseng saponin metabolite was evaluated on angiogenesis in vitro and in vivo. Basic fibroblast growth factor (bFGF) is a potent angiogenic factor found in various tumors. In the present study, we have found that compound K suppressed bFGF-induced human umbilical vein endothelial cells (HUVECs) proliferation, migration and tube formation in a concentration-dependent manner (12.5 μM, 25 μM and 50 μM). Compound K also effectively disrupted the bFGF-induced neo-vascularization in Matrigel plugs excised from mice in a dose dependent manner. Furthermore, compound K downregulated the phosphorylation of Akt, which was known to be involved in endothelial cell survival, proliferation and migration. Taken together, these findings indicate that compound K exerts anti-angiogenic activity via inhibition of AKT signaling pathway. This work was supported by grants from KOSEF (R01-2-005-000-10993-0), Ministry of Health and Welfare (B050007), Agricultural Research & Development Promotion Center (105054-03-1-SB010) and Biogreen 21 program.

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Differential regulation of NF-κB activation and apoptosis by camptothecin in HL60 cells

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Camptothecin (CPT), a potent topoisomerase I inhibitor, has been reported to induced both apoptotic cell death and NF-kB activation. In this study, however, it is unexpectedly provided that CPT elicits apoptosis independently of NF-kB activation in HL60 cells. NF-kB activation by CPT treatment revealed that IkBa$\alpha$was degraded leading to the nuclear translocation of p50/NF-kB1, as evidenced by restoration of IkBa by proteasome inhibitor I (ProI) and reduction of p50 DNA binding activity kamebakaurin (KA), a p50-specific NF-kB inhibitor. CPT-induced DNA fragmentation coincided with the activation caspase-3, 8, clearly indicating the apoptotic process by CPT in HL60 cells. Interestingly, however, the level of Akt1 was decreased in a time-dependent pattern by CPT. In addition, neither of the NF-kB inhibitors, ProI and KA, did affect the Akt1 level, suggesting the location of Akt1 downstream of NF-kB. When cells were challenged to the inhibitors of NF-kB and caspases, it was unexpectedly found that NF-kB activation by CPT does not affect apoptotic cell death and vice versa. Thus, it is concluded that CPT activation of NF-kB has no relation with apoptosis and suggested that other signaling events than NF-kB activation might be targets for anti-tumorigenic effect of CPT.

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DMNQ S64 induces apoptosis via ROS activation and NFkB inhibition in human nonsmall lung cancer cells

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6-ppim (1-propoxyiminoalkyl)-5,8-dimethoxyoxy 1,4-naphtoquinone S-64 (DMNQ S64) was synthesized as a shikonin derivative. In the present study, the underlying apoptotic mechanism of DMNQ S64 was examined. DMNQ S64 exerted cytotoxicity against A549 lung carcinoma cells with IC50 of 27.3 μM. Apoptotic bodies were observed in DMNQ S64 treated A549 cells by DAPI staining assay. However, DMNQ S64 also increased ROS portion in time dependent manner by flow cytometric analysis. Western blotting revealed that DMNQ S64 effectively reduced the expression of mitogen activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK), cleaved poly(ADP-ribose) polymerase (PARP) and activated caspase-8 and 3. Furthermore, Luciferase assay has showed DMNQ S64 significantly inhibits NF-kB and the phophorylation of p38. Taken together, these results suggest that DMNQ S64 may used as an anticancer agent via apoptosis induction through ROS activation and inhibition of NF-kB and phopho-p38. This work was supported by grants from KOSEF (R01-2-005-000-10993-0), Ministry of Health and Welfare (B050007), SRC program of KOSEF (R11-2005-014-03003-0), Agricultural Research & Development Promotion Center (105054-03-1-SB010) and Biogreen 21 program.

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Doxorubicin induces serine-phosphorylation of STAT3 by JNK pathway in breast cancer cells

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While doxorubicin is widely used for breast cancer, patients develop resistance to the drug, particularly after a previous round of chemotherapy. Therefore, it is highly useful to identify growth signaling proteins whose activation or inactivation correlates with to doxorubicin-resistance. As Stat3 is frequently activated in breast cancer and can contribute to tumorigenesis, we assume that its activity might be associated with chemotherapeutic resistance. We investigated whether MDA-MB231 breast cancer cells could activate Stat3 or any growth signaling protein in half survival cells after doxorubicin-treatment. We found that tyrosine-phosphorylation of Stat3 was inactivated by doxorubicin. The drug, on the contrary, increased another activation signal, serine-phosphorylation for Stat3. In addition, JNK pathway was required for the serine-phosphorylation of STAT3 because the inhibition of JNK pathway resulted in the absence of serine-phosphorylation. The serine-phosphorylation by doxorubicin also contributed to increase cellular viability, and occurred in another breast cancer cell line, Hs578T. These observations, in order to overcome apoptosis by doxorubicin, suggest that breast cancer cells could associate with serine-phosphorylation of STAT3 via JNK pathway.