P139

Effect of Treadmill Training on Schwann Cell Proliferation Activated by p-ERK1/2 and Cdc2 after Sciatic Nerve Injury in Rat

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Trauma to peripheral nerves often produces devastating clinical problems. Proliferation of Schwann cells after sciatic nerve injury facilitates axonal regeneration, and increase of physical activity after central and peripheral nervous system injury has been shown to promote nerve regeneration. Cell division cycle 2 (Cdc2) initiates the progression of G2 to M phase during the cell cycle and Extracellular signal-regulated kinase 1/2 (ERK1/2) activity can mediate neuronal responses to lesion signals, but these role in non-neuronal cells in the injury area is largely unknown. Here we report that treadmill training (TMT) facilitates axonal regeneration via upregulation of Cdc2 and phospho-ERK1/2 protein levels in Schwann cells in the injured sciatic nerve. Low-intensity TMT elevated Cdc2 kinase activity and phosphorylation of ERK1/2 protein in the injured sciatic nerves. TMT also enhanced phospho-c-Jun protein levels after nerve injury, and in vivo administration of ERK1/2 inhibitor PD98059 eliminated phospho-c-Jun. Inhibition of ERK1/2 protein signals decreased levels of BrdU-labeled proliferating Schwann cells in the distal to injury site, and delayed axonal re-growth that was promoted by TMT. The present data suggest that increased Cdc2 and ERK1/2 activity in Schwann cells may play an important role in TMT-mediated enhancement of axonal regeneration in the injured peripheral nerve.

Key words: Treadmill training, Cdc2, ERK1/2, sciatic nerve, Schwann cell, Migration, PD98059.

P140

Pro-apoptotic Effects of Ethanol Extract of *Hizikia fusiforme* in Human Leukemic U937 Cells

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Hizikia fusiforme, well known as Sea weed fusiforme, is reported to possess many pharmacological activities including antioxidant, antimutagenic and anticoagulant effect. However, the molecular mechanisms of *H. fusiforme* on biochemical actions in cancer have not been clearly elucidated yet. The purpose of the present study was to examine the effect of the ethanol extract of *H. fusiforme* (EEHF) on the anti-proliferative effects of human leukemic U937 cells. It was found that EEHF could inhibit the cell proliferation of U937 cells in a concentration-dependent manner, which was associated with apoptotic cell death such as formation of apoptotic bodies, DNA fragmentation and increased populations of apoptotic-sub G1 phase. The induction of apoptotic cell death by EEHF was connected with a down-regulation of anti-apoptotic Bcl-2, Bcl-X_L and IAPs expression. MEHC treatment induced the proteolytic activation of caspase-3, caspase-8 and caspase-9, and a concomitant inhibition of PARP, β-catenin, PLC-γ1 and DFF45/ICAD proteins. Furthermore, caspase-3 specific inhibitor, z-DEVD-fmk, significantly inhibited EEHF-induced apoptosis demonstrating the important role of caspase-3 in the observed cytotoxic effect. Taken together, these findings suggest that EEHF may be a potential chemotherapeutic agent for the control of human leukemic U937 cells and further studies will be needed to identify the active compounds that confer the anti-cancer activity of EEHF. [This work was supported by a grant from Marine Bioprocess Research Center of the Marine Bio 21 Center funded by the Ministry of Land, Transport and Maritime, Republic of Korea.]

Key words: *Hizikia fusiforme*, U937, apoptosis, Bcl-2, caspase-3