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Snake venom toxin from *Vipera lebetina turanica* sensitizes cancer cells to TRAIL through ROS- and JNK-mediated upregulation of death receptors and downregulation of survival proteins

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We investigated whether the snake venom toxin (SVT) from *Vipera lebetina turanica* enhances the apoptotic cell death ability of tumor necrosis factor (TNF)-related cell death inducing ligand (TRAIL) in the cancer cells. TRAIL inhibited HCT116 cell growth dose dependently, but not in TRAIL resistant HT-29, A549 and HepG2 cells with even higher dose of TRAIL. SVT enhanced expression of cell death receptor (DR) in TRAIL resistant cancer cells in a dose dependent manner but not by TRAIL. Combination of SVT with TRAIL significantly inhibited cell growth of TRAIL resistant HT-29, A549 and HepG2 cells. Consistent with cell growth inhibition, the expression of TRAIL receptors; DR4 and DR5 was significantly increased as well as apoptotic cell death related proteins such as cleaved caspase-3, -8, -9 and Bax. But the expression of survival proteins such as cFLIP, survivin, XIAP and Bcl2 was decreased by the combination treatment of SVT and TRAIL in HCT116 and HT29 cells. Deletion of DR4 or DR5 by small interfering RNA significantly reversed cell growth inhibitory and apoptotic cell death blocking effects of SVT not only in HCT116 but also in HT-29 cells. Pretreatment of JNK inhibitor SP600125 and ROS scavenger N-acetylcysteine reduced the SVT and TRAIL-induced upregulation of DR4 and DR5 expression and apoptotic cell death related protein expression such as caspase-3 and-9 as well as cell growth inhibitory effects. Our results suggested that SVT facilitates TRAIL-induced apoptotic cell death in cancer cells through up-regulation of the TRAIL receptors; DR4 and DR5 via ROS/ JNK pathway signals.

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Flatfish (*Paralichthys olivaceus*) oil suppresses T helper cells type 1/2 response and up-regulates CD4+CD25+Foxp3+ T cells

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Regulatory T cells (Tregs) play key roles in the immune response by preventing or suppressing the differentiation, proliferation and function of various immune cells. Recent studies report that the omega-3 polyunsaturated fatty acids (n-3 PUFAs) in fish oil can reduce inflammation in allergic patients. The beneficial effects of natural fish oil (NFO) have been described in many diseases, but the mechanism by which fermented fish oil (FFO) modulates the immune system and the allergic response is poorly understood. In this study, we produced FFO and tested its ability to suppress the allergic inflammatory response and to activate CD4+CD25+Foxp3+ Tregs. The ability of FFO and NFO to modulate the immune system was investigated using a mouse model of AD. Administration of FFO or NFO in the drinking water alleviated the allergic inflammation in the skin, and FFO was more effective than NFO. Neither FFO nor NFO increased forkhead box P3 (Foxp3) expression and/or affected the number of CD4+CD25+ T cells without any stimulation. However, FFO treatment did increase the expression of the immune-suppressive cytokines transforming growth factor-β (TGF-β) and Interferon-10 (IL-10). In addition, ingestion of FFO increased Foxp3 expression and the number of CD4+CD25+Foxp3+ Tregs in CD4+ T cells stimulated with anti-CD3 and anti-CD28 compared with NFO. These results suggest that the anti-allergic effect of FFO is associated with enrichment of CD4+CD25+Foxp3+ T cells at the inflamed sites and that FFO may be effective in treating the allergic symptoms of AD.

Key word : Atopic dermatitis AD, natural fish oil, fermented fish oil, transforming growth factor-β, forkhead box P3, regulatory T cells