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O-09

The Immunomodulatory Effect of ABNOBaviscum® "Mistletoe" in the Treatment of Ovarian Malignancy

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Background: To clarify the immunomodulatory effect and document the clinical usefulness of ABNOBaviscum® "Mistletoe" during chemotherapy in the patients with epithelial ovarian malignancy by evaluating the status of the immune markers. **Methods:** 32 epithelial ovarian cancer patients was divided into treatment group (n=16) who received ABNOBaviscum® "Mistletoe" injection and control group (n=16). All patients were received at least 6 cycles of platinum-based chemotherapy. Blood sampling was taken before, and 21st day of each cycle until 52 weeks. The blood samples were analyzed for absolute number of leukocyte, monocyte, lymphocyte and eosinophil in all samples; CD (cluster determinant) 3, CD4, CD8 and CD56 in 0, 12 and 30th weeks; IL (interleukin)-2, IL-4, IL-12, TNF (tumor necrotizing factor)- α and INF (interferon)- γ in 0, 6, 12, 18, 30th week. The basic laboratory tests including liver function were done in every cycle to evaluate adverse effects of the ABNOBaviscum® "Mistletoe". **Results:** The number of monocyte (p=0.0027) and macrophage were significantly increased in ABNOBaviscum® "Mistletoe"-treated group compared with control group, but not in lymphocyte and eosinophil. There was significant increase in the concentrations of NK (natural killer) cell and CD8 (p=0.0007), but not in CD3, CD4, CD56. In cytokines, there was statistically significant increase of the concentrations of IL-2 (p=0.0026), IL-4 (p=0.0004), IL-12 (p=0.0017) in ABNOBaviscum® "Mistletoe"-treatment group, but no differences in TNF- α and INF- γ . There was no clinical adverse effect in the laboratory tests including liver function tests. **Conclusion:** ABNOBaviscum® "Mistletoe" may improve the innate and acquired immunity by immunomodulation in the patients receiving anti-neoplastic chemotherapy. These results suggest that ABNOBaviscum® "Mistletoe" may be useful adjuvant in ovarian cancer patients by improving immune status and maintaining effective schedules of the chemotherapeutic drugs.

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Role of 2B4 in Tumor Killing

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Background: NK cells are critical in the immune responses to tumor cells and virally-infected cells. NK cells mediate lysis of tumor cells as a result of activation upon binding of NK activating receptors with their specific ligands expressed on tumor cells. NK cells can directly kill tumor cells via secreting lytic molecules, perforin and granzymes. NK cells also release

cytokines, IFN-gamma and TNF-alpha, thus activate other immune cells including macrophages and T cells. 2B4, expressed on all NK cells, belongs to the CD2 subset of the IgG family of receptors. Both 2B4 and CD2 bind to CD48, another member of this family. Since all three molecules are expressed on NK cells, a question arises as to the binding of 2B4 and CD2 to CD48 among NK cells may have functional consequences. **Methods:** Using murine NK cells isolated from mice, effect of homotypic NK cell interaction through 2B4 and CD48 was performed using cytotoxicity assay, proliferation assay, and cytokine measurement assay against tumor targets, RMAS. **Results:** Using specific monoclonal antibodies and gene-deficient NK cells, we found that 2B4/CD48, but not CD2/CD48, interaction is essential for IL-2-driven expansion and activation of murine NK cells. In the absence of 2B4/CD48 interaction, NK cytotoxicity and IFN-gamma secretion upon tumor target exposure is severely impaired. Impaired activation of NK cells in 2B4-deficient mice was also demonstrated by poor NK-mediated clearance of syngeneic tumor cells in these mice. Functional impairment of NK cells in the absence of 2B4/CD48 interactions was accompanied by defective calcium signaling, suggesting that the early signaling pathway of NK receptors is inhibited. **Conclusion:** Together, these data identify a novel mechanism whereby NK effector function is regulated via homotypic 2B4/CD48 interactions. Thus, anti-tumor function of NK cells can be maximized in the presence of 2B4-CD48 interaction.

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Phosphatidylinositol-3 Kinase Mediates Inactivation of Bcl-2 by JNK during Ionizing Radiation-induced Apoptotic Cell Death in Human Cervical Cancer Cells

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Background: Ionizing radiation induces simultaneous activation or down regulation of multiple signaling pathways. These signals play critical role in controlling cell death and cell survival after irradiation in a cell type specific manner. **Methods:** We show here that γ -irradiation induces phosphorylation/inactivation of Bcl-2 by JNK, and that radiation-induced JNK activation is phosphatidylinositol-3 kinase dependent. Inhibition of JNK by pretreatment of SP600125, or by expressing a dominant negative forms of JNK attenuated Bcl-2 phosphorylation and degradation, mitochondrial membrane potential loss, and translocation of AIF to the nucleus seen after irradiation, suggesting that JNK activation is involved in mitochondrial dysfunction-mediated cell death through inactivation of Bcl-2. **Results:** Moreover, inhibition of PI3K by chemical inhibitors or dominant negative forms of PI3K effectively inhibited radiation-induced JNK activation and JNK-dependent inactivation of Bcl-2, and subsequent cell death. **Conclusion:** These results suggest that phosphatidylinositol-3 kinase mediates inactivation of Bcl-2 by JNK during ionizing radiation-induced apoptotic cell death in human cervical cancer cells. Molecular dissection of the signaling pathways that regulate the apoptotic cell death machinery