A Novel Use of Valeryl Salicylate in the Inhibition of CML Cell Proliferation

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Interleukin-4 (IL-4), a cytokine found in excess in the tumor microenvironment, is known to induce cancer cell proliferation. In vitro research suggests that the IL-4-induced activation of the JAK/STAT6 pathway drives this proliferation. Interestingly, previous findings show that aspirin and sodium salicylate inhibit STAT6 activation in murine lymphoma. Salicylates have also been shown to downregulate prostaglandin E2 (PGE2), another protein which induces cancer cell proliferation. However, research is lacking on valeryl salicylate, a selective COX-1 inhibitor, in the context of cancer cell proliferation and metastases. It was hypothesized that valeryl salicylate would inhibit IL-4-induced proliferation and migration in K-562, a chronic myelogenous leukemia (CML) cell line. K-562 cells were treated with IL-4 (100 ng/mL) for 96 hours. Valeryl salicylate (1-4 mM) was added at 72 hours. An MTS assay showed that valeryl salicylate (1-4 mM) reduced IL-4-induced proliferation ($p<.05$). To elucidate valeryl salicylate's mechanism of action, STAT6, BCL-2, SHIP-1, PI3K, ERK1/2, PGE2, JAK-1, JAK-3 and Src kinase were measured as each are reported to influence proliferation through independent pathways. Results from ELISA demonstrated valeryl salicylate (2-4 mM) decreased levels of pSTAT6 ($p<.05$) and PGE2 ($p<.05$) at 1-4 mM. In addition, valeryl salicylate (1-4 mM) decreased migration ($p<.05$) and perturbed the cell cycle. Valeryl salicylate increased levels of pJAK-3 and pSrc kinase ($p<.05$) and did not affect BCL-2, pJAK-1, pSHIP-1, pPI3K and pERK1/2, suggesting valeryl salicylate inhibits IL-4-induced proliferation independent of these proteins. Therefore, valeryl salicylate is a potential therapeutic option in preventing CML proliferation through STAT6- and PGE2-mediated pathways.

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