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Effects of namodenoson on pancreatic carcinoma: Preclinical evidence.

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Background: Namodenoson, an A3 adenosine receptor (A3AR) agonist, is currently in a phase 3 trial for the treatment of advanced liver cancer. The mechanism of action of namodenoson involves de-regulation of the Wnt and NF- κ B signaling pathways, followed by an increase in pro-apoptotic proteins and Fas-ligand, resulting in tumor growth inhibition. As the Wnt signaling pathway is also highly implicated in pancreatic carcinogenesis, we examined the anti-growth effect of namodenoson on pancreatic carcinoma cell lines and investigated the molecular mechanism involved. **Methods:** BxPC-3 human pancreatic carcinoma cells were cultured in the presence and absence of 0.01, 0.1, and 1 nM namodenoson. A combined treatment of namodenoson (0.1 nM) and gemcitabine (0.2 μ M) was also studied. 3 [H]-thymidine proliferation and MTT assays were used to monitor cell growth, and Western blot analyses were performed to identify the involved regulatory cell growth proteins. **Results:** Results of the 3 [H]-thymidine proliferation assays demonstrated significant dose-dependent inhibition of the growth of BxPC-3 cells with namodenoson (1 nM: 67.4% \pm 1.7%, $p < 0.001$; 0.1 nM: 53.7% \pm 6.3%, $p < 0.05$; 0.01 nM: 27.9% \pm 2.3%, $p < 0.005$). The MTT results revealed that a combined treatment with namodenoson plus gemcitabine had an additive inhibitory effect (namodenoson: 48.6% \pm 1.4%; gemcitabine: 44.4% \pm 0.7%; namodenoson plus gemcitabine: 65.4% \pm 1.4%; $p < 0.001$ for all). Western blot analyses showed that namodenoson treatment was associated with downregulation of the Wnt pathway regulatory proteins including p-Akt, NF- κ B, GSK-3 β , and β -catenin. **Conclusions:** Our findings showed that nanomolar concentrations of namodenoson inhibit the growth of pancreatic carcinoma via A3AR activation and de-regulation of the Wnt/ β -catenin pathway, both as a monotherapy and in combination with gemcitabine. Thus, these results support a potential role for namodenoson in treating pancreatic cancer, thereby opening a novel therapeutic opportunity for this disease. Research Sponsor: Can-Fite BioPharma.