Over-expression of Cox-2 in human gastric tumors and cell lines and its suppression by aspirin and SC-236 in vitro

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Background Over-expression of cyclooxygenase (Cox)-2 has been observed in various tumors and many specific Cox-2 inhibitors are under development as a chemotherapeutic and chemopreventive agent. We studied Cox-2 expression in human gastric tumors and the effect of non-specific (aspirin) and specific (SC-236) Cox-2 inhibitors in human gastric cancer cell lines in vitro.

Method & Results Cox-2 protein was expressed in ~80% and ~20% of glandular epithelial cells in tumor tissue and adenomatous polyp, respectively, and mainly localized in the luminal side. No expression was seen in atrophic gastritis. Infiltrated inflammatory cells showed over-expression of Cox-2 protein. Cox-1 protein expression was negligible in all tissues. Cox-2 mRNA level, determined by RT-PCR, was higher in tumor tissue than the adjacent normal tissue. Cox-2 mRNA and protein in four human gastric cancer cell lines were significantly expressed with different rank orders. Among these cell lines, SNU-216 showed significant level of both mRNA and protein, hence, was selected for in vitro inhibition experiments. The suppression of Cox-2 mRNA was shown after 24hr and 48hr at 10 mM and 5 mM of aspirin, respectively. Compared to Cox-2, Cox-1 protein was expressed at a lower level and suppressed by lower concentration of aspirin (1 mM vs 20 mM) after 48hr exposure. PGE_2 production decreased to 50% after 24hr exposure at 20 mM of aspirin as determined by enzyme immunoassay. Cox-2 protein expression was significantly suppressed after 48hr exposure to 1μM of SC-236. The cytotoxic IC_{50,72hr} was 14.9μM as determined by XTT and apoptotic cells were detected after 12hr exposure at this concentration, shown by DAPI staining. In summary, over-expression of Cox-2 mRNA and protein was observed in patient tumor tissues and cancer cell lines, and SC-236 effectively suppressed Cox-2 protein expression and showed potent cytotoxicity via apoptosis.

Conclusion These data indicate that (1) Cox-2 over-expression may contribute to carcinogenesis of human gastric cancers and (2) studies on the detailed cytotoxic mechanisms of selective Cox-2 inhibitors including SC-236 are needed for their clinical development.