New Agents for Cancer Prevention

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In this issue of the Journal, Zhu et al. (1) report that they have synthesized new compounds that stimulate apoptosis. The synthesis is based on the structure of selective cyclooxygenase-2 (COX-2) inhibitors. This work is a tour-de-force in chemical synthesis but appears to lack some important biochemical and biological data required for definitive conclusions. These compounds are said to lack clinically important cyclooxygenase inhibitory activity; however, the authors present no actual experimental data to support this contention. Unfortunately, the authors incorrectly refer to a news report in Science magazine (2) about a National Institutes of Health-sponsored cancer prevention workshop held a few years ago as evidence that “COX-2 inhibition may not play a role in [non-steroidal anti-inflammatory drug] NSAID-mediated apoptotic death” (1). The outcome of that meeting was not so straightforward. Having attended that meeting, I know that a substantial amount of data was presented that carefully documented a role of COX-2 in carcinogenesis and suggested that COX-2 does play an important role in regulating apoptosis. Since that workshop was held, the role of COX-2 in cancer has become even more clear. The most direct and compelling evidence implicating a role for COX-2 in colorectal cancer has come from genetic studies in mice. Oshima et al. (3) determined intestinal polyp number in APC^Δ716 mice (a mouse model similar to the APC^Min mouse model but in which there is a truncating mutation in the adenomatosis polyposis coli [APC] gene) in both wild-type and homozygous null COX-2 genetic backgrounds. The number and size of polyps were reduced in the COX-2 null mice compared with those in the COX-2 wild-type mice. Treatment of the APC^Δ716 COX-2 wild-type mice with either a novel COX-2 inhibitor or the NSAID sulindac also reduced the number of polyps. A recent study by Liu et al. (4) is the first to demonstrate that overexpression of COX-2 alone in transgenic mice is sufficient to induce cellular transformation. This group developed transgenic mice in which COX-2 expression was under the control of the murine mammary tumor virus promoter/enhancer. Multiparous female mice expressing the COX-2 transgene showed statistically significant increases in mammary gland carcinomas compared with age-matched control mice. Treatment of these animals with cyclooxygenase inhibitors was associated with a reduction in mammary gland carcinomas. Another group (5) has reported that transgenic mice programmed to overexpress COX-2 in skin tissue develop skin cancer at a much higher rate than control animals lacking the COX-2 transgene. So the role of COX-2 in carcinogenesis is quite well established, and certainly some component of the chemoprotective effect of selective COX-2 inhibitors is likely due to the inhibition of this enzyme (6). Additional reports (7–9) clearly document a role for COX-2 in the regulation of apoptosis.

Zhu and colleagues have taken an interesting approach that may yield new agents for development as chemopreventive and/or chemotherapeutic drugs. However, the approach to developing chemopreventive agents that are based on the structure of NSAIDs is not novel. Others have utilized derivatives of NSAIDs as potential chemopreventive agents that have been shown to stimulate apoptosis. For example, sulindac sulfone, which is an inactive metabolite of the nonselective cyclooxygenase inhibitor sulindac sulfide, stimulates apoptosis but does not inhibit cyclooxygenase activity in vitro (10). Interestingly, one report indicates that sulindac sulfone alone can inhibit prostaglandin production in carcinoma cells in culture (11). Because Zhu et al. did not measure the biochemical effect of these compounds on prostaglandin synthesis in vivo or in vitro, their effects on the prostaglandin biosynthetic or downstream signaling pathways remain an open question and should be tested directly.

Importantly, Zhu and colleagues have successfully synthesized several new compounds that stimulate cells to undergo apoptosis in culture. They go on to speculate that these agents may be useful compounds to inhibit angiogenesis, but no data to support this hypothesis are provided. The authors demonstrate that these compounds can reduce the viability of cultured PC-3 and other prostate carcinoma cells when given at a concentration of 50 μM as shown in their Fig. 2. This finding is not surprising because others have shown that celecoxib has similar properties in COX-1/COX-2 double knockout cells when given at a concentration of 40 μM and that this effect was not related to inhibition of COX-1 or COX-2, because both genes had been deleted from these cells (12). However, in animal studies, celecoxib treatment resulted in a substantial inhibition of tumor growth at maximum serum drug concentrations (i.e., in the 3–5 μM range) (12). The conclusion from these studies by Williams et al. was that a substantial portion of the effect on tumor growth inhibition was likely due to inhibition of COX-2 activity because celecoxib at 3–5 μM has no discernible effect on the growth of carcinoma cells grown in culture. These studies and the current report by Zhu et al. raise several important questions that must be addressed experimentally. What is the role of COX-2 in the stromal versus the epithelial compartment of solid malignancies? Are there other important targets of these drugs in vivo that are not present in cultured cells grown in vitro? If an agent induces apoptosis when given at a concentration of 40–50 μM to cultured cells, would this agent be effective in vivo or would it cause severe toxicity to the organism because of induction of global cell death?
New agent development is extremely important for the success of the entire field of cancer prevention. These new agents must be studied and tested in a systematic way to ensure their safety and efficacy (13). The challenge now is to determine whether these agents are effective in vivo and if they have any untoward toxic effects in the whole organism. The data presented by Zhu and colleagues showing that they can induce apoptosis in cultured cells is an important step but only a first step. Next steps should include testing the efficacy of these new compounds in nontransformed as well as other transformed cells, in animal models of cancer, and in other available preclinical contexts to determine whether they are global inducers of apoptosis in living cells or whether they have specificity for malignant and/or premalignant cells. It will also be important to determine whether the molecular modeling data presented by Zhu et al. is correct and if these agents have any effect on the prostaglandin biosynthetic pathway in complex biologic systems.

REFERENCES