Keynote Lecture 2

S22. Cox-2-Cancer Chemoprevention: Picking up the Pieces

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For more than 100 years, NSAIDs have been used to treat pain and inflammation, an activity related to their inhibition of cyclooxygenase, a key enzyme of arachidonic acid metabolism. Strong biological evidence also supports an association between chronic inflammation and development of epithelial cancers. The link between arachidonic acid metabolism, NSAIDs, and cancer prevention was further strengthened by the discovery of a distinct form of cyclooxygenase, cyclooxygenase-2 (Cox-2), induced by mitogens and overexpressed in tumors and peri-tumoral stromal cells. Cox-2 expression within the epithelial microenvironment mediated increased and sustained production of tumorigenic signaling factors, such as PGE2. A key role of Cox-2 in epithelial tumorigenesis was confirmed by studies showing that selective blockade of Cox-2 activity by gene deletion or pharmacological inhibition reduced tumor formation in both animals and human clinical trials.

Selective Cox-2 inhibitors were developed to reduce the toxicity of long-term NSAID use, which for non-selective NSAIDs includes potentiation of bleeding, gastric ulceration, and renal toxicity. Selective Cox-2 inhibitors have been used by millions of arthritis patients worldwide, and these drugs demonstrated reduced GI and renal toxicity in placebo-controlled studies. Unfortunately, recently completed placebo-controlled adenoma prevention trials showed that selective Cox-2 inhibitors also had adverse side effects. In two large studies, long-term use of selective Cox-2 inhibitors was associated with an increase in serious cardiovascular adverse events, such as myocardial infarction and stroke. The risk for these events developed after approximately 18-24 months of drug use. The etiology of this cardiovascular toxicity is unknown, and it is unclear whether or not this problem also occurs following long-term use of non-selective NSAIDs. Selective Cox-2 inhibitors have many advantages as chemopreventive agents. Their beneficial effects include anti-inflammatory and analgesic activities, and they demonstrate activity against a variety of epithelial tumors, including tumors of the GI tract, head and neck, esophagus, bladder, lung, and breast. In order for these promising drugs to be used for cancer prevention, however, the risks and benefits of their use for this indication must be fully understood. This will require quantitative understanding of the cancer risk of individual patients, and the degree of risk reduction provided by selective Cox-2 inhibitor use. Future work must also develop optimal long-term drug dosing schedules that will minimize toxicity and maximize anti-tumor activity.