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Fluorescent inhibitors hold promise for early-stage tumor detection

29. April 2010 02:01

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"It was a real challenge to make a compound that is COX-2 selective (doesn't bind to the related COX-1 enzyme), has desirable fluorescence properties, and gets to the tissue in vivo," Marnett said.

To develop such compounds, Jashim Uddin, Ph.D., research assistant professor of Biochemistry, started with the "core" chemical structure of the anti-inflammatory medicines indomethacin and celecoxib. He then tethered various fluorescent parts to the core structure, ultimately synthesizing more than 200 compounds. The group tested each compound for its interaction with purified COX-2 and COX-1 proteins and then assessed promising compounds for COX-2 selectivity and fluorescence in cultured cells and in animals. Two compounds made the cut.

In studies led by senior research specialist Brenda Crews, the investigators evaluated the potential of these compounds for in vivo imaging using three different animal models: irritant-induced inflammation in the mouse foot pad; human tumors grafted into mice; and spontaneous tumors in mice.

In each case, the two fluorocoxibs - injected intravenously or into the abdominal cavity - accumulated in the inflamed or tumor tissue, giving it a fluorescent "glow."

To move the agents toward human clinical trials, the team will conduct additional toxicology and pharmacology testing and develop the tools for particular settings that are amenable to fluorescence imaging, such as skin or sites accessible by endoscope (e.g., esophagus and colon).

In the esophagus, for example, a pre-malignant lesion called Barrett's esophagus can transition to a low-grade dysplasia, then to a high-grade dysplasia, and finally to malignant cancer, which has a one-year survival of only 10 percent. For a patient with Barrett's esophagus, detecting the transition to dysplasia is critical. The problem is that dysplasia is not visibly different from the pre-malignant Barrett's lesion, so physicians collect random biopsy samples - which might miss areas of dysplasia.

"If instead, the physician could look through the endoscope and see a nest of cells lighting up with these fluorocoxibs - that is where they could biopsy," Marnett said.

"Because COX-2 levels increase during cancer progression in virtually all solid tumors,

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we think these imaging tools will have many, many different applications."

The investigators also are exploring using the compounds to target delivery of chemotherapeutic drugs directly to COX-2-expressing cells - by tethering an anti-cancer drug instead of a fluorescent marker to the COX-2 inhibitor core.

Source: Vanderbilt University Medical Center

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