ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Guest Section Editor: Axel Grothey, MD

Colorectal Cancer in Focus

Aspirin, the New Targeted Therapy in Colorectal Cancer

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H&O Could you briefly describe the relationship between aspirin and colorectal cancer (CRC)?

CF As far as prevention is concerned, randomized clinical trials have clearly demonstrated that taking aspirin reduces the risk of developing adenomas and cancer. These trials include work by Sandler and colleagues and by Baron and coauthors.

Observational studies conducted by our group and others also have found that CRC patients who have taken aspirin appear to have superior survival compared with their counterparts who have not taken aspirin. These are not randomized clinical trials, of course, so the evidence is still preliminary. We therefore have level 1 evidence for prevention, but not for treatment.

H&O What is the mechanism by which aspirin may improve survival in people with CRC?

CF The precise mechanism for a possible effect needs to be determined. In our own work, we anticipated that cyclooxygenase-2 (COX-2) might be the relevant target for aspirin. Indeed, in the laboratory aspirin does suppress COX-2 and inhibit the growth and development of tumors. Furthermore, about two-thirds of colorectal polyps and cancers overexpress COX-2.

On the prevention side, our group has conducted cohort studies that have looked at whether aspirin might preferentially inhibit tumors that overexpress COX-2. If inhibition of COX-2 is the mechanism by which aspirin works, it should prevent tumors that overexpress COX-2 but not those that grow without expressing COX-2. A study that we published in 2007 in the *New England Journal of Medicine*, with Chan as the lead author, showed us that aspirin preferentially reduces the risk of tumors that overexpress COX-2. This finding suggests that aspirin might be working by targeting COX-2 in the tumor.

Not only do we have clear evidence from the laboratory that aspirin inhibits the growth of tumors that overexpress COX-2, at higher doses it seems to work even in tumors that are COX-2–negative. That finding suggests that although targeting COX-2 appears to be a mechanism by which aspirin produces an effect, it likely is not the only mechanism.

Another finding that supports targeting of COX-2 as a mechanism is the fact that randomized trials with COX-2 inhibitors, such as the Bertagnolli trial using celecoxib that was published in the *New England Journal of Medicine* in 2006, also show an effect on prevention.

In 2009, our group published an article in the *Journal of the American Medical Association* with Chan as the lead author in which we looked at aspirin and survival in the Nurses' Health Study. What we found is that those patients with CRC who were taking aspirin after diagnosis had a significant improvement in mortality. Moreover, the benefit was principally found in the patients whose tumors overexpressed COX-2, which was approximately two-thirds of the patients. These

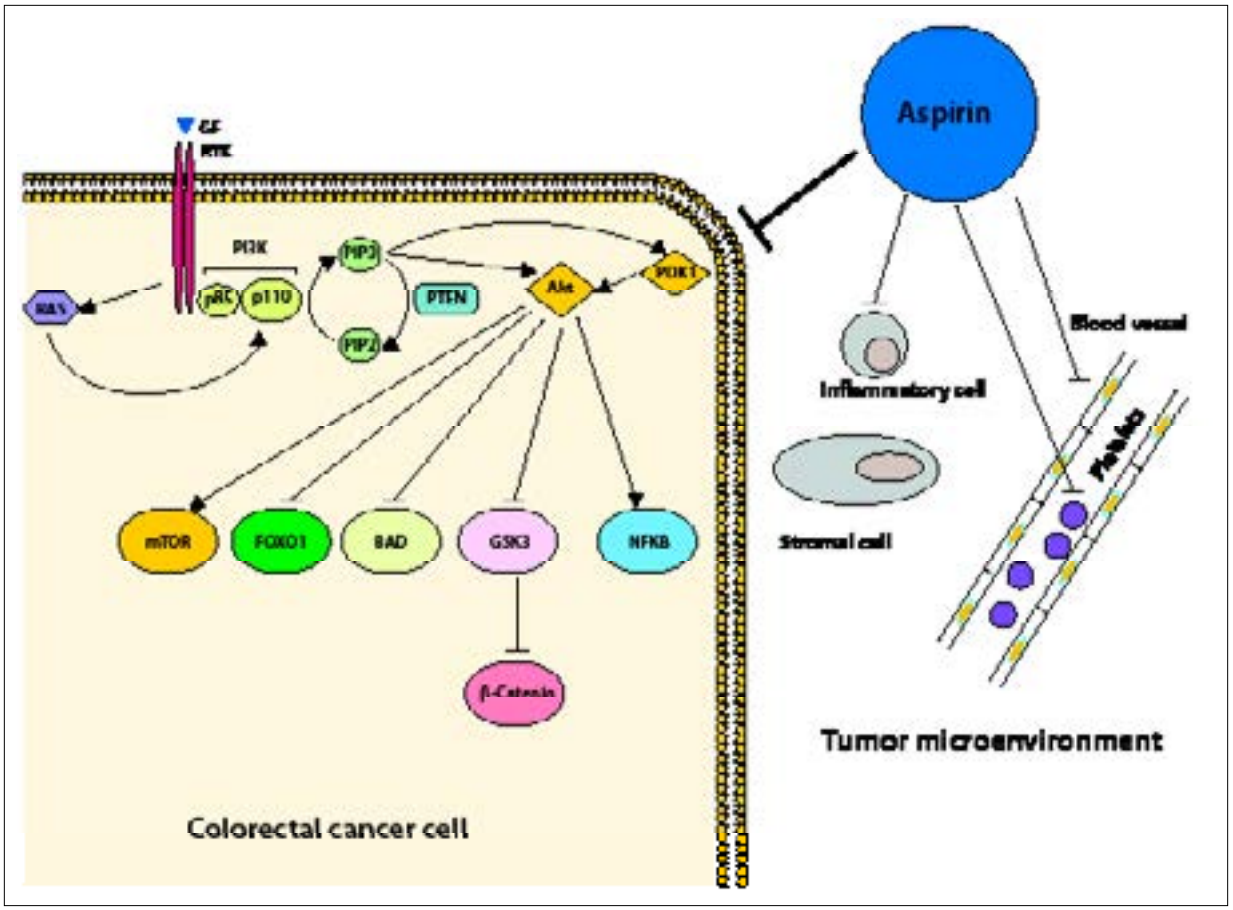

Figure. The phosphatidylinositol 3-kinase (PI3K) signaling pathway and its potential interaction with the influence of aspirin on colorectal cancer (CRC) and the tumor microenvironment. Arrows represent activation, whereas bars reflect inhibition. Activated PI3K converts phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3), leading to activation of the Akt and 3'-phosphoinositide-dependent kinase 1 (PDK1) kinases, which in turn phosphorylate several downstream effector pathways, thereby regulating a range of cellular processes, including cancer-cell proliferation, survival, motility, and metabolism. The tumor suppressor phosphatase and tensin homolog (PTEN) antagonizes PI3K activity by dephosphorylating PIP3. The mechanisms by which aspirin influences CRC cell growth and progression are poorly understood. Beyond a potential direct inhibitory effect of aspirin on CRC cells, aspirin may indirectly inhibit CRC progression through influences on the tumor microenvironment, including immune and inflammatory cells, platelets, and several other cell types. Note that the sizes and shapes of various cells and cellular compartments in this illustration do not reflect actual sizes and shapes.

BAD, Bcl-2 antagonist of cell death; FOX01, forkhead box 01; GF, growth factor; GSK, glycogen synthase kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; RTK, receptor tyrosine kinase.

results support the idea that targeting of COX-2 is the mechanism behind this purported effect, or at least a major mechanism. We still suspect that aspirin has other targets in addition to COX-2 that affect CRC.

Aspirin, of course, affects numerous components of cancer cells, including blood clotting factors and endothelial cells. These are relevant because people who die of CRC ultimately die from metastases. By targeting endothelial cells and blood clotting factors, aspirin might be able to reduce the ability of a tumor to successfully spread hematogenously and metastasize.

To make matters even more intriguing, our group published an interesting study on CRC survival in the *New England Journal of Medicine* in 2012 with Liao as the lead author. In this study, we found that tumors that had a *PIK3CA* mutation were uniquely sensitive to the benefits of aspirin; patients whose tumors harbored that mutation had a profound benefit. The cause of this relationship remains to be determined, but I have several hypotheses. For example, phosphatidylinositol 3-kinase (PI3K)/Akt appears to activate nuclear factor κB (NF-κB), a transcription factor that plays a pivotal role in upregulating proinflammatory genes,

including COX-2. Laboratory studies have found that aspirin inhibits the activity of NF-κB, reducing NF-κB expression (see the figure). Another possibility is that PI3K/Akt may activate the signaling of Wnt, which is an essential oncogenic pathway in CRC; several studies have suggested that aspirin inhibits the Wnt/β-catenin pathway.

The true story of how aspirin works remains complicated, however, and we are committed to figuring this out via our ongoing studies.

H&O Which types of colorectal tumors besides those that overexpress COX-2 and those with a *PIK3CA* mutation may be affected by the use of aspirin?

CF We published an article in the *Journal of the American Medical Association* in 2013—Nishihara was the first author—that examined aspirin use and the risk of CRC according to *BRAF* mutation status among participants in the Nurses' Health Study and the Health Professionals Follow-up Study. What we found is that people who used aspirin regularly were less likely to develop *BRAF*–wild-type CRC, but not *BRAF*-mutated CRC. In other words, CRC cells with a mutation in *BRAF* may be less sensitive to the effects of aspirin.

As far as survival is concerned, we do not have the answers yet. One might think that aspirin would work to treat the same types of tumors it appears to prevent, but agents that prevent a disease do not always work as treatments. One mutation might relate to tumor development, whereas a different mutation might play a role in progression of metastases. It will be interesting to see whether aspirin affects CRC survival based on *BRAF* mutation status, which is a question we are working to answer now.

H&O What are the other important studies that have examined the relationship between aspirin and improved survival in CRC?

CF One study was an analysis by Rothwell and colleagues of 5 clinical trials of daily aspirin vs control for the prevention of vascular events that was published in the *Lancet* in 2010. The researchers found that taking aspirin for several years reduced long-term incidence and mortality due to CRC. Many other studies have had similar findings.

H&O How much aspirin was required to produce an association in these studies?

CF The dose effect has been carefully studied in the prevention studies, and there does appear to be a dose response—more aspirin seems to confer a greater reduction in risk. On the survival side, we do not know yet. Most of the studies did not have enough statistical power to address the dose question because most people were taking either low-dose aspirin or 1 adult tablet per day.

H&O What are the potential downsides of using aspirin in patients with CRC?

CF The principal risk is bleeding, either gastrointestinal bleeding or bleeding from other sources. That risk is relatively low, which is why aspirin is recommended for primary prevention of heart disease. We have not seen significant toxicity issues in our studies. For the right patient who does not have an issue in terms of a prior history of acid peptic disease or a bleeding disorder, aspirin may be a reasonable medication to take as a chemopreventive agent or as an adjunct to cancer treatment.

H&O Are you working on any new studies that are examining the relationship between aspirin and CRC?

CF Absolutely; we are committed to testing this hypothesis in the context of a clinical trial. Right now I am working on CALGB-80702 (Cancer and Leukemia Group B Study 8072), which is a cooperative group, randomized trial sponsored by the National Cancer Institute. In this trial, individuals who have been diagnosed with stage III, lymph node–positive colon cancer following surgical resection are receiving postoperative adjuvant chemotherapy and are concurrently being randomly assigned to receive either celecoxib or a placebo. Our colleagues at the National Cancer Institute and many of our coinvestigators wanted to use a COX-2 inhibitor because it presumably acts on CRC with the same mechanism that aspirin does, and they thought that it might be more efficacious than aspirin. The study has so far enrolled approximately 1400 patients of the 2500 that are needed; we encourage our colleagues to enroll their stage III CRC patients in the study.

Another related study, which is taking place in Singapore, is ASCOLT (Aspirin for Dukes C and High Risk Dukes B Colorectal Cancers), in which patients who have been treated for stage II or III CRC are being randomly assigned to receive either aspirin or placebo (ClinicalTrials.gov identifier: NCT00565708).

H&O Has aspirin been linked to better survival in any types of cancer besides CRC?

CF The studies by Rothwell and colleagues have found a relationship between aspirin and better overall cancer mortality. Observational studies of specific types of cancer have suggested a benefit in breast cancer, lung cancer, and prostate cancer, but the data tend to be a little less

consistent with those cancers than with CRC. Whether a benefit exists remains to be determined. Some small studies have suggested that aspirin might benefit other types of gastrointestinal cancer, namely esophageal and gastric cancer.

Suggested Readings

Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med*. 2003;348(10):891-899.

Benson AB, Venook AP, Bekaii-Saab T, et al; National Comprehensive Cancer Network. NCCN guidelines version 3.2014: colon cancer. http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf. Updated January 27, 2014. Accessed January 28, 2014.

Bertagnolli MM, Eagle CJ, Zauber AG, et al; APC Study Investigators. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med*. 2006;355(9):873-884.

Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med*. 2007;356(21):2131-2142.

Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. *JAMA*. 2009;302(6):649-658.

ClinicalTrials.gov. Aspirin for Dukes C and High Risk Dukes B Colorectal Cancers (ASCOLT). http://clinicaltrials.gov/show/NCT00565708. Identifier: NCT00565708. Accessed January 28, 2014.

Fuchs CS, Ogino S. Aspirin therapy for colorectal cancer with PIK3CA mutation: simply complex! *J Clin Oncol*. 2013;31(34):4358-4361.

Kunzmann AT, Murray LJ, Cardwell CR, McShane CM, McMenamin UC, Cantwell MM. PTGS2 (cyclooxygenase-2) expression and survival among colorectal cancer patients: a systematic review. *Cancer Epidemiol Biomarkers Prev*. 2013;22(9):1490-1497.

Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. *N Engl J Med*. 2012;367(17):1596-1606.

McCowan C, Munro AJ, Donnan PT, Steele RJ. Use of aspirin post-diagnosis in a cohort of patients with colorectal cancer and its association with all-cause and colorectal cancer specific mortality. *Eur J Cancer*. 2013;49(5):1049-1057.

Nishihara R, Lochhead P, Kuchiba A, et al. Aspirin use and risk of colorectal cancer according to BRAF mutation status. *JAMA*. 2013;309(24):2563-2571.

Rothwell PM, Price JF, Fowkes FG, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet*. 2012;379(9826):1602-1612.

Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet*. 2010;376(9754):1741-1750.

Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med*. 2003;348(10):883-890.

Tsujii M, Kawano S, Tsuji S, Sawaoka H, Hori M, DuBois RN. Cyclooxygenase regulates angiogenesis induced by colon cancer cells. *Cell*. 1998;93(5):705-716.