

## Metastasis

**Major Finding:** Metastatic colorectal cancer may be seeded by clinically undetectable tumors.

**Approach:** Exome sequencing and a spatial computational model were used to model tumor growth and metastasis.

**Impact:** Mutations associated with early metastasis might help find patients who need aggressive treatment.

### SEEDS OF METASTATIC COLORECTAL CANCER ARE PLANTED EARLY IN DISEASE PROGRESSION

Although the dominant model of cancer progression is based on the assumption that the ability of cancer cells to metastasize arises in well-established primary tumors, there is some evidence that the evolution of metastatic capability may actually be an early event. Using exome-sequencing data from 118 biopsies gathered from 23 patients with metastatic colorectal cancer combined with a spatial computational model of tumor growth and a Bayesian statistical inference framework to time to metastasis, Hu and colleagues found further evidence supporting this notion, showing that metastases may be seeded by cells disseminated from primary tumors that are too small to be clinically detected—potentially years prior to diagnosis. By analyzing tumor-sequencing data (obtained in the MSK-Impact and Project GENIE studies) from 938 patients with metastatic colorectal cancer and 1,813 patients with early-stage colorectal cancer, the authors also demonstrated that combinations of mutations in specific genes (including clas-



sic colorectal cancer drivers) were far more prevalent in metastatic cases. For example, mutations in the *PTPRT* gene in combination with *APC*, *KRAS*, or *TP53* mutations were almost exclusively found in metastatic cases, suggesting their potential roles as prognostic biomarkers. Of note, *PTPRT*-mutated tumors have been reported to upregulate the *STAT3* pathway and hence may be responsive to *STAT3* inhibitors. Overall, these results highlight the need to develop noninvasive screening methods to assist in early cancer detection and illustrate the importance of identifying biomarkers to stratify early-stage patients at high risk of relapse for more aggressive therapy. Ultimately, it may also be possible to use such markers to guide molecularly targeted therapies directed at these specific genomic aberrations. ■

Hu Z, Ding J, Ma Z, Sun R, Seoane JA, Shaffer JS, et al. Quantitative evidence for early metastatic seeding in colorectal cancer. *Nat Genet* 2019;51:1113–22.

## Inflammation

**Major Finding:** Preoperative ketorolac, resolvins eliminated micrometastases, dormancy escape post-tumor resection.

**Mechanism:** COX1 inhibition is responsible for ketorolac's antitumor effects, and T-cell activity is required.

**Impact:** Potential of preoperative COX1 inhibitors or stimulation of inflammation should be further studied.

### SOME PREOPERATIVE NSAID<sub>s</sub> EXTEND LIFE AFTER TUMOR RESECTION IN MICE

Chemotherapy, radiation, tumor resection, and even biopsy can cause inflammation that leads to dormancy escape or metastasis. Panigrahy and colleagues showed that in multiple mouse models, a dose of ketorolac or resolvins promoted elimination of lung micrometastases, helped prevent dormancy escape, and enhanced long-term survival after tumor resection. Additionally, ketorolac prevented post-chemotherapy dormancy escape in mice injected with cisplatin-, vincristine-, or 5-fluorouracil-stimulated cancer cells. Importantly, all these results held only when ketorolac was administered preoperatively, but not postoperatively, when anti-inflammatory drugs are typically prescribed. Ketorolac's protective effects appear dependent on inhibition of COX1, which is preferentially inhibited by ketorolac; preoperative treatment with other selective COX1 inhibitors or resolvins also improved long-term survival after tumor resection. LC-MS/MS profiling showed thromboxane B<sub>2</sub> (TXB<sub>2</sub>), a hydration product of COX1-derived thromboxane A<sub>2</sub> (TXA<sub>2</sub>), was reduced in ketorolac-treated mice compared with controls after tumor resection, implying TXA<sub>2</sub> may be involved in ketorolac's effects. Further highlighting TXA<sub>2</sub>'s role, thromboxane prostanoid (TP) receptor (which is activated by TXA<sub>2</sub>) KO mice had greater long-term survival than wild-type mice. Moreover, a TP-TXA<sub>2</sub> antagonist prolonged survival following

tumor resection, whereas a TP receptor agonist increased lung metastasis and reduced ketorolac's protective effects. Because the selective COX2 inhibitor celecoxib abolished ketorolac's life-span extension when the two drugs were coadministered before tumor resection, basal COX2 activity may also be important for ketorolac's effects and stimulation of inflammation resolution. Immune checkpoint blockade improved the antitumor activity of ketorolac, whereas athymic mice did not exhibit antitumor effects, indicating that T-cell activity is also required. Preoperative administration of resolvins, omega-3 fatty acid-derived immunoresolvent agonists, also exhibited antitumor activity, but an omega-3 fatty acid-rich diet combined with low-dose aspirin did not yield any long-term survivors. Combination of chemotherapy with anti-inflammatory or proresolution therapies may be useful as it unleashes T-cell immunity to help fight therapy-stimulated cancer. Further investigation on this treatment's potential to enhance the effectiveness of current cancer therapies and possibly prevent tumor recurrence may be fruitful. ■

Panigrahy D, Gartung A, Yang J, Yang H, Gilligan MM, Sulciner ML, et al. Preoperative stimulation of resolution and inflammation blockade eradicates micrometastases. *J Clin Invest* 2019;129:2964–79.