Liquid Biopsy

Major Finding: A liquid biopsy–based method, dubbed EV-CLUE, discerned breast cancer invasiveness and metastasis.

Concept: Plasma analysis detected molecular and functional properties of cancer cell extracellular vesicles.

Impact: If validated in larger cohorts, this technique could be used in diagnosis and disease surveillance.

LIQUID BIOPSY METHOD IDENTIFIES CANCER INVASIVENESS AND METASTASIS

Extensive efforts are under way to develop and validate liquid biopsy methods for cancer diagnosis and surveillance due to these techniques' low invasiveness and potential for high throughput, among other features. Among these liquid biopsy methods are nascent techniques that involve analysis of extracellular vesicles (EV), which are produced by both cancer cells and normal cells. The origins of EVs can be determined based on molecular and functional characteristics, such as the presence and activity of certain metalloproteinases (MMP), making EVs attractive candidates for liquid biopsy analytes. Zhang and colleagues developed a nanopatterned lab-on-a-chip system dubbed EV-CLUE to detect the presence and proteolytic activity of MMP14 on EVs. Using this as a readout, *in vitro* experiments showed that the chips were able to correctly discern cancer cells based on their invasiveness. Additional experiments using both spontaneous and xenograft-based mouse models of metastatic breast cancer demonstrated that EV-CLUE could be used to detect *in vivo* tumor growth and metastasis in individual mice in a minimally invasive manner. Importantly, EV-CLUE was also able to discern whether plasma specimens were derived from patients diagnosed with ductal carcinoma *in situ*, invasive ductal carcinoma, or locally metastatic breast cancer with an accuracy of 96.7% in a 30-patient training cohort and 92.9% in a 70-patient validation cohort. In summary, this work describes a novel EV-based liquid biopsy method with demonstrated functionality in patients. Planned future work on EV-CLUE includes adapting the technology to work with whole blood rather than plasma alone, ensuring that the chips can be manufactured at scale, validating the technique using much larger patient cohorts, and longitudinally monitoring patients with high-risk *in situ* breast carcinomas for development of invasive or metastatic disease. ■

Zhang P, Wu X, Gardashova G, Yang Y, Zhang Y, Xu L, et al. Molecular and functional extracellular vesicle analysis using nanopatterned microchips monitors tumor progression and metastasis. Sci Transl Med 2020;12:eaaz2878.

Microbiome

Major Finding: Oxaliplatin caused ileal apoptosis and T_{fh}-cell enrichment and perturbed microbiota in colon cancer.

Mechanism: T_{fh} cells are primed by ileal microbiota–induced caspase activation in IECs and dendritic cell cytokines.

Impact: These findings provide insight into how bacteria mediate responses to chemotherapy or immunotherapy.

ILEAL APOPTOSIS AND MICROBIOTA MEDIATE COLON CANCER TREATMENT EFFICACY

In colon cancer, standard-of-care cytotoxic chemotherapy with oxaliplatin can elicit an immune response against the cancer but can also affect crypt-derived intestinal epithelial cells (IEC), thus having an impact on the local microbiota. To investigate the effects of this, Roberti and colleagues started by examining the effect of oxaliplatin-based chemotherapy–induced ileal cell apoptosis in colon cancer. In patients with stage IV proximal colon cancer, ileal apoptosis was associated with substantial perturbation of the local microbiota and an enrichment of the tumor bed with follicular helper T (T_{fh}) cells, which may influence prognosis. These results were also seen in an oxaliplatin-treated syngeneic mouse model of microsatellite instability (MSI)-high colon cancer, in which ileal apoptosis was accompanied by alterations in the local microbiota and the balance between T_{fh} and T_h17 cells in the tumor-draining lymph nodes. Further confirming these findings, similar observations were made in other mouse models, and experiments in these mice also revealed that suppression of caspase-3– and caspase-7–mediated IEC apoptosis reduced protective oxaliplatin-driven immunosurveillance against colon cancer. T_{fh} cells were crucial for this effect, with oxaliplatin-induced IEC death stimulating the T_{fh}-cell response to colon cancer. Mechanistically, T_{fh} priming was dependent not only on ileal IEC-derived caspase-3 and caspase-7, but also on the cytokines IL1β and IL12 produced by $BATF3^+$ conventional type 1 dendritic cells, and both the activation of the two caspases and the production of the two cytokines depended on the ileal microbiota. Preclinical data from experiments using organoids and mouse models revealed that ileal microbiota had a major role in the efficacy of oxaliplatin alone or with anti–PD-1 independently of MSI status, with the presence of certain commensal bacterial species enhancing the antitumor effects of these treatments. Collectively, these results suggest that ileal apoptosis and the local microbiota may substantially contribute to treatment efficacy in colon cancer and provide a mechanistic rationalization for this finding. ■

Roberti MP, Yonekura S, Duong CPM, Picard M, Ferrere G, Alou MT, et al. Chemotherapy-induced ileal crypt apoptosis and the ileal microbiome shape immunosurveillance and prognosis of proximal colon cancer. Nat Med 2020;26:919–31.