Tumor Microenvironment

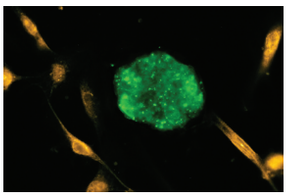
Major finding: Vascular permeability and immune cell infiltration are key determinants of drug efficacy.

Approach: Fluorescent reporter mice enabled live imaging of drug distribution and stromal cell tracking.

Impact: Inhibitors of matrix metalloproteinases or chemokine signaling may improve drug responses.

THE TUMOR MICROENVIRONMENT PROMOTES DRUG RESISTANCE

Most of what is known about tumor responses to cytotoxic chemotherapies is based on cell culture or tumor xenografts that do not accurately recapitulate the microenvironment of human cancers. To visualize tumor progression and drug response in the context of the tumor microenvironment and track stromal cells, Nakasone and colleagues crossbred the mammary tumor virus (MMTV) promoter-driven polyoma middle T oncogene (PyMT) mouse model to various fluorescent reporter lines and imaged live mice using spinning disk confocal microscopy. Treatment with doxorubicin reduced tumor volume in MMTV–PyMT mice with multiple tumors but induced more necrotic cell death in intermediate-stage tumors compared with early- or late-stage tumors. However, cancer cells from all tumor stages were similarly sensitive to doxorubicin *in vitro*, indicating that extrinsic drug resistance mechanisms operate *in vivo*. Real-time imaging following treatment with doxorubicin revealed that myeloid cells (labeled by colony-stimulating factor 1 receptor–enhanced GFP) were recruited to tumors and



that intratumoral doxorubicin concentrations were associated with vascular permeability (as measured by leakage of fluorescently labeled dextran into the extravascular space). Notably, mammary tumors transplanted into mice deficient for matrix metalloproteinase 9, a host inhibitor of vascular permeability, or chemokine (C-C motif) receptor 2, which mediates recruitment of myeloid cells to tumors, showed increased sensitivity to doxorubicin. These findings indicate that vascular permeability and chemokine signaling regulated by components of the tumor microenvironment mediate extrinsic drug resistance and that combining matrix metalloproteinase or chemokine signaling inhibitors with traditional chemotherapy may improve clinical outcomes. ■

Nakasone ES, Askautrud HA, Kees T, Park JH, Plaks V, Ewald AJ, et al. Imaging tumor-stroma interactions during chemotherapy reveals contributions of the microenvironment to resistance. Cancer Cell 2012;21:488–503.

Lung Cancer

Major finding: Phased, but not concurrent ipilimumab plus paclitaxel and carboplatin improves NSCLC outcome.

Concept: Chemotherapy-induced antigen release prior to ipilimumab treatment may increase efficacy.

Impact: The sequence of chemotherapy and immunotherapy administration affects outcome in NSCLC.

PHASED IPILIMUMAB IMPROVES SURVIVAL IN NON–SMALL CELL LUNG CANCER

Ipilimumab, a monoclonal antibody that blocks the binding of cytotoxic T-cell lymphocyte-4 (CTLA-4) to its ligands and augments antitumor T-cell responses, has previously been shown to improve overall survival in patients with metastatic melanoma. Preclinical studies have suggested that cytotoxic agents such as taxanes and platinum-based compounds may potentiate ipilimumab activity and promote T-cell–mediated responses to tumor-specific antigens released by dying tumor cells. Based on these clinical and preclinical findings, Lynch and colleagues conducted a randomized, double-blind, international, multicenter phase II study to determine whether ipilimumab is also effective in non–small cell lung cancer (NSCLC) in combination with paclitaxel and carboplatin, a common first-line treatment for NSCLC. Previously untreated NSCLC patients were randomly assigned to receive paclitaxel and carboplatin plus either placebo or ipilimumab in either a concurrent regimen or a phased regimen in which several doses of paclitaxel and carboplatin were given prior to ipilimumab, with the rationale that antigen release and T-cell activation would presumably occur before ipilimumab treatment. Phased ipilimumab improved immune-related progression-free survival to 5.7 months compared with 5.5 months for concurrent ipilimumab and 4.6 months for placebo. Phased ipilimumab also increased the median overall survival compared with concurrent ipilimumab and placebo (12.2, 9.7, and 8.3 months, respectively). The most common adverse events were typically those associated with paclitaxel and carboplatin, and immune-related adverse events were similar to those observed in previous ipilimumab clinical trials. Collectively, these findings suggest that the use of chemotherapy prior to anti–CTLA-4 immunotherapy may improve clinical outcome and indicate that further studies of ipilimumab in combination with chemotherapy are warranted in NSCLC. ■

Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non–small cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 2012 Apr 30 [Epub ahead of print].

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