

## Chemotherapy

**Major finding:** Inflammasome activation in MDSCs induced by gemcitabine and 5-FU suppresses antitumor immunity.

**Mechanism:** The NLRP3 inflammasome stimulates IL-1 $\beta$  release, which enhances IL-17 secretion by CD4<sup>+</sup> T cells.

**Impact:** Inhibitors of IL-1 $\beta$  or the NLRP3 inflammasome may increase the efficacy of chemotherapeutic agents.

### CHEMOTHERAPY EFFICACY IS LIMITED BY INFLAMMASOME ACTIVATION

Chemotherapeutic agents exert cytotoxic effects on tumor cells but can also affect host immune responses. Some drugs, such as gemcitabine and 5-fluorouracil (5-FU), can selectively eliminate a population of immunosuppressive host cells known as myeloid-derived suppressor cells (MDSC), but their antitumor effects are limited. Bruchard and colleagues further characterized the effects of gemcitabine and 5-FU on MDSCs to gain insight into resistance mechanisms and found that both drugs induced lysosome permeabilization in the MDSCs of tumor-bearing mice, causing cathepsin B release. Cathepsin B bound and activated the NOD-like receptor family, pyrin domain containing-3 protein (NLRP3)-dependent caspase-1 activation complex (also known as the NLRP3 inflammasome), culminating in caspase-1 activation and production of interleukin (IL)-1 $\beta$ . Induction of this pathway leading to IL-1 $\beta$  secretion by MDSCs reduced the antitumor activity of the chemotherapeutic agents, as 5-FU was more effective in tumor-bearing *Nlrp3*- and *Casp1*-null mice as well as in wild-type mice treated with anakinra, an IL-1 receptor (IL-1R) antagonist approved for

treatment of rheumatoid arthritis. The level of IL-1 $\beta$  produced by MDSCs in response to gemcitabine and 5-FU was sufficient to drive IL-17 production by inflammatory CD4<sup>+</sup> T cells. CD4 depletion or genetic inactivation of IL-17 enhanced the antitumor effect of 5-FU in an IL-1R-dependent manner, indicating that MDSC-induced IL-17 production in CD4<sup>+</sup> T cells serves to limit the efficacy of chemotherapeutic agents. Importantly, cathepsin B and caspase-1 induction were observed in circulating MDSCs and serum IL-1 $\beta$  levels were elevated in the majority of a group of patients with metastatic colorectal cancer treated with 5-FU, suggesting that these findings have clinical relevance and raising the possibility that agents already approved or in development for inflammatory disorders may increase the efficacy of chemotherapeutic agents. ■

*Bruchard M, Mignot G, Derangère V, Chalmin F, Chevriaux A, Végran F, et al. Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth. Nat Med 2012 Dec 2 [Epub ahead of print].*

## Metastasis

**Major finding:** Reversion of EMT is necessary for proliferation and colonization of disseminated tumor cells.

**Approach:** TWIST1 was induced systemically or locally in a mouse model of skin carcinogenesis.

**Impact:** Inhibition of EMT reversion may prevent the metastatic outgrowth of dormant tumor cells.

### DYNAMIC EPITHELIAL-MESENCHYMAL TRANSITION DRIVES METASTASIS

Epithelial-mesenchymal transition (EMT) promotes the invasion and dissemination of tumor cells and enhances metastasis in xenograft models. However, in human carcinoma, distant metastases often exhibit an epithelial phenotype, casting doubt on the contribution of EMT to metastasis *in vivo*. To address this controversy, Tsai and colleagues used a mouse model of chemically-induced skin carcinogenesis in which TWIST1, an EMT-inducing transcription factor that is associated with increased metastasis and poor survival, was conditionally activated in skin cells by either systemic or topical administration of doxycycline to model irreversible or reversible EMT, respectively. TWIST1 expression in both models facilitated progression of benign papillomas to invasive squamous cell carcinomas with a mesenchymal morphology. Intriguingly, only restricted induction of TWIST1 at the primary tumor site, but not continuous TWIST1 induction in disseminated tumor cells, resulted in increased incidence of distant metastases. These metastases lacked TWIST1 but expressed E-cadherin, indicative of an epithelial morphology and supporting the idea that reversible EMT promotes metastasis. TWIST1-mediated EMT was



necessary for intravasation of circulating tumor cells, which expressed TWIST1 and other EMT markers, into the circulation and extravasation of tumor cells out of the lung vasculature, suggesting that reversion of EMT may drive metastatic colonization. Indeed, carcinoma cell proliferation was inversely correlated with TWIST1 expression, and turning off TWIST1 induction increased the proliferation of early metastatic colonies and augmented the establishment of lung nodules compared with tumor cells that maintained TWIST1 expression. In addition, in a panel of human breast carcinoma samples, among the primary tumors with high TWIST1 expression, most of the patient-matched lymph node metastases showed reduced TWIST1 levels. These findings demonstrate that EMT plays a dynamic role in tumor metastasis and suggest that blocking EMT reversion in disseminated dormant tumor cells may prevent metastasis development. ■

*Tsai JH, Donaher JL, Murphy DA, Chau S, Yang J. Spatiotemporal regulation of epithelial-mesenchymal transition is essential for squamous cell carcinoma metastasis. Cancer Cell 2012;22:725-36.*

**Note:** Research Watch is written by Cancer Discovery Science Writers. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit Cancer Discovery online at <http://CDnews.aacrjournals.org>.