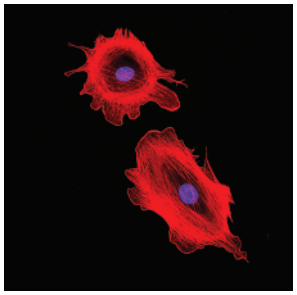
Metastasis

Major Finding: Overexpression of some essential genes for metastasis led to cell stiffness–based immunosurveillance.

Concept: These genes encode isoforms of a transcription factor that regulates expression of cytoskeletal genes.

Impact: This study reveals that immunosurveillance by cytotoxic T lymphocytes has a mechanical component.

CYTOTOXIC IMMUNE CELLS SUPPRESS METASTASIS VIA MECHANICAL SENSING



To acquire metastatic capabilities, cancer cells must undergo cytoskeletal alterations. These changes are mediated in part by myocardin-like transcription factors (MRTF) A and B, which promote transcription of the genes encoding G-actin and other cytoskeletal components. Tello-Lafoz and colleagues found that metastatic colonization by melanoma or breast cancer cells was reduced by *Mrtfa* or *Mrtfb* knockdown, as expected. However, in seeming contradiction with the two MRTF isoforms' essentiality for metastatic seeding, *Mrtfb* overexpression also compromised the cancer cells' metastatic potential. This phenotype was suppressed by depletion of natural killer cells or $CD8^+$ T cells, suggesting a role for immunosurveillance by these lymphocytes in constraining metastasis by *Mrtfb*-overexpressing tumor cells. Consistent with this notion, *in vitro* experiments showed *Mrtfa* or *Mrtfb* overexpression rendered cancer cells more sensitive to cytotoxic T lymphocyte–mediated killing, with each immune synapse formed being more likely to induce (and more rapidly promoting) cancer cell death. Mechanistically, *Mrtfa* or *Mrtfb* overexpression led to increased levels of transcripts encoding actins and other cytoskeletal proteins, suggesting a possible role for MRTF-mediated cytoskeletal changes in the higher immunogenicity of cancer cells overexpressing either of these genes. Accordingly, atomic force microscopy experiments showed that overexpression of *Mrtfa* or *Mrtfb* rigidified cancer cells both on average and at peak stiffness levels, effects that were diminished in the presence of an F-actin depolymerizing agent. Further experiments confirmed that it was not cell-surface features, but rather cellular features generated by components enclosed by the plasma membrane—presumably the actin cytoskeleton—that caused *Mrtfa*- and *Mrtfb*-overexpressing cancer cells to be more susceptible to immune control. Correspondingly, expression of a *Salmonella enterica* gene encoding a protein that severs F-actin reduced cell stiffness and abolished the increased sensitivity to cytotoxic T lymphocyte–mediated killing otherwise observed with *Mrtfa* or *Mrtfb* overexpression in cancer cells. Collectively, these findings support the idea that mechanical sensing is an important component of immunosurveillance that may act to suppress metastasis. ■

Tello-Lafoz M, Srpan K, Sanchez EE, Hu J, Remsik J, Romin Y, et al. Cytotoxic lymphocytes target characteristic biophysical vulnerabilities in cancer. Immunity 2021 Mar 22 [Epub ahead of print].

Clinical Trial

Major Finding: A phase I/II trial demonstrated a response rate of 72% in patients with relapsed or refractory disease.

Concept: Copanlisib is a PI3Kα/δ inhibitor, and PI3K pathway hyperactivation is common in this malignancy.

Impact: This combination may provide a new option for these patients, for whom prognosis is otherwise poor.

COPANLISIB PLUS GEMCITABINE HAS EFFICACY IN PERIPHERAL T-CELL LYMPHOMAS

The median overall survival for patients with relapsed or refractory (R/R) peripheral T-cell lymphomas (PTCL), a group that includes a variety of mature T– and natural killer–cell lymphomas that often exhibit hyperactivation of the PI3K–AKT–mTOR pathway, is 5.5 months, underscoring the need for more effective treatments. Phase II clinical trials have demonstrated moderate efficacy for both the PI3Kα/δ inhibitor copanlisib and the pyrimidine antimetabolite gemcitabine as monotherapies in patients with R/R PTCLs, and preclinical data have suggested that copanlisib and gemcitabine may act synergistically. In a phase I/II clinical trial, Yhim, Kim, and colleagues evaluated the combination of copanlisib and gemcitabine in patients with R/R PTCL. Six patients were treated in the dose-escalation, phase I portion of the trial, and the three of these patients treated at the determined maximum tolerated dose proceeded into the phase II portion of the trial, which enrolled an additional 22 patients for a total of 25 patients. Among these 25 patients whose disease was evaluable for response, the overall response rate was 72% and the complete response rate was 32%. Of those whose disease responded to the combination treatment, the median duration of response was 8.2 months. Promisingly, after a median follow-up period of 8.9 months, the median overall survival was not reached. An exploratory biomarker analysis showed that mutations in *TSC2, PIK3C2B*, or *YTHDF2* were found only in patients whose disease responded to treatment, whereas mutations in *VAV1* occurred only in those whose disease did not respond. The safety and tolerability profile of the combination treatment was favorable compared with the previously observed profiles of copanlisib and gemcitabine alone, with the most common treatment-emergent grade 3 or greater adverse events being transient hyperglycemia, neutropenia, thrombocytopenia, and hypertension. In summary, this work demonstrates the potential of combination treatment with copanlisib and gemcitabine in patients with R/R PTCLs, providing a possible option for addressing this unmet clinical need. ■

Yhim HY, Kim T, Kim SJ, Shin HJ, Koh Y, Kim JS, et al. Combination treatment of copanlisib and gemcitabine in relapsed/refractory PTCL (COSMOS): an open-label phase I/II trial. Ann Oncol 2021;32:552–9.

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