Chemotherapy Triggers T Cells to Remodel the Extracellular Matrix and Promote Metastasis

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Chemotherapy can impede cancer progression and is a well-demonstrated component of curative care for some patients with nonmetastatic cancer. However, cancer often relapses in high-risk patients due to acquired chemoresistance and progression to an incurable metastatic stage. There is building evidence from mouse models suggesting a possible stimulatory effect of chemotherapy on metastasis. While clinical trial data from patients with cancer supports the benefits of chemotherapy, the potential adverse effects of chemotherapeutics in a yet unidentified subset of patients are important to consider. In a study by Haj-Shomaly and colleagues, the interaction between the immune system and extracellular matrix remodeling is investigated for its role in the process. The study sheds light on the role of lysyl oxidase secreted by $CD8^+$ T cells in priming the lung microenvironment for metastatic cell seeding, which may represent a targetable axis to further enhance the efficacy of chemotherapy agents.

See related article by Haj-Shomaly et al., p. 278

While there has been great progress in approaches to treat primary tumors, metastatic cancer dissemination still brings a grim prognosis for patients with cancer. Despite an initial and at times even prolonged response to chemotherapy or targeted therapies in breast cancer, tumor cells eventually develop resistance in virtually all cases and patients subsequently succumb to cancer mortality due to metastatic disease progression. A growing number of preclinical observations have raised a question of whether chemotherapy may push select cancers toward lethal metastatic stages as a survival mechanism (1), although clinical investigations demonstrating the translational relevance of this phenomenon are still lacking. Mechanisms underlying chemotherapy-mediated metastatic progression have started to emerge (2), which may provide new avenues for combination therapies to further improve cancer outcomes and potentially reduce off-target toxicity from these drugs.

In this issue of *Cancer Research*, a collaborative study led by Yuval Shaked at the Israel Institute of Technology discovers a new mechanism through which chemotherapy may complicate cancer intervention (3). Using mouse models of breast cancer, the researchers show that T cells promote metastasis by regulating extracellular matrix (ECM) remodeling and mechano-structural changes in the lungs following chemotherapy with paclitaxel. The role of leukocytes in promoting metastasis has been a subject of active pursuit (4). Previously, $CD4^+$ T cells have been implicated in metastasis promotion (5). Here, Haj-Shomaly and colleagues identify $CD8^+$ T cells being responsible for promoting metastasis upon paclitaxel treatment. Adoptive transfer of cells from paclitaxel-treated mice confirmed that $CD8^+$ T cells, but not $CD4^+$ cells or B cells, increase pulmonary ECM changes.

In this study, plasma transplantation experiments indicated that metastasis seeding was promoted by a soluble factor (3). Lysyl oxidase (LOX), an extracellular enzyme that catalyzes collagen and elastin cross-linking and hence stabilizes collagen fibrils, was identified as a key enabling factor. This was confirmed by LOX inhibition experiments in which the metastasis-promoting effects of paclitaxel were suppressed. While depletion of LOX from plasma reduced lung ECM remodeling, other molecules could also contribute to the process. The study provides evidence that $CD8^+$ T cells express higher levels of LOX in the spleen and lungs and that their presence in the circulation is elevated upon paclitaxel treatment. $CD8^+$ T cells were also shown to be responsible for LOX elevation upon paclitaxel treatment through the use of a chimeric mouse LOX knockout model and adoptive transfer. The relative importance of systemic elevation of circulating LOX versus LOX locally secreted by infiltrating $CD8^+$ T cells remains to be determined. Interestingly, paclitaxel-activated $CD8^+$ T cells did not contribute to ECM remodeling in the spleen. This again suggests that factors other than LOX are important for enabling metastatic seeding. Previously, the same group reported that paclitaxel chemotherapy promoted metastases by matrix metalloproteinase-9 (MMP9) expressed by bone marrow–derived cells. The exact identity of these cells is still unclear, and the possible cooperation of MMP9 and LOX in modifying the ECM remains to be explored.

Research over the past decade has shed light on other mechanisms underlying chemoresistance and metastasis. The epithelial-to-mesenchymal transition (EMT) is one of the processes linked with increased chemoresistance and invasiveness. Importantly, studies by the Kolonin lab and others have revealed that EMT is promoted in carcinoma cells treated with chemotherapy in preclinical models (2). The involvement of LOX and MMP9 in EMT induction observed in previous studies remains to be investigated. The report by Haj-Shomaly and colleagues also needs to be put into the context of other studies linking chemotherapy and metastasis. Chemotherapy has been shown to induce immuno-evasive properties in cancer cells (6), and ECM softening in residual tumors and NF-κB activation has been linked with chemoresistance in breast cancer models (7). Chemotherapy also changes the tumor microenvironment at the primary site to enable metastatic cell dissemination (8). Because ECM remodeling in primary tumors may also be rate-limiting for metastasis, it would be important to consider the effects of chemotherapy on LOX and the collagen matrix in primary tumors.

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A number of other questions remain unanswered. First, it is not clear how T cells respond to different kinds of chemotherapy. Both taxanes and anthracyclines have been found to elicit tumor-derived extracellular vesicles that tune the pulmonary premetastatic niche to facilitate lung metastasis (9). Only paclitaxel has been investigated by Haj-Shomaly and colleagues, and it would be interesting to test LOX induction in response to different types of drugs including those relevant in different subtypes of breast cancer. Also, it is not known if these interesting findings are applicable to other cancer types. So far, the link of sublethal chemotherapy to cancer metastasis has only been reported for breast cancer models.

While the body of evidence from animal models is building, clinical evidence including hundreds of thousands of patients and long, uniform follow-up has demonstrated the benefits of chemotherapy. The disconnect between preclinical studies implying chemotherapy-induced complications and phase III trials showing the benefits of chemotherapy (10) might be explained by either of two hypotheses. First, the metastasis models used and treatments given in the lab may not adequately or relevantly model patient care, making the findings clinically irrelevant. Alternatively, in addition to the patients clearly shown to benefit from systemic therapy in phase III studies (10), there may be a small number who are harmed but whose outcomes are obscured by the heterogeneity of the population studied. It will be important to evaluate the factors identified in this study (3) and other animal studies as potential predictors of clinical risk.

Authors' Disclosures

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