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Imaging

Major finding: Imaging of liver premicrometastases identified a link between cell migration and outgrowth.

Approach: High-resolution imaging through an abdominal window was used for long-term study of metastasis.

Impact: This technique can also be used to dissect biologic processes in other abdominal organs.

AN ABDOMINAL IMAGING WINDOW PROVIDES INSIGHT INTO EARLY METASTASIS

Intravital microscopy using imaging windows in tumor-bearing mice has provided insight into the complex, multistep process of metastasis. However, existing windows are not well suited for long-term visualization of metastasis-prone abdominal organs, such as the lung and liver. To better study the dynamics of metastatic colonization, Ritsma and colleagues developed an abdominal imaging window (AIW) consisting of a titanium ring and a coverslip inserted into the skin and abdominal wall of mice using purse-string sutures. The AIW remained securely in place, did not impair the mobility or health of the animals, and did not alter abdominal tissue structure. Long-term imaging through the AIW enabled visualization of biologic processes in various abdominal organs, including stem cell division in the small intestine, islet cell engraftment in the kidney, and immune responses in the spleen, suggesting that this technique may have broad applications. Furthermore, the AIW allowed for imaging of clonal metastatic outgrowth from single fluorescently labeled colorectal tumor cells in a standardized liver metastasis assay. Tracking of proliferating tumor cells at subcellular resolution suggested that tumor cells grow into loosely packed premicrometastases in which cells are migratory and subsequently condense into micrometastases in which cells are nonmotile. Indeed, quantification of cell motility revealed enhanced migration of these premicrometastatic cells compared with cells within micrometastases, which did not form protrusions. Suppression of colorectal tumor cell migration using a phospholipase C inhibitor or LIM kinase overexpression specifically diminished the proliferation of premicrometastatic cells but not cells at later stages and resulted in decreased formation of larger metastatic outgrowths. Although further research is necessary to confirm these data in other tumor models and in human samples, these findings suggest a contribution for migration in the early steps of colonization and that blockade of this process may limit metastatic outgrowth. ■

Ritsma L, Steller EJ, Beerling E, Loomans CJ, Zomer A, Gerlach C, et al. Intravital microscopy through an abdominal imaging window reveals a pre-micrometastasis stage during liver metastasis. Sci Transl Med 2012;4:158ra145.

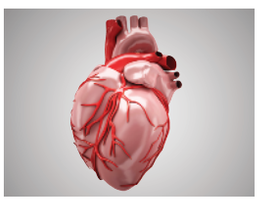
Chemotherapy

Major finding: Deletion of *Top2b* in cardiomyocytes protects mice from cardiotoxicity caused by doxorubicin.

Concept: Doxorubicin and TOP2β induce DSBs and transcriptional changes that result in mitochondrial dysfunction.

Impact: *TOP2B* may be useful as a predictor of susceptibility to doxorubicin-induced cardiotoxicity.

TOPOISOMERASE IIβ MEDIATES DOXORUBICIN-INDUCED CARDIOTOXICITY



Doxorubicin is a widely used chemotherapeutic agent, but its clinical use is often limited by dose-dependent cardiotoxicity. Doxorubicin induces double-strand breaks (DSB) and cell death by intercalating into DNA and blocking the activity of the topoisomerase II (TOP2) enzymes, TOP2α and TOP2β. TOP2α is highly expressed in tumors compared with quiescent tissues and is thus thought to mediate doxorubicin's cytotoxic effects on cancer cells. Zhang and colleagues hypothesized that doxorubicin-induced cardiotoxicity might be mediated by TOP2β, the only TOP2 enzyme expressed in cardiomyocytes. To evaluate the role of TOP2β in doxorubicin-induced cardiac dysfunction, the authors generated conditional mice with cardiomyocyte-specific deletion of *Top2b* and treated them with doxorubicin. After 16 hours of treatment, wild-type cardiomyocytes showed marked upregulation of apoptotic genes and activation of the DNA damage response compared with *Top2b*-null cardiomyocytes, consistent with a role for TOP2β in doxorubicin-induced DSBs and cell death. After 72 hours of exposure to doxorubicin, genes required for mitochondrial biogenesis and oxidative phosphorylation were selectively repressed in wild-type cardiomyocytes, suggesting a mechanism by which doxorubicin might exert negative effects on mitochondria in the presence of TOP2β. Indeed, mitochondrial membrane potential and oxygen consumption were compromised, and structural damage and reactive oxygen species generation were increased in wild-type cardiomyocytes compared with their *Top2b*-null counterparts. Chronic doxorubicin exposure also increased end systolic and end diastolic volumes and reduced ejection fraction in wild-type mice but not *Top2b*-null mice, further indicating that the harmful effects of doxorubicin on cardiac function require TOP2β. These findings suggest that high expression of TOP2β in cardiomyocytes may be a predictive biomarker for doxorubicin-induced cardiotoxicity and that anticancer agents that selectively target TOP2α may be less cardiotoxic. ■

Zhang S, Liu X, Bawa-Khalfe T, Lu LS, Lyu YL, Liu LF, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med 2012;18:1639–42.

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AACR American Association for Cancer Research

CANCER DISCOVERY

An Abdominal Imaging Window Provides Insight into Early Metastasis

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