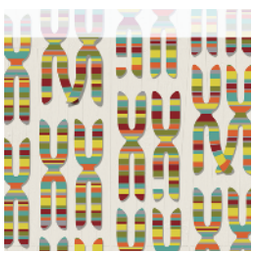
IN THIS ISSUE

HORMAD1 Drives Genomic Instability in Triple-Negative Breast Cancer

- Allelic-imbalanced copy number aberrations (AiCNA) are elevated in platinum-sensitive TNBC.
- Increased expression of the meiotic gene *HORMAD1* is associated with a high AiCNA frequency.
- HORMAD1 suppresses homologous recombination and confers sensitivity to cisplatin and PARP inhibitors.



Triple-negative breast cancers (TNBC) display a wide range of genomic alterations, but the associations between mutational patterns and drug response and the underlying mechanisms are poorly understood. Watkins and colleagues analyzed SNP array data to obtain allele-specific profiles from a cohort of TNBCs and identified distinct patterns of genomic instability. A subset of TNBCs was distinguished by frequent allelic-imbalanced copy-number aberrations (AiCNA), and a high degree of allelic imbalance was associated with response to platinum-based chemotherapy. *HORMAD1*, a meiotic gene normally expressed only in germline cells, was the most differentially expressed gene in tumors with a high allelic imbalance score and was expressed in approximately 60% of TNBCs. As in meiotic cells, HORMAD1 localized to the nuclei of TNBC cells and associated with chromatin, but overexpression of HORMAD1 in TNBC cells significantly increased AiCNAs and structural chromosomal abnormalities. Similar to its role in meiosis, where HORMAD1 suppresses RAD51-dependent conservative sister chromatid recombination to promote crossover and genetic exchange between homologous chromosomes, inappropriate HORMAD1 expression in TNBC cells suppressed RAD51-dependent homologous recombination in favor of nonhomologous end joining. HORMAD1 expression also conferred sensitivity to cisplatin and PARP inhibitors, which are active in homologous recombination–deficient cells, and predicted response to platinum-based therapy. Collectively, these results provide evidence that aberrant expression of a meiotic protein can suppress homologous recombination to induce distinct patterns of genomic instability in cancer cells and may have implications for stratification and treatment of patients with TNBC. ■

See article, p. 488.

Loss of RAI2 Promotes Early Hematogenous Dissemination in Breast Cancer

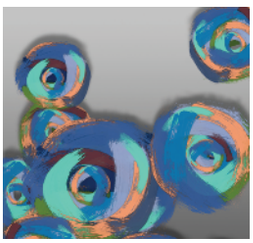
- Low *RAI2* expression is significantly associated with DTCs and poor overall survival.
- RAI2 depletion increases the dedifferentiation and invasion of luminal breast cancer cells.
- RAI2 regulates transcription and cell migration via interaction with CtBP corepressors.

Outgrowth of dormant disseminated tumor cells (DTC) in the bone marrow drives metastasis and tumor relapse after chemotherapy. However, the molecular pathways that regulate early hematogenous dissemination of DTCs to the bone marrow remain poorly defined. Werner and colleagues found that downregulation of retinoic acid–induced 2 (*RAI2*) was significantly associated with the presence of DTCs in the bone marrow of patients with luminal breast cancer and with poor overall survival in 10 datasets of various cancer types. High RAI2 levels correlated strongly with estrogen receptor α (ERα)–positive status and the luminal breast cancer subtype, which are associated with well-differentiated tumors and good clinical outcome. RAI2 depletion in luminal breast cancer cells resulted in decreased expression of ERα and key regulators of breast epithelial differentiation, including FOXA1 and GATA3, implicating RAI2 in the maintenance of breast epithelial integrity. In addition, RAI2 loss resulted in increased cell migration and invasion, AKT activation, and phenotypic changes characteristic of epithelial-to-mesenchymal plasticity. Functional analyses revealed that RAI2 interacted with C-terminal binding protein (CtBP) transcriptional repressors to modulate gene expression, and that the ability of RAI2 to suppress cell migration was partially dependent on its interaction with CtBP. Together, these data suggest that RAI2 may function as a suppressor of early hematogenous tumor spread and that its loss is critical for the onset of bone metastasis in ERα-positive breast cancer. ■

See article, p. 506.

Functional Crosstalk between Cell Subpopulations Drives Tumor Initiation

- Mesenchymal-like $CD29^{hi}CD24^{lo}$ tumor cells interact with TICs in a *Trp53*-null breast cancer mouse model.
- $CD29^{hi}CD24^{lo}$ niche cells secrete factors that promote TIC self-renewal and tumorigenicity.
- Suppression of the WNT pathway in niche cells or TICs decreases TIC tumorigenicity.

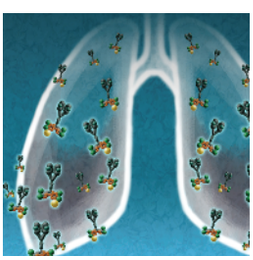


Intratumoral heterogeneity affects patient response to treatment and correlates with clinical prognosis. While previous studies have focused on deciphering the interactions between tumor cells and their microenvironment, little is known about how paracrine signaling between different tumor cell subpopulations contributes to tumorigenesis. Using a mouse model of breast cancer driven by *Trp53* loss, Zhang and colleagues found that a subpopulation of lineage $(Lin)^{-}CD29^{hi}CD24^{lo}$ tumor cells expressed high levels of WNT ligands, whereas $Lin^{-}CD29^{hi}CD24^{hi}$ tumor-initiating cells (TIC) exhibited upregulation of WNT targets and receptors, suggesting potential cross-talk between the two cell populations. Further characterization of the $CD29^{hi}CD24^{lo}$ niche subpopulation revealed a lower proliferative index compared with TICs and a mesenchymal-like phenotype. Importantly, $CD29^{hi}CD24^{lo}$ niche cells promoted the self-renewal capacity of TICs *in vitro* via secretion of soluble factors including WNT2 and chemokine (C-X-C motif) ligand 12 (CXCL12). In support of the notion that specific paracrine signals play a functional role in modulating the tumorigenic potential of TICs, knockdown of WNT2 and CXCL12 in $CD29^{hi}CD24^{lo}$ niche cells or depletion of the corresponding receptors, FZD7 and CXCR4, in TICs inhibited the ability of $CD29^{hi}CD24^{lo}$ cells to promote TIC self-renewal *in vitro*. Furthermore, in limiting dilution transplantation assays, $CD29^{hi}CD24^{lo}$ niche cells enhanced the tumor-initiating potential of TICs, which was reduced by downregulation of WNT2 in the $CD29^{hi}CD24^{lo}$ subpopulation. Together, these data highlight the importance of paracrine crosstalk between different tumor cell subpopulations in promoting tumor initiation. ■

See article, p. 520.

MIG6 Acts as a Tumor Suppressor in Mutant EGFR–Driven Lung Adenocarcinoma

- *Mig6* loss accelerates mutant EGFR–driven lung tumorigenesis in genetically engineered mouse models.
- MIG6 is constitutively phosphorylated at Y394/Y395 by mutant EGFR in lung cancer cells.
- MIG6 phosphorylation at Y394/Y395 enhances its interaction with and decreases its inhibition of EGFR.

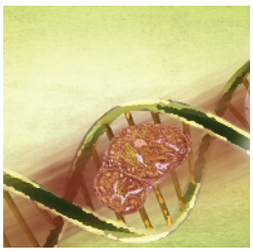


Constitutively activating mutations in EGFR are frequently detected in lung adenocarcinomas and render cells sensitive to EGFR-directed tyrosine kinase inhibitors (TKI) such as erlotinib. However, acquired resistance to TKI therapy remains a challenge, underscoring the need to better understand the signaling circuitry downstream of mutant EGFR. Previous studies have identified mutant EGFR substrates, including ERBB receptor feedback inhibitor 1 (ERRFI1, also known as MIG6), a negative regulator of EGFR signaling with potential tumor suppressor function that is hyperphosphorylated in the presence of mutant EGFR. Maity, Venugopalan, and colleagues found that homozygous, and to a lesser extent heterozygous, loss of *Mig6* accelerated lung adenocarcinoma formation and reduced overall survival in transgenic mice expressing mutant EGFR. *Mig6*-deficient *EGFR*-mutant tumors were characterized by hyperactivated MAPK signaling and increased phosphorylation of EGFR, despite decreased levels of mutant EGFR protein. A quantitative global phosphoproteomic approach revealed that MIG6 was constitutively phosphorylated at tyrosine 394 (Y394) or both Y394/Y395 in *EGFR*-mutant lung cancer cell lines and that erlotinib treatment inhibited these phosphorylation events in cells sensitive to EGFR inhibition, but not in resistant cell lines. Mechanistically, phosphorylation of MIG6 at Y394/Y395 promoted its binding to both wild-type and mutant EGFR and suppressed the ability of MIG6 to inhibit EGFR, resulting in enhanced mutant EGFR stability. Together, these findings reinforce the role of MIG6 as a tumor suppressor in the initiation and progression of *EGFR*-mutant lung cancer and highlight a potential mechanism by which mutant EGFR bypasses MIG6 inhibition. ■

See article, p. 534.

ETS-Mediated Downregulation of CHK1 Promotes Prostate Tumorigenesis

- The ETS factors ERG and ETV1 directly suppress *CHK1* transcription in prostate cancer cells.
- *Chk1* heterozygosity facilitates DNA damage accumulation and tumor progression in *Pten*$^{+/-}$ mice.
- CHK1 downregulation sensitizes prostate cancer cells to DNA replication inhibitors.



Chromosomal rearrangements involving the genes encoding ETS transcription factors, including *ERG* and *ETV1*, result in their aberrant expression and have been suggested to contribute to prostate tumorigenesis via dysregulation of ETS-dependent target genes. However, the mechanisms by which ETS transcription factors drive prostate cancer progression remain incompletely understood. Lunardi, Varmeh, and colleagues found that the expression levels of ERG and checkpoint kinase 1 (CHK1), a critical regulator of the DNA damage response, were inversely correlated in primary human prostate carcinoma samples, and that overexpression of ERG or ETV1 resulted in *CHK1* downregulation in prostate cancer cell lines and mouse prostates. ERG directly repressed *CHK1* transcription by binding the *CHK1* promoter, suggesting that ETS factors may stimulate genomic instability and tumor progression via *CHK1* downregulation. In support of this idea, heterozygosity for *Chk1* resulted in increased high-grade prostatic intraepithelial neoplasia, accumulation of unrepaired DNA damage, and accelerated progression to invasive prostate carcinomas in *Pten*$^{+/-}$ mice, similar to the phenotype induced by prostate-specific *ERG* overexpression in a *Pten*$^{+/-}$ genetic background. Furthermore, consistent with the role of CHK1 in maintaining replication fork integrity in response to replicative stress, CHK1 depletion specifically enhanced the sensitivity of human prostate cancer cell lines to agents targeting the DNA replication machinery such as etoposide, but not docetaxel. These findings identify *CHK1* as an important transcriptional target of ETS factors in prostate tumorigenesis and suggest that DNA replication inhibitors may be effective in ETS-positive tumors. ■

See article, p. 550.

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