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Osteosarcoma

Major finding: Osteosarcoma driver genes are enriched in the ERBB, PI3K–AKT–mTOR, MAPK, and axon guidance pathways.

Concept: A forward genetic screen identified genes that accelerate primary and metastatic osteosarcoma.

Impact: Lineage tracing using common insertion sites reveals multiple patterns of metastatic spread.

A *SLEEPING BEAUTY* SCREEN HIGHLIGHTS CANCER DRIVERS IN OSTEOSARCOMA

Osteosarcoma is a common primary bone cancer with high metastatic potential. However, characterization of cancer driver genes and potential therapeutic targets has been limited due to the highly heterogeneous and genomically unstable nature of osteosarcoma tumors. To identify genes that are involved in driving osteosarcoma, Moriarity and colleagues performed a *Sleeping Beauty* (SB) transposon-based forward genetic screen in mice harboring wild-type (SBmut) or mutant *Trp53* (Trp53-SBmut). SB mutagenesis promoted the formation of osteosarcomas that faithfully recapitulated the human disease and accelerated tumor formation in *Trp53*-mutant mice. Analysis of common insertion sites (CIS) from 96 Trp53-SBmut and 23 SBmut osteosarcomas identified known osteosarcoma-associated genes, as well as 36 putative proto-oncogenes and 196 potential tumor suppressor genes, including *Nf1* and *Pten*, which were observed in both genetic backgrounds. Pathway analysis highlighted an enrichment of genes involved in the PI3K–AKT–mTOR, MAPK, and ERBB signaling cascades, as well as mutations in upstream regulators of CIS-associated genes, including miRNAs that have been previously implicated in osteosarcoma. Comparison of CIS-associated gene expression, genomic alterations, and methylation across human osteosarcoma samples revealed that a significant proportion of candidate genes was altered in tumor samples compared with normal tissue. Functional validation of CIS-associated genes reinforced the notion that loss of *Pten* and *Trp53* cooperatively accelerate osteosarcomagenesis in mice and confirmed that overexpression of the axon guidance genes *SEMA4D* and *SEMA6D* in human osteosarcoma cells was sufficient to promote anchorage-independent growth and xenograft formation via activation of the PI3K and MAPK pathways. Furthermore, analysis of 134 metastases identified 43 CIS-associated candidate metastasis driver genes and revealed multiple patterns of metastatic spread, including both parallel and clonal evolution. Together, these data demonstrate that forward genetic screens represent a useful tool to identify cancer driver genes in tumors with high genetic variability and highlight oncogenic pathways that may be targetable in osteosarcoma. ■

Moriarity BS, Otto GM, Rahrmann EP, Rathe SK, Wolf NK, Weg MT, et al. A Sleeping Beauty *forward genetic screen identifies new genes and pathways driving osteosarcoma development and metastasis. Nat Genet 2015;47:615–24.*

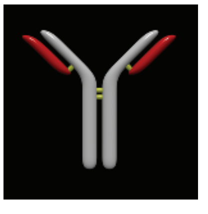
Antibodies

Major finding: FcγRIIIA on macrophages and FcγRIIA on dendritic cells mediate ADCC and vaccinal effects, respectively.

Concept: Long-term mAb-dependent immune responses require expression of FcγRs on CD11c+ cells.

Impact: Antibody engagement of both FcγRIIIA and FcγRIIA is required for maximal antitumor responses.

FCγRIIIA AND FCγRIIA ENGAGEMENT MEDIATES ANTITUMOR CELLULAR IMMUNITY



Passive delivery of antitumor mAbs has been shown to promote rapid tumor cell death via transient induction of Fc-receptor for IgG (FcγR)–mediated antibody-dependent cellular cytotoxicity (ADCC), which is determined by the relative binding affinity of antibodies for activating and inhibitory FcγR receptors on effector cell surfaces. In addition, antitumor mAb therapy has also led to durable antitumor cellular immune responses in some patients, prompting DiLillo and Ravetch to study the mechanisms that underlie this long-term vaccinal effect. In a murine lymphoma model expressing the tumor neoantigen human CD20 (hCD20), treatment with the murine IgG2a isotype anti-hCD20 mAb led to rapid clearance of lymphoma cells via FcγR-mediated ADCC, as well as sustained antitumor immune responses when mice were subsequently rechallenged with tumor cells that expressed hCD20, but not cells lacking hCD20 expression. Mechanistically, CD11c+ cell–specific deletion of the activating receptor mFcγRIV revealed that expression of mFcγRIV was required to generate long-term mAb-stimulated vaccinal effects, but was dispensable for ADCC-mediated tumor cell killing. In order to bypass interspecies differences and assess the individual contributions of hFcγRs in generating mAb-induced antitumor responses, FcγR-humanized mice expressing hFcγRs in the absence of mFcγRs were treated with hIgG1 anti-hCD20 variants engineered to selectively engage hFcγRIIIA, hFcγRIIA, or both hFcγRIIIA and hFcγRIIA. Engagement of hFcγRIIIA, but not hFcγRIIA, was necessary and sufficient to promote ADCC-mediated primary tumor cell clearance via clodronate liposome–sensitive macrophages. In contrast, however, long-term vaccinal effects required hFcγRIIA expressed by dendritic cells. Together, this work highlights the role of differential FcγR engagement in primary and long-term mAb-mediated antitumor immune responses and suggests that targeting both FcγRIIIA and FcγRIIA may be required for maximal clinical benefit of antitumor antibodies. ■

DiLillo DJ, Ravetch JV. Differential Fc-receptor engagement drives an anti-tumor vaccinal effect. Cell 2015;161:1035–45.

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CANCER DISCOVERY

AACR American Association for Cancer Research

A *Sleeping Beauty* Screen Highlights Cancer Drivers in Osteosarcoma

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