Published OnlineFirst April 28, 2017; DOI: 10.1158/2159-8290.CD-RW2017-079

Immunotherapy

Major finding: SLAMF7 expression is required for macrophage-mediated phagocytosis of hematopoietic tumor cells.

Mechanism: SLAMF7 interacts with the integrin Mac-1 on macrophages to promote phagocytosis.

Impact: SIRPα–CD47 blockade may be most effective in patients with hematologic cancers that express SLAMF7.

SIRPα–CD47 BLOCKADE-MEDIATED TUMOR CELL PHAGOCYTOSIS REQUIRES SLAMF7

Tumor cell phagocytosis by macrophages can be enhanced by therapeutic blockade of the signal regulatory protein-α (SIRPα) inhibitory receptor or its ligand CD47. However, prophagocytic receptors remain largely unknown, prompting Chen and colleagues to test bone marrow–derived macrophages for their ability to phagocytose various target cells. SIRPα–CD47 blockade with anti-CD47 enhanced phagocytosis of a subset of hematopoietic tumor cells (including B-cell lineage and myeloid tumor cell lines), but not of nonhematopoietic tumor cells. Based on these findings, the involvement of the SLAM family of receptors, which are expressed only on hematopoietic cells, was evaluated. Macrophages from mice lacking the SLAM receptors did not display increased phagocytic activity in response to SIRPα–CD47 blockade, and, specifically, SLAMF7 expression on macrophages and tumor cells was both necessary and sufficient for hematopoietic cell phagocytosis. SLAMF7 acted independently of the SAP adaptor proteins to promote phagocytosis. Further, SLAMF7-dependent phagocytosis required expression of two immunoreceptor tyrosine-based activation motif (ITAM)–containing proteins, DAP12 and FcRγ, which interact with the integrin Mac-1 and mediate immune cell activation via the SRC, SYK, and BTK kinases, and SLAMF7 interacted with macrophage Mac-1 to facilitate phagocytosis. Analysis of gene expression data revealed that some hematologic cancers, including chronic lymphocytic leukemia, myelodysplastic syndrome, multiple myeloma, and diffuse large B-cell lymphoma, frequently display high levels of both SLAMF7 and CD47, suggesting that patients with these cancers may be sensitive to SIRPα–CD47 blockade. The identification of SLAMF7 as a prophagocytic receptor elucidates a mechanism by which macrophages selectively target hematopoietic cells, and suggests that patients with SLAMF7-positive tumors may be most likely to respond to SIRPα–CD47 blockade. ■

Chen J, Zhong MC, Guo H, Davidson D, Mishel S, Lu Y, et al. SLAMF7 is critical for phagocytosis of haematopoietic tumour cells via Mac-1 integrin. Nature 2017;544:493–7.

Stem Cells

Major finding: Tumors exhibit persistent stem cell lineage plasticity that occurs transiently in wound repair.

Concept: Lineage plasticity maintained by stress-induced transcription factors drives cell proliferation.

Impact: Understanding how tumors hijack wound-repair programs may lead to discovery of new therapeutic targets.

PROLONGED STEM CELL LINEAGE PLASTICITY UNDERLIES CANCER PROGRESSION

During wound repair, resident stem cells temporarily favor cell growth and proliferation over differentiation. Tumors exploit this normal process to maintain uncontrolled growth, but the mechanisms underlying the homeostatic shift of stem cells in both wound repair and tumorigenesis are unknown. Using mouse skin as a model, Ge and colleagues utilized the assay for transposase-accessible chromatin with high-throughput sequencing (ATAC-seq) coupled with RNA and chromatin immunoprecipitation sequencing to compare *in vivo* chromatin states in homeostatic, wound-induced, and squamous cell carcinoma (SCC) stem cells. SCC stem cells had distinct accessibility profiles compared with those of homeostatic hair follicle and epidermal stem cells, and binding motifs for SOX9, normally expressed only in the hair follicle lineage, and KLF5, normally expressed in the epidermis stem cell lineage, were highly accessible in SCC stem cells. SCC stem cells coexpressed both SOX9 and KLF5, and CRISPR/Cas9-mediated deletion of *Sox9* or *Klf5* in SCC stem cells markedly impaired tumor growth *in vivo* and proliferation and invasion *in vitro*, confirming that lineage plasticity contributes to tumor maintenance. Of note, lineage plasticity marked by coexpression of SOX9 and KLF5 also occurred in wound-induced stem cells but was transient and reverted to homeostatic patterns as wounds healed. Accessible chromatin in both wound-induced and SCC stem cells contained unique enhancer elements and was enriched for binding motifs of stress-induced transcription factors such as ETS2, which is known to be required for SCC maintenance and phosphorylated by ERK1/2 during wounding. ETS2 was sufficient to induce lineage plasticity, and sustained ETS2 activity, which occurs in the setting of constitutive MAPK signaling caused by *HRAS* mutations in SCC, maintained lineage plasticity and commissioning of tumor-specific enhancers. In addition to providing insight into how tumor-associated stem cells lock in what is typically a transient wound-induced stem cell state in the skin, these findings suggest that drivers of sustained lineage plasticity represent potential therapeutic targets. ■

Ge Y, Gomez NC, Adam RC, Nikolova M, Yang H, Verma A, et al. Stem cell lineage infidelity drives wound repair and cancer. Cell 2017;169:636–50.e14.

Published OnlineFirst April 28, 2017; DOI: 10.1158/2159-8290.CD-RW2017-079

AACR American Association for Cancer Research

CANCER DISCOVERY

Prolonged Stem Cell Lineage Plasticity Underlies Cancer Progression

Cancer Discov 2017;7:547. Published OnlineFirst April 28, 2017.