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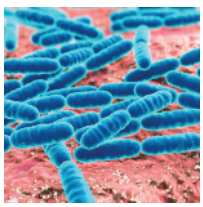
Microbiome

Major finding: TET2 deficiency increases systemic bacterial dissemination to promote preleukemic myeloproliferation (PMP).

Concept: Microbiota-dependent increases in IL6 levels are required for PMP in *Tet2*$^{-/-}$ mice.

Impact: Microbiota-dependent inflammation may underlie PMP development and provide potential therapeutic targets.

MICROBIAL SIGNALS PROMOTE PRELEUKEMIC MYELOPROLIFERATION IN *TET2*$^{-/-}$ MICE



Mutations in *TET2*, which promotes DNA demethylation by converting 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), can drive the development of hematopoietic malignancies. However, *TET2* mutation is not sufficient to drive preleukemic myeloproliferation (PMP), suggesting that cell-extrinsic factors are required to induce malignancy. Meisel, Hinterleitner, and colleagues sought to identify factors that cooperate with *TET2* mutation to promote PMP. *Tet2*$^{-/-}$ mice had increased systemic bacterial dissemination that was associated with increased intestinal permeability and PMP, suggesting that disrupting intestinal barrier integrity may induce PMP in *Tet2*$^{-/-}$ mice. Consistent with these findings, *Lactobacillus* species normally found in the small intestine were detected predominantly in the peripheral organs of *Tet2*$^{-/-}$ mice. TLR2 is a cell wall component of several *Lactobacillus* strains, and using TLR2 agonists to mimic bacterial stimuli resulted in PMP induction in *Tet2*$^{-/-}$ mice. In germ-free conditions, *Tet2*$^{-/-}$ mice failed to develop PMP. Further, antibiotic treatment was sufficient to prevent and reverse PMP, directly linking PMP to bacterial signals. A microbiota-dependent increase in IL6 plasma levels, which led to an expansion of IL6Rα^{+} granulocyte-macrophage progenitors, occurred in *Tet2*$^{-/-}$ mice and was required for the induction of PMP. Neutralizing IL6 suppressed the self-renewing capacity of *Tet2*$^{-/-}$ hematopoietic progenitor cells and prevented PMP development *in vivo* without restoring intestinal barrier function. Taken together, these findings suggest that microbial-dependent inflammatory signals induce PMP development in the context of TET2-deficiency. Further, these data raise the possibility of targeting inflammatory bacterial signals in patients with TET2-deficient PMP to suppress the progression to hematopoietic malignancy. ■

Meisel M, Hinterleitner R, Pacis A, Chen L, Earley ZM, Mayassi T, et al. Microbial signals drive pre-leukaemic myeloproliferation in a Tet2-deficient host. Nature 2018;557:580–4.

Sarcoma

Major finding: SS18–SSX targets BAF complexes away from enhancers to broad domains where they activate bivalent genes.

Mechanism: SS18–SSX-containing BAF complexes oppose PRC2-mediated repression at broad polycomb domains.

Impact: Synovial sarcoma is transcriptionally distinct from other malignancies driven by aberrant BAF complexes.

SS18-SSX RETARGETS THE BAF COMPLEX TO DRIVE SYNOVIAL SARCOMA

Synovial sarcoma is characterized by a chromosomal translocation that generates the SS18–SSX fusion oncoprotein. SS18 is a subunit of the BAF (SWI/SNF) chromatin remodeling complex, and SS18–SSX dominantly incorporates into BAF complexes, replacing wild-type SS18 and triggering the eviction of the BAF47 tumor suppressor subunit. In order to elucidate the mechanism by which BAF complexes containing SS18–SSX promote tumorigenesis, McBride, Pulice, and colleagues performed chromatin immunoprecipitation sequencing to determine the genome-wide occupancy of wild-type SS18, SS18–SSX, and the core BAF complex subunits BAF155 and BRG1 in a synovial sarcoma cell line with and without SS18–SSX depletion. SS18–SSX promoted genome-wide targeting of BAF complexes to broad domains distinct from wild-type BAF complexes. RNA sequencing demonstrated that SS18–SSX BAF complexes directly activated a consistent set of oncogenic target genes across synovial sarcoma cell lines, and analysis of primary synovial sarcomas revealed distinct genomes and transcriptomes distinct from those of other tumors driven by BAF complex perturbations. Synovial sarcomas exhibited a low mutational burden and could be split into subgroups based on expression of the myogenic genes *PAX3* and *PAX7* or the largely mutually exclusive expression of *MYC*. There was a high degree of overlap between sites occupied by BAF complexes and PRC2 complexes. Mechanistically, SS18–SSX retargeted BAF complexes away from enhancers to broad polycomb domains, thereby opposing PRC2-mediated gene repression and recruiting RNA Pol II to activate transcription of bivalent genes. Suppression of SS18–SSX induced a proliferative arrest in synovial sarcoma cells that could not be rescued by BAF47-mediated enhancer activation, indicating that BAF47 eviction is not sufficient to explain the oncogenic function of SS18–SSX. Altogether, these findings define a mechanism by which SS18–SSX retargets BAF complexes from enhancers to activate broad polycomb domains to drive synovial sarcoma. ■

McBride MJ, Pulice JL, Beird HC, Ingram DR, D'Avino AR, Shern JF, et al. The SS18-SSX fusion oncoprotein hijacks BAF complex targeting and function to drive synovial sarcoma. Cancer Cell 2018;33:1128–41.e7.

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AACR American Association for Cancer Research

CANCER DISCOVERY

Microbial Signals Promote Preleukemic Myeloproliferation in *Tet2*$^{-/-}$ Mice

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