Metastasis

**Major finding:** NCAM+CD45+ medulloblastoma cells were shown to be medulloblastoma circulating tumor cells (CTCs).

**Mechanism:** Activation of the CCL2/CCR2 axis in medulloblastomas promotes metastasis.

**Impact:** The identification of medulloblastoma CTCs may enhance diagnosis and therapeutic regimen design.

**MEDULLOBLASTOMA CIRCULATING TUMOR CELLS FORM LEPTOMENINGEAL METASTASES**

Most medulloblastoma metastases are located in the leptomeninges, the two innermost layers of tissue covering the brain and spinal cord that contain cerebrospinal fluid (CSF); thus, it has been postulated that leptomeningeal medulloblastoma metastases result from the dissemination of medulloblastoma cells through the CSF. To elucidate the mechanisms underlying the metastatic spread of medulloblastoma to the leptomeninges, Garzia, Kijima, Morrisy, and colleagues performed whole-genome sequencing of a set of matched patient primary medulloblastomas, leptomeningeal metastases, and peripheral blood. Heterozygous variant allele fractions present in the metastases were subclonal in the matched primary tumors and highly subclonal in the matched peripheral blood, suggesting the presence of circulating tumor cells (CTC). The presence of CTCs was confirmed by flow cytometric analysis of patient peripheral blood mononuclear cells and peripheral blood from mice with orthotopic murine or human medulloblastoma. Further, mice implanted subcutaneously with murine or human medulloblastoma as well as a medulloblastoma parabiosis mouse model resulted in leptomeningeal metastases. Gene expression profiling revealed that the chemokine CCL2, which is present on chromosome 17q, was overexpressed in human metastatic group 3 (MYC) medulloblastomas compared to matched primary medulloblastomas. Concurrent, but not single, expression of Cxcl12 and its receptor Ccr2 enhanced the metastatic potential of poorly metastatic medulloblastoma cells. Because group 3 medulloblastoma exhibit the highest propensity to metastasize, the CCL2/CCR2 axis was evaluated in the context of MYC-driven murine medulloblastoma: Co-expression of CCL2 and CCR2 was necessary for the metastatic spread of MYC-driven medulloblastoma. Conversely, genetic CCL2 knockdown reduced the metastatic potential of the highly metastatic human medulloblastoma cell line Med411H compared to control knockdown; similarly, leptomeningeal metastases were reduced in Ccr2−/− mice implanted with D425S cells. These results identify a hematogenous route for medulloblastoma dissemination and show that medulloblastoma CTCs contribute to leptomeningeal spread, which has implications for the precision medicine field.


Leukemia

**Major finding:** SETD1A enhances leukemic cell growth and survival independent of its methyltransferase activity.

**Mechanism:** The FLOS domain of SETD1A interacts with cyclin K to promote DNA damage response gene transcription.

**Impact:** The SETD1–cyclin K complex may be a potential therapeutic target in patients with acute myeloid leukemia.

**SETD1A INTERACTS WITH CYCLIN K TO PROMOTE LEUKEMIA CELL SURVIVAL**

Histone 3 lysine 4 (H3K4) methylation has important functions in transcriptional regulation and cancer, and H3K4 methylation is catalyzed by SET domain–containing proteins including SETD1A, SETD1B, and MLL1–4, each of which are found in multiprotein histone methyltransferase (HMT) complexes. These SET domain–containing proteins are frequently mutated or rearranged in leukemia, but it is not clear if the methyltransferase activity is required for leukemia cell survival or if there is redundancy between HMTs. Hoshii and colleagues performed an shRNA screen, depleting individual MLL/SET complex subunits to determine which are required for the growth of MLL-AF9 acute myeloid leukemia (AML) cells and determined that SETD1A was required for leukemia cell growth in vitro and in vivo. However, the SETD1A SET domain and methyltransferase activity were not required for leukemia cell growth. Instead, a domain termed the functional location on SETD1A (FLOS) was essential for leukemia cell survival. Disrupting SETD1A reduced expression of DNA damage response genes including Fancl, thereby suppressing the DNA damage response and inducing apoptosis of AML cells in a p53-dependent manner. Mechanistically, the SETD1A FLOS domain interacted with cyclin K, which is required for regulation of CDK12/13 kinase activity and controls transcription of multiple DNA damage response genes, and this association was required for leukemia cell growth. Despite the homology with SETD1A, SETD1B did not associate with cyclin K, indicating a nonredundant function for SETD1A in leukemia cell growth. Further, in human MLL-AF9 leukemia cells, treatment with the CDK12/13 inhibitor THZ531 induced apoptosis, indicating a cell-cycle dependent requirement for cyclin K/CDK12 control of DNA damage repair genes. Collectively, these findings reveal an essential role for SETD1A in leukemia cell survival that is independent of its H3K4 methyltransferase activity and suggest the potential for therapeutic targeting of SETD1A and cyclin K complexes in AML.

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