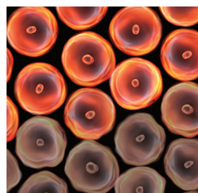
Ewing Sarcoma

Major finding: Ewing sarcoma is epigenetically heterogeneous despite the lack of genomic heterogeneity.

Concept: DNA methylation occurs on a spectrum between mesenchymal and pluripotent stem cell signatures.

Impact: DNA methylation can measure epigenetic heterogeneity and may potentially predict aggressive disease.

DNA METHYLATION ANALYSIS SHOWS EPIGENETIC HETEROGENEITY IN EWING SARCOMA



Ewing sarcoma is a pediatric bone cancer characterized by a chromosomal translocation that produces the *EWS–FLI1* fusion oncogene. These clinically heterogeneous tumors harbor few somatic mutations (with recurrent genetic alterations occurring only in *CDKN2A*, *STAG2*, and *TP53*), suggesting that epigenetic heterogeneity may explain the clinical presentation. Sheffield and colleagues performed DNA methylation sequencing of 140 Ewing sarcoma tumors and 16 Ewing sarcoma cell lines to characterize the interindividual and intratumor epigenetic heterogeneity, and compared the DNA methylation profiles with published data from other tumor types to determine the intercancer epigenetic heterogeneity. Ewing sarcomas clustered separately from other cancers based on DNA methylation profiles, due to a characteristic Ewing sarcoma methylation signature that distinguishes them from other tumor types. Ewing sarcomas exhibited a high level of interindividual heterogeneity, which occurred on an epigenetic continuum instead of clustering into discrete Ewing sarcoma subtypes. The tumors fell on a continuous disease spectrum between mesenchymal and pluripotent stem cell-like methylation signatures, and between more and less "Ewing-like" signatures based on the strength of the EWS–FLI1 regulatory signature. Ewing sarcomas also displayed high and variable intratumor heterogeneity. Genetic alterations correlated with DNA methylation heterogeneity, with *STAG2*-mutant tumors on average displaying more stem-like methylation signatures. Further, primary tumors from patients who had metastatic disease at diagnosis exhibited higher intratumor heterogeneity. In addition to identifying a characteristic Ewing sarcoma DNA methylation signature, these findings indicate that, despite the scarcity of genetic mutations, Ewing sarcomas exhibit high intratumor and intertumor epigenetic heterogeneity that may be linked with metastatic disease. ■

Sheffield NC, Pierron G, Klughammer J, Datlinger P, Schönegger A, Schuster M, et al. DNA methylation heterogeneity defines a disease spectrum in Ewing sarcoma. Nat Med 2017;23:386–95.

Epigenetics

Major finding: *DNMT3A*^{R882} mutations induce focal hypomethylation in AML cells and normal hematopoietic cells.

Concept: CpG island hypermethylation is a consequence of rapid cell growth and is independent of gene silencing.

Impact: CpG island hypermethylation may be not a pathogenic change, but a consequence of proliferative stress.

CpG ISLAND HYPOMETHYLATION MAY CONTRIBUTE TO AML INITIATION

Mutations in the DNA methyltransferase DNMT3A, most commonly *DNMT3A*^{R882H}, occur in approximately 25% of patients with acute myeloid leukemia (AML). *DNMT3A*^{R882H} mutations occur early in the development of leukemia and act in a dominant negative manner to reduce DNA methylation activity. However, it is not clear how DNMT3A-mediated methylation changes contribute to leukemogenesis, prompting Spencer and colleagues to investigate genome-wide DNA methylation patterns in primary AML samples and cell lines with and without *DNMT3A*^{R882} mutations. Whole-genome bisulfite sequencing (WGBS) of hematopoietic cells from a patient with the *DNMT3A*^{R882H} allele, but without leukemia, and the patient's wild-type sibling indicated that *DNMT3A*^{R882H} is associated with focal methylation loss even in nonleukemic cells. Further, WGBS of primary AML samples revealed that *DNMT3A*^{R882} mutations were associated with enhanced focal hypomethylation in CpG dense regions, whereas *DNMT3A*-wild-type AML was associated with enhanced CpG island hypermethylation. These hypomethylated and hypermethylated regions were associated with distinct genomic and epigenomic features; however, mutant DNMT3A did not substantially alter the epigenetic marks or transcriptional activity of nearby genes. Although *DNMT3A*–wild-type AML was associated with hypermethylated CpG islands, the hypermethylation was not linked to gene silencing, suggesting that AML-associated gene silencing was more dependent on AML "state" than on hypermethylation of CpG island promoters. Moreover, DNMT3A-mediated hypermethylation of CpG islands occurred in nontransformed primary hematopoietic stem/progenitor cells during cytokine-induced proliferation, and *DNMT3A*^{R882H} AML cells had largely overlapping regions of hypomethylation that developed before the onset of leukemia, indicating that CpG island hypomethylation may be an AML-initiating phenotype in *DNMT3A*-mutant cells. Collectively, these findings suggest that *DNMT3A*^{R882H}-induced CpG island hypomethylation may contribute to the initiation of AML and that CpG island hypermethylation may be a consequence of cellular proliferation and not a pathogenic driver. ■

Spencer DH, Russler-Germain DA, Ketkar S, Helton NM, Lamprecht TL, Fulton RS, et al. CpG island hypermethylation mediated by DNMT3A Is a consequence of AML progression. Cell 2017;168:801–16.

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