Abstract

ATP-dependent chromatin remodelers in human acute myeloid leukemia pathobiology

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Acute myeloid leukemia (AML) is the second most common leukemia worldwide with a median age of ~65 years at diagnosis. In the past decade cancer genome sequencing studies have identified somatic mutations in genes that encode chromatin regulators. However, mutational profiling alone may not help identify tumor associated transcriptional plasticity, one important hallmark in tumorigenesis. ATP-dependent chromatin remodeling complexes play critical roles in pluripotency and cellular reprogramming. SWI/SNF is an evolutionarily conserved multi-subunit chromatin remodeling complex that regulates epigenetic architecture and cellular identity. Although SWI/SNF genes are frequently altered in human malignancies, the evidence showing their involvement in tumor cell-autonomous chromatin regulation and transcriptional plasticity is limiting. Nucleosome remodeling and deacetylase (NuRD) is another important ATP-dependent chromatin remodeling complex that regulates stem cell lineage fate mapping and transcriptional architecture. Rac GTPases belong to family of small GTPase proteins that play a crucial role in myeloid leukemia cell engraftment and survival in vivo. Although myeloid leukemia cells generally display an elevated Rac GTPase level, the mechanism of Rac activation in AML is incompletely understood. Interestingly, we have identified that, loss of specific subunits in SWI/SNF and NuRD complexes in human primary AML cells associates with nucleation of oncogenic chromatin remodelers, which promotes Rac GTPase guanine nucleotide exchange factors (GEFs) expression, Rac activation, migration, and survival of AML cells. Importantly, pharmacological inhibition of Rac GEFs using specific small molecule inhibitors selectively attenuated survival of AML cells. Together, our findings inform tumor cell-autonomous novel epigenetic plasticity and transcriptional dependency, and connect epigenetic regulation with cell trafficking implicated in human AML pathobiology.