Epigenetics

Major finding: PADI4 regulates stem cell gene expression and chromatin compaction by citrullinating histones.

Mechanism: Histone H1 citrullination reduces its nucleosomal binding and causes global chromatin decondensation.

Impact: PADI4 overexpression in tumors may lead to an open chromatin state and transcriptional deregulation.

HISTONE CITRULLINATION MAINTAINS OPEN CHROMATIN AND PLURIPOTENCY

Peptidylarginine deiminases (PADI) catalyze the posttranslational conversion of arginine to citrulline, a noncoded, uncharged amino acid, in a process known as citrullination. Christophorou and colleagues sought to determine whether PADI4-mediated citrullination, which has been implicated in cancer progression as well as chromatin decondensation in neutrophils, plays a role in pluripotency, a state that requires an open chromatin structure to maintain unrestricted differentiation capabilities. *Padi4* expression, global citrullination, and histone H3 citrullination (H3cit) were detected in pluripotent mouse embryonic stem cells (ES) and induced pluripotent stem cells (iPS) but were absent in a multipotent neural stem cell line. PADI4 was found to reside within the pluripotency transcriptional network, as the pluripotency reprogramming factor OCT4 occupied the *Padi4* promoter and induced *Padi4* transcription. In addition, PADI4 positively regulated several genes involved in stem cell development and maintenance, such as *Tcl1* and *Nanog*, in a manner dependent on its enzymatic activity, as chemical disruption of citrullination inhibited pluripotency gene expression. Consistent with these findings, H3cit was present on the regulatory regions of *Tcl1* and *Nanog* in ES and iPS cells, and inhibition of PADI4 expression or catalytic activity in pre-iPS cells impaired global H3cit, reduced reprogramming efficiency, and ablated *Tcl1* and *Nanog* expression. Furthermore, PADI4 activity was found to promote the maintenance of pluripotent cells in early mouse embryos. Unbiased proteomic analysis of mouse ES cells also identified linker histone H1 variants, which facilitate chromatin condensation, to be PADI4 targets. PADI4-induced citrullination of histone H1 arginine 54 resulted in the displacement of histone H1 from chromatin and chromatin decondensation. Taken together, these results highlight the involvement of PADI4-induced citrullination in the regulation of pluripotency-inducing factors and chromatin compaction, which suggests a possible role for upregulation of PADI4 during cancer development. ■

Christophorou MA, Castelo-Branco G, Halley-Stott RP, Slade Oliveira C, Loos R, Radzisheuskaya A, et al. Citrullination regulates pluripotency and histone H1 binding to chromatin. Nature 2014 Jan 26 [Epub ahead of print].

Lymphoma

Major finding: *RHOA*^{G17V} mutations occur in over two thirds of angioimmunoblastic T-cell lymphomas.

Concept: The G17V mutant protein may act in a dominant-negative manner by sequestering activated GEF proteins.

Impact: Altered RHOA signaling may contribute to angioimmunoblastic T-cell lymphoma pathogenesis.

RHOA MUTATIONS ARE A HALLMARK OF ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive subtype of peripheral T-cell lymphoma (PTCL) that accounts for approximately 20% of all T-cell lymphomas. Although recurrent mutations in *TET2*, *IDH2*, and *DNMT3A* that are common in other hematologic malignancies have been identified in AITL, the molecular mechanisms that specifically promote AITL development are unknown. Sakata-Yanagimoto and colleagues performed whole-exome sequencing on 6 AITL samples and identified a recurrent *RHOA*^{G17V} mutation in 3 AITL samples. Targeted RHOA sequencing in an extended AITL cohort identified *RHOA*^{G17V} mutations in 49 of 72 (68%) AITLs. Similarly, Palomero and colleagues analyzed the exomes of 12 PTCL cases and identified recurrent *RHOA*^{G17V} mutations in 22 of 35 (67%) AITLs. No *RHOA*^{G17V} mutations were identified in other hematologic malignancies other than in a subset of PTCL not otherwise specified that shared AITL features, suggesting that somatic RHOA mutations are a specific feature of AITL. Of note, most *RHOA*-mutant AITLs also harbored *TET2* mutations, but *TET2* mutations had higher allelic frequencies than *RHOA* mutations and were also found in normal T cells, suggesting that they occurred prior to a driving *RHOA* mutation. GTP binding by the RHOA^{G17V} mutant protein was severely reduced despite increased guanine nucleotide exchange factor (GEF) protein binding compared with wild-type RHOA, indicating that the G17V mutant protein is inactive and may act in a dominant-negative manner by sequestering GEF proteins. Indeed, the G17V mutant protein also suppressed activation-associated binding of wild-type RHOA to the rhotekin effector protein and reduced RHOA-dependent actin stress fiber formation and gene activation. Mechanistically, expression of wild-type RHOA, but not RHOA^{G17V}, slowed T-cell proliferation, raising the possibility that the *RHOA*^{G17V} mutation may promote AITL by abrogating tumor-suppressive functions of RHOA in the T-cell lineage. ■

Sakata-Yanagimoto M, Enami T, Yoshida K, Shiraishi Y, Ishii R, Miyake Y, et al. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. Nat Genet 2014;46:171–5.

Palomero T, Couronné L, Khiabanian H, Kim MY, Ambesi-Impiombato A, Perez-Garcia A, et al. Recurrent mutations in epigenetic regulators, RHOA *and* FYN *kinase in peripheral T cell lymphomas. Nat Genet 2014;46:166–70.*