New insights into the epigenetic control of hematopoiesis

June 28 2018

Scientists at The Wistar Institute have characterized a novel function for the INTS13 protein that is part of a large protein complex regulating gene transcription, called Integrator. According to study results, published online in *Molecular Cell*, INTS13 is required for monocytic maturation, promoting expression of lineage-specific genes.

Integrator is a recently discovered major component of the RNA polymerase transcription machinery that plays a pivotal role in the regulation of gene expression and RNA maturation. Detailed function has been characterized only for a few of the 14 components of this multi-protein complex.

In the new study, Alessandro Gardini, Ph.D., assistant professor in the Gene Expression & Regulation Program at Wistar, and his team describe the role of the INTS13 subunit, showing that it can function independently of the rest of the complex and that it regulates transcription of lineage-specific genes that control monocytic differentiation.

"Our work shows for the first time that the components of the Integrator complex can operate as independent sub-modules, in this case to control cell fate determination in hematopoiesis," said Gardini. "Monocytic differentiation is disrupted in acute myeloid leukemia and myelodysplastic syndromes and we hope that unveiling the molecular mechanisms that govern this physiologic process will provide novel molecular targets for these diseases."

Monocytes and macrophages are specialized bone marrow-derived white blood cells that play important roles in immunity, eliminating foreign substances, cellular debris and cancer cells. Their differentiation from progenitors to mature cells entails critical transcription factors that regulate expression of specific genes, including Early Growth Response (EGR) 1 and 2.

Gardini and colleagues discovered that INTS13 is indispensable for the maturation of monocytic progenitor cells to monocytes and macrophages, as depletion of INTS13 prevents proper activation of monocytic/macrophagic genes.

Through proteomics and genomics approaches, the researchers characterized the binding activity of INTS13 on the genome, showing that it activates gene enhancers, short regulatory DNA sequences that, when bound by specific transcription factors, enhance the transcription of the associated genes and are critical to coordinating cell-type-specific gene expression. Specifically, INTS13 regulates enhancers of genes associated with immune cell development and hematopoiesis.

Results also showed that INTS13 is recruited to the enhancers through interaction with EGR1/2 and the transcription co-activator NAB2, which acts as a molecular bridge between the two partners in a ternary complex.

"Based on our results, it will be interesting to study other components of the Integrator complex and characterize their specific function in transcriptional regulation," said Elisa Barbieri, Ph.D., a postdoctoral researcher in the Gardini Lab and co-first author of the study.

More information: *Molecular Cell* (2018). DOI: 10.1016/j.molcel.2018.05.031

Provided by The Wistar Institute