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Using omics approaches to address complex questions in hematopoietic malignancies

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Abstract

The PML/RARa fusion protein triggers a multi-step process of leukemogenesis in APL, eventually blocking cell differentiation at the promyelocytic stage primarily through transcriptional repression of genes essential for myeloid differentiation. With the presence of *all trans* retinoid acid (ATRA), the transcriptional repression is released and the myeloid differentiation is restored. However, mechanistic studies of the PML/RAR a-mediated transcriptional repression or the ATRA-induced differentiation have lagged behind, largely due to lack of information about PML/RARa binding sites and their associated epigenomic modifications. Accordingly, we have investigated genome-wide binding sites of PML/RARa upon its induction in hematopoieitic precursor cells and found that this fusion protein primarily binds to chromatin regions pre-bound by PU.1 and with the nearby presence of RARE half sites, creating a PML/RARa-PU.1 complex. This PML/RARα-PU.1 complex appears to be able to suppress the expression of genes (including PU.1 itself) essential for myeloid differentiation in APL and its suppressive effect is released upon the treatment of ATRA. In addition, we have profiled seven types of histone methylation and five types of histone acetylation, together with binding sites of four co-factors and Pol II in APL-derived NB4 cells, before and after ATRA treatment using chromatin immune-precipitation combined with high-throughput sequencing (ChIP-seq). In parallel, binding sites of PU.1 and CEBPe, two crucial transcription factors in myeloid differentiation, have been profiled in detail as well. Thus, comprehensive analysis of the binding sites of PML/RARα, PU.1 and CEBPe, and their associated histone modifications may allow insights into multi-level regulatory mechanisms underlying the leukemogenesis in APL, and probably in other types of AML as well.

Biography

Dr. Ji Zhang has completed his PhD from University of Leuven (Belgium) in 1991 and postdoctoral studies from University of Michigan in 1993. He is professor and deputy director of State Key Laboratory of Medical Genomics in China, as well as a PI of Institute of Health Science, SIBS, CAS. He has developed extensive experience and expertise in a wide range of research areas and his research interests are centered on the application of global approaches to address pathological and therapeutic questions in cancer biology based on his multi-disciplinary background. He has published over 60 peer-reviewed publications and several book chapters, inventor or co-inventor of several issued or pending international/domestic patents.