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Synergistic and coordinated actions of three DNMT enzymes for the establishment and maintenance of DNA methylation patterns

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Abnormal DNA methylation patterns including global hypomethylation and focal promoter hypermethylation are hallmarks of cancer cells. Global hypomethylation and promoter hypermethylation of tumor suppressor genes contribute to the cancer biogenesis. However, it remains to be determined how cancer cells obtain these abnormal methylation patterns and how such patterns exactly contribute to oncogenesis. Currently, it has been broadly accepted that de novo DNA methyltransferases 3a/3b (DNMT3a/3b) methylate the unmethylated cytosines to initiate the methylation patterns in the genome of early embryos, and subsequently, these patterns are faithfully copied from parental strands to daughter strands during DNA replication by maintenance DNMT1. This 'two-step' model highlights the importance of DNMT1 maintenance in transmitting epigenetic information to next generations of cells. Because of this importance, inhibitor drugs specifically targeting DNMT1 have been developed and used in clinical trials. Despite promising results against hematologic malignancies, the efficacy of DNMT1 inhibitors in solid tumors has been "disappointing", raising the concern of the guiding 'two-step' model.

To determine the mechanism of the establishment and maintenance of DNA methylation patterns, we have examined genome-wide DNA methylation patterns in mouse embryonic stem (ES) cells and DNMT-deficient ES cells. Indeed, investigations suggest that both maintenance DNMT1 and de novo DNMT3a/3b function complementarily and simultaneously to establish and maintain methylation patterns. These results partially explain the limitations of inhibiting only one DNMT1 enzyme in current trials, because DNMT3a/3b still methylate CpGs. Furthermore, data demonstrate that even complete demethylation in the genome surprisingly only de-silenced a minority of genes in the genome. Only genes with low CpG density tend to be re-activated. Lastly, we demonstrate that maintenance DNMT1 activity is crucial for inhibition of retrotransposon long terminal repeats (LTRs), whereas de novo DNMT3a/3b activities are for suppressing retrotransposon long interspersed nuclear elements (LINEs). Our novel mechanistic insights of the establishment and maintenance of DNA methylation patterns help to develop next-generation DNMT inhibitor drugs.

Biography:

Dr. Zhibin Wang obtained his Ph.D from the Ohio State University. He started his biomedical research with the development of chromatin immunoprecipitation plus deep sequencing (ChIP-seq) method in the National Heart, Lung, and Blood Institute. His pioneering reports shed lights on what kind of "histone code" in the human genome and revealed the binding of corepressor histone deacetylase (HDAC) for active genes instead of broadly accepted silent genes. The resulting concept changes are important for the understanding/development/application of HDAC inhibitors in the treatment of cancers. New model for the establishment and maintenance of DNA methylation patterns also helps the application of the DNMT inhibitor drugs for cancers.