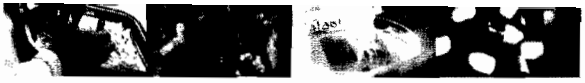

Methylation in Haemic Malignancies: Profile and Prognostic Significance

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Dr James Chim graduated from the Chinese University of Hong Kong in 1986, and joined the Division of Haematology in the University Department of Medicine, Queen Mary Hospital in 1991. He has been research fellow with Professor AV Hoffbrand in the Academic Department of Haematology, Royal Free Hospital, London, and subsequently in the Comprehensive Cancer Research Center, University of Chicago, USA. Dr Chim has been awarded the Croucher Foundation Fellowship, and conferred Doctor of Medicine in the University of Hong Kong.

Apart from clinical studies in leukemia and lymphoma, Dr Chim's research interest focuses on the role of methylation in haematological cancers. Dr Chim has been invited to review manuscripts for international journals including *BLOOD, Leukemia, British Journal of Haematology, International Journal of Cancer, Journal of Pathology*, etc.

Dr Chim has been awarded Fellowship of the Royal College of Physicians of London, Edinburgh and Glasgow; and the American College of Physicians. Currently, Dr Chim is the Honorary Associate Professor, Department of Medicine, Queen Mary Hospital, University of Hong Kong and the Chairman of the Hong Kong Society of Haematology.

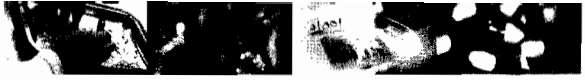
Cancers are characterized by dysregulation of cellular proliferation and apoptosis. Uncontrolled cell proliferation is characteristic of most cancer cells, implying dysregulation of cell cycle check-points. On the other hand, apoptosis is an important mechanism to dispose cells carrying abnormal genetic composition.

DNA methylation involves the addition of a methyl group to the carbon 5 position of the cytosine ring in the CpG dinucleotide. Normally, CpG islands in the gene promoters are protected from methylation, so that the genes are in a transcription-ready state. In cancers, CpG islands of various genes have been shown to be aberrantly methylated, leading to gene silencing and thus gene inactivation.

Acute promyelocytic leukemia (APL) is characterized by t(15;17), which results in the fusion gene PML/RARα that is leukemogenic. Moreover, it is the only AML subtype that responds to differentiation therapy with all-trans retinoic acid (ATRA), and arsenic trioxide. Therefore, APL is a unique clinical and molecular AML subtype.

Methylation of putative suppressor genes have been investigated in APL by methylation-specific PCR. The INK4 and CIP/KIP families of cyclin-dependent kinase inhibitors (CKI) involved in the regulation of G_1S check-point have been studied, which showed frequent methylation of *CDKN2B* portending an inferior disease-free survival. The adverse prognostic significance was subsequently validated in Caucasian APL patients and Chinese patients uniformly induced with ATRA. Moreover, putative tumor suppressor genes in the DAP kinase/p14/MDM2/p53/Apaf-1 pathway have been studied, which revealed frequent methylation of *DAP kinase* in APL but not other subtypes of AML.

On the other hand, while $RARA_2$ has been implicated in APL leukemogenesis due to translocation, the other $RARA_2$ allele on the untranslocated allele is structurally intact. The untranslocated $RARA_2$ is found to be frequently methylated in APL but not other leukemia subtypes. Demethylation treatment of NB4 (APL cell line) showed progressive demethylation and re-expression of $RARA_2$ transcript. The data suggested that methylation of $RARA_2$ is important in APL leukemogenesis.



Taken together, a leukemia-specific methylation profile is present in APL. Methylation of tumor suppressor genes in a defined celullar pathway appear mutually exclusive. Moreover, methylation of certain genes is prognostically important. Last but not the least, transcription factor involved in reciprocal translocation may be involved in leukemogenesis, and the prospect of epigenetic therapy such as DNA methyl transferase and histone deacetylase inhibitors warrants study.