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THE CANCER EPIGENOME AS A PREVENTION/THERAPY TARGET

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The last decade has seen exciting advances in understanding the epigenetic control of our genome or those factors that determine heritable patterns of gene expression independent of changes in primary DNA sequence. The key element of this epigenetic control is the nucleosome comprised of ~ 160 bp of DNA wrapped around a core octamer of histones[1]. In turn, a myriad of modifications of these histones on key amino acid residues, mediated by a growing list of enzymes, collaborate with remodeling proteins which determine nucleosome positions, to help set the gene expression patterns during development and in cells of different differentiation lineages[2-5]. Superimposed on these controls is the process of DNA methylation which takes place on cytosines located 5' to guanosines in the mammalian genome. This DNA modification can stabilize repressed gene expression patterns that might otherwise be more readily converted to active gene expression patterns[6]. In turn, the position of DNA methylation may be determined by key histone modifications and, the transcriptional repression usually associated with DNA methylation found in gene promoter regions is dependent on key chromatin patterns recruited by this DNA modification.

If the above chromatin and DNA methylation patterns comprise what is being termed the "epigenome" then the growing list of their alterations in cancer can be collectively termed the "cancer epigenome" - and these changes can be found in virtually every cancer type[7, 8]. Very broadly speaking, there are at least two broad coexisting overall constituents of the cancer epigenome. First, widespread areas of the normal mature cell genome are packaged by chromatin and DNA methylation such that they are maintained in a transcriptionally repressive, closed conformation. In cancers, these regions often have markedly decreased DNA methylation and have a more "open" structure. These changes may be associated with abnormal chromosome structure and inappropriate gene expression. Second, more localized regions of the genome in normal cells, and especially those associated with the promoters of the approximately half of our genes which are CpG rich, or have so called "CpG islands", are maintained in an open chromatin organization, characterized by less compacted nucleosome arrangement and a lack of DNA methylation. This comprises a transcriptionally favorable environment for these genes. In all types of cancers, there are a large number of such genes where the above promoter CpG islands have abnormal DNA hypermethylation and a closed mucleosomal structure. This situation is associated with transcriptional loss of gene function that can serve as an alternative to coding region mutations for tumor suppressor gene inactivation[7, 8]. This latter aspect of the cancer epigenome is the best characterized in terms of cancer biology.

The history of characterizing these above DNA hypermethylated genes, among which are contained approximately half of all well characterized tumor suppressor genes, has been reviewed extensively[7, 8]. To even better characterize this abnormality in cancer, our group, and others, have been employing various approaches to randomly screen cancer genomes for detection of these DNA hypermethylated genes[9]. These studies suggest that an individual cancer may harbor several hundred of these genes. The findings have important implications for how screening for epigenetic changes complement, and help interpret, the meaning of gene changes in cancer.

One important translational hope for the above identification of the above hypermethylated genes in cancer is the potential for targeting, for cancer prevention/therapy, the abnormal gene silencing, with the aim of reactivating the involved genes. This possibility is already being increasingly pursued. Great promise is being seen in the hematopoietic neoplasias with robust clinical responses to the DNA

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demethylating agents, 5-aza-cytidine and 5-deoxy-azacytidine in the pre-malignant disease, myelodysplasia, and acute myelocytic leukemias which are derived from this state[10, 11]. However, the exact mechanisms underlying these responses must still be clarified and this is a major challenge to the field in terms of taking the therapeutic approaches further – and extrapolating them to solid tumors.

The above abnormal gene silencing occurs very early in tumor progression, possibly even contributing initial steps in some common cancers, and features of stem cell chromatin have now been identified as a potential clue to the origins of the silencing abnormalities[12-14]. Defining the entire gene composition of this silencing component in major tumor types is the goal of cancer genome projects. The known chromatin and DNA methylation components of the cancer gene silencing, including how they interact, and implications for targeting these components individually, and together, for cancer control is a rich area of ongoing research.

1. Kornberg RD, Lorch Y. Twenty-five years of the nucleosome, fundamental particle of the eukaryote chromosome. *Cell* 1999; 98: 285-94.
2. Li H, Ilin S, Wang W, et al. Molecular basis for site-specific read-out of histone H3K4me3 by the BPTF PHD finger of NURF. *Nature* 2006; 442: 91-5.
3. Wysocka J, Swigut T, Xiao H, et al. A PHD finger of NURF couples histone H3 lysine 4 trimethylation with chromatin remodelling. *Nature* 2006; 442: 86-90.
4. Kouzarides T. Chromatin modifications and their function. *Cell* 2007; 128: 693-705.
5. Jenuwein T. The epigenetic magic of histone lysine methylation. *Febs J* 2006; 273: 3121-35.
6. Bird A. DNA methylation patterns and epigenetic memory. *Genes Dev* 2002; 16: 6-21.
7. Baylin SB, Jones, PA. Epigenetic Determinants of Cancer. In Allis CD, Jenuwein T, Reinberg D (eds) Epigenetics. Cold Spring Harbor: Cold Spring Harbor Press, 2006, pp 457-476.
8. Jones PA, Baylin SB. The epigenomics of cancer. *Cell* 2007; 128: 683-92.
9. Suzuki H, Gabrielson E, Chen W, et al. A genomic screen for genes upregulated by demethylation and histone deacetylase inhibition in human colorectal cancer. *Nat Genet* 2002; 31:141-9.
10. Issa JP. Optimizing therapy with methylation inhibitors in myelodysplastic syndromes: dose, duration, and patient selection. *Nat Clin Pract Oncol* 2005; 2 Suppl 1: S24-9.
11. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *J Clin Oncol* 2002; 20: 2429-40.
12. Schlesinger Y, Straussman R, Keshet I, et al. Polycomb-mediated methylation on Lys27 of histone H3 pre-marks genes for de novo methylation in cancer. *Nat Genet* 2007; 39: 232-6.
13. Widschwendter M, Fiegl H, Egle D, et al. Epigenetic stem cell signature in cancer. *Nat Genet* 2007; 39: 157-8.
14. Baylin SB, Ohm JE. Epigenetic gene silencing in cancer - a mechanism for early oncogenic pathway addiction? *Nat Rev Cancer* 2006; 6: 107-16.

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Science cannot be divided into what is up to date and what is merely of antiquarian interest; it is to be regarded as the product of a growth of thought.

La ciencia no puede dividirse en lo que es de actualidad y lo meramente antiguo; debe considerarse como el producto de sostenida reflexión.

Peter B. Medawar (1915-1987)