Meeting Report

Cancer: the chromatin connection

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The American Association for Cancer Research's 93rd Annual Meeting was held in San Francisco, California, USA, from 6 to 10 April 2002.

The interface between genetics and cancer research has never been stronger than it is today. With more than 15 000 scientists in attendance, this meeting highlighted not only the immense progress in clinical research, but also the vast contributions of basic research. Public forums engagingly portrayed the state-of-the-art, and rallied the lay community to increase funding for research. No single review can convey the array of new ideas making an impact from the laboratory bench to the clinic to the bedside. However, many significant presentations at the meeting discussed mechanisms to maintain genomic integrity and the involvement of epigenetics in cancer, and I shall focus on these.

In the early 1980s, Lawrence A. Loeb (University of Washington, Seattle, WA, USA) introduced the 'mutator hypothesis' for cancer cells, whereby a catastrophic loss of genomic integrity occurs, with each genetic change making the next one more likely. At first, comparative genomic hybridization at the chromosome level, and more recently microarray analyses, demonstrated just what a parody of normal gene arrangement and expression we see in cancer cells (Fig. 1). The molecular pathways that maintain genomic integrity are interconnected with other cellular pathways in ways no one could have imagined five years ago.

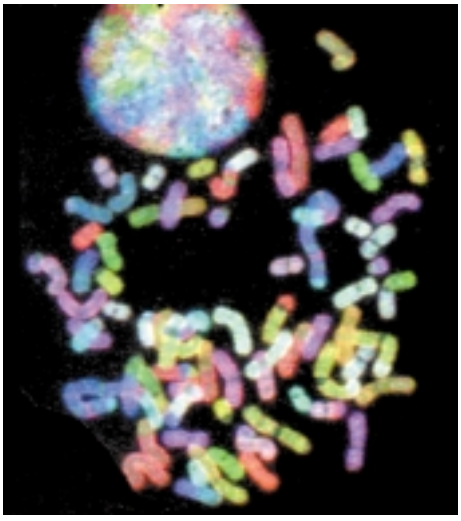

Fig. 1. Spectral karyotyping (SKY) of a breast cancer cell line. Each chromosome is 'painted' a different color, and the numerous rearrangements demonstrate the typical genomic instability in cancer cells. Courtesy of Drs Hesed Padilla-Nash and Thomas Ried (National Cancer Institute, Bethesda, MD, USA).

X inactivation and BRCA1

BRCA1 was the first familial breast cancer gene discovered. The fruit of many years of sleuthing in the laboratory of Mary-Claire King (University of Washington), BRCA1 is now becoming recognized as playing a central role in maintenance of genome stability. David Livingston (Dana Farber Cancer Institute, Boston, MA, USA) wondered why this protein should affect cancer in women and men differently. Livingston found that BRCA1 protein was concentrated in X–Y meiotic figures in males. One X chromosome is inactive in female somatic cells, whereas in male meiosis the single X chromosome is silent. XIST, an RNA molecule, associates tightly with one of the two X chromosomes in female cells, and with the single X in male meiosis, and ensures the transcriptional silencing of that X. Termed X-chromosome inactivation, this process compensates for the dosage difference in X-linked genes between males and females. In breast tumor cells lacking BRCA1 protein, Livingston and colleagues showed that the usual coating of the inactive X chromosome by XIST did not occur. Transfecting these cells with a vector supplying normal BRCA1 protein resulted in the accumulation of XIST around the X chromosome, strongly suggesting that BRCA1 protein is required for the accumulation of XIST RNA. Proteins similar to BRCA1 are apparently involved in RNA-mediated dosage compensation in *Drosophila*. The final story will probably be complex, but these results are interesting in light of studies suggesting that the lack of a Barr body (inactive X chromosome) in breast tumor tissue is a negative prognostic indicator. Thus BRCA1 seems central not only to the maintenance of the genome, but also to dosage compensation.

Epigenetic regulation and the histone code

It was abundantly clear in a symposium on chromatin structure that the 'epigenome' is now becoming more important in our understanding of cancer. Fyodor Urnov (Sangamo BioSciences, Richmond, CA, USA) views epigenetic marking as the 'formatting' of the genome, defining domains of active and inactive genes. A key feature in epigenetic regulation is the 'histone code' (a term advanced by Strahl and Allis [1]), which is composed by the modification of specific amino acid residues in the projecting tails of histone molecules, especially acetylation and methylation of parts of histone H3 and H4. Once the purview of obscure biochemists preaching to the converted, histone acetylation was cast in the limelight when Brian Turner and colleagues showed that increased acetylation was a signature of broad zones of active chromatin [2]. Now, histone acetyltransferases (HATs) and histone deacetylases (HDACs) are seen as central to gene regulation [1]. Moreover, as Steve Baylin (Johns Hopkins University, Baltimore, MD, USA) pointed out, the histone code interacts with epigenetic modification of the DNA itself, with HDACs attracting DNA methyltransferases, and methylated histones interacting with heterochromatin proteins. Baylin thinks that the sharp boundaries between active and inactive chromatin (e.g. Ref. [3]) break down in cancer cells, and that understanding these boundaries will be key in unraveling the epigenome.

DNA methylation

The importance of nutrition in cancer prevention is well known, and there was great interest in this field at the AACR meeting. Rudi Jaenisch (MIT) pointed

 0168-9525/02/$ – see front matter PII: S0168-9525(02)02735-X

out some mechanistic connections between gene expression, DNA methylation and food intake. He carefully outlined earlier experiments by George Wolff (FDA, Jefferson, AR, USA) [4], using mice with a pseudoagouti phenotype. In some mice, a yellow coat color results from the constitutive expression of the agouti locus under the regulation of an intracisternal A particle (IAP) insertion upstream from the promoter. Hypermethylation of the IAP long terminal repeat (LTR) results in normal regulation of agouti because the interfering IAP promoter is silenced, and an agouti coat color is seen (reviewed in Ref. [5]). Coat color in these mice can be affected by giving a maternal diet that is high or low in methyl donors. This ability to affect methylation and gene expression by diet, as well as drugs, is exciting, because cancers generally exhibit an overall decrease in DNA methylation compared with normal cells.

However, the situation is not clear-cut. Although overall methylation in cancer cells decreases, some local regions actually undergo an increase in methylation and silencing; for example, a tumor suppressor locus. Jaenisch had shown previously that mutations in DNMT1 (DNA methyl transferase I, the *de novo* methylating enzyme) resulting in about 10% of normal activity could result in the reactivation of genes. He showed that in mice carrying the adenomatous polyposis coli (APC) mutation, the number of polyps can be reduced dramatically from the average of 120 at six months of age by reducing methylation with 5-aza-cytidine [6]. This suggested an alternative – that the demethylating effect of reduced DNMT1 activity could possibly alleviate colon cancer. Jaenisch verified this, and now refers to DNMT1 as a kind of oncogene, because the more methylating activity an animal has, the more tumor production is observed. However, further work suggested that the decrease in methylation might actually destabilize the genome, resulting in increased mutation rates and chromosome breakage, as demonstrated in fibroblasts and embryonic stem cells. In fact, Jaenisch observed an increase in some cancers, including lymphoma, in animals with reduced DNA methylation. The effects of altered methylation levels could differ dramatically from one tissue to another.

If there was considerable optimism and excitement at the meeting in general, there was even more in the community of 'epigeneticists' because of the rapid convergence of work in cancer biology, chromatin remodeling, DNA modification, DNA repair and genomic instability. There is today a real prospect for understanding cancer biology, prevention and therapy at the most fundamental genomic level.

References

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