Advances in Understanding the Molecular Pathogenesis of Neoplastic Hematologic Disorders

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The 45th Annual Meeting of the American Society of Hematology was held December 6–9, 2003, at the San Diego Convention Center in California. As with past meetings, there were exciting new developments, comprehensive educational programs, and phenomenal exhibits. There was also an ever increasing ASCLS presence at the meeting, as more hematology/hemostasis educators and researchers are finding their way to this very excellent scientific meeting.

A group of us who attended the meeting would like to share with our colleagues who were unable to attend some of the new information in select areas, covered in the following two articles with a third to follow in the next issue of CLS. While a comprehensive summary of the entire meeting would be desirable, the scope of the meeting makes such an endeavor unfeasible. Consequently, we have chosen the areas of myeloproliferative disorders and myelodysplastic syndromes, acute lymphocytic leukemias, and acute myelocytic leukemias.

This is an exciting and rapidly changing time in the study of malignant and premalignant hematologic disorders. As we evolve from a morphology-based assessment of these disorders to an era in which we are beginning to understand the basic underlying mechanisms, the development of new diagnostic and prognostic tests, as well as the development of interventions specifically targeted at the molecular defects unique to individual disease processes are being realized. By understanding the molecular mechanisms of these diseases, and the genetic and epigenetic changes that underlie their evolution and progression, it may be possible in the not too distant future, to not only detect (and possibly eliminate) the disease at its earliest phases of development but also to modulate or control its behavior in terms of its evolution to a lethal phenotype.[1]

There has been a veritable revolution in our understanding of cancer since the early 1970s. As more has been learned about the pathogenesis of cancer, it has become clear that specific molecular events underlie the malignant process.[2] There are many different changes within cells that contribute to tumorigenesis. A genetic change is an aberration in nucleotide sequences that cause a particular disease phenotype. The vast majority of these genetic alterations has been found to involve one of two broad classes of genes: tumor suppressor genes and proto-oncogenes. The former normally function to inhibit inappropriate growth of the target cell, and 'loss of function' alterations of these genes can promote cancer. Proto-oncogenes, by contrast, stimulate growth of the cell, prevent growth arrest, or inhibit apoptosis. Activated proto-oncogenes (called oncogenes) also contribute to inappropriate cell growth and may promote cancer. Point mutations, gene deletions, and chromosomal translocations often underlie these functional changes. The classic example of a genetic mutation, and the first identified in the study of human malignancy, is the Philadelphia chromosome, characteristic of chronic myelocytic leukemia.

However, it is now becoming clear that there are also many epigenetic changes (stable, inheritable) which can also cause

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or contribute to a disease phenotype in the absence of nucleotide aberration. The Presidential Symposium for this year's meeting, "Epigenetics in Hematology", provided the background for understanding some of the new discussions concerning disease mechanisms. Arthur L Beaudet MD of the Baylor College of Medicine began with an overview of genetic disease vs. epigenetic disease, and Stephen Baylin, MD of Johns Hopkins University followed with a presentation on the fundamental role of epigenetics in cancer.[3]

Epigenetics (meaning literally "on top of genetics") refers to the fact that there is another layer of stable or semi-stable gene regulation on top of that controlled by the primary nucleotide sequences. Epigenetics is the study of the changes in gene function that are stably inheritable (or potentially inheritable), which do not entail a change in DNA sequence. One of the most common epigenetic changes found in the human genome involves the methylation of certain cytosine nucleotides within genes and/or their promoter regions. Cytosine nucleotides particularly susceptible to methylation are those found adjacent to a guanine nucleotide, the so-called "CpG dinucleotide".

$$CGATCGATCGAT \rightarrow C^{M}GATC^{M}GATC^{M}GAT$$

These methylations or epigenetic changes can be translated across mitosis or meiosis, and thus become incorporated into the heritable genetic/epigenetic regulatory mechanisms of the organism. Although the methylation of CpG dinucleotides is a potentially reversible process, approximately 70% to 75% of CpG dinucleotides in our genome are methylated. In addition, CpG dinucleotides are often clustered in 'CpG islands', many of which are in and around the promoter regions of genes. The unmethylated state of the promoter regions of genes favors a 'transcription ready status' or accompanies active transcription. Typically, methylation of the promoter regions is associated with 'gene silencing' and is part of the normal terminal differentiation process seen in many diverse tissue types.

Cancer is a complex disorder of DNA methylation. One may see demethylation of the genome in regions where it should be methylated, or methylation of regions of the genome which are typically unmethylated. There is a growing list of genes, somewhere along the road to tumorigenesis, which acquire hypermethylation of CpGs in their promoter regions. This change is associated with transcriptional silencing of these genes, and is the explanation for one of the most common causes of loss of function of key tumor suppressor genes.

Extensive information can also be encoded in the protein component of the chromatin, in what is now being called the "histone code". Modifications of the histone proteins include lysine acetylation, serine phosphorylation, lysine methylation, and arginine methylation. These modifications can be stably passed from one cell generation to the next as well. These modifications, constituting the histone code, play an essential role in the very complex system responsible for regulating the potentially reversible euchromatin to heterochromatin transitions. Various types of malignant cells utilize enzymes called histone deacetylases (HDACs) to modify the histone code, and induce transcription of genes which favor cell growth over differentiation.

Hematology researchers have been trying to define the genes whose genetic and epigenetic changes contribute to the evolution of a malignancy. One result of this evolving process has been a realignment and redefinition of the malignant and premalignant hematologic diseases, proposed by the WHO working group.[5] An understanding of the relevant mechanisms underlying cancer will result in not only the development of improved clinical and laboratory tools for the detection, diagnosis, and prognosis of cancer, but will also lead to the development of better and more targeted therapies for the treatment, and perhaps even the prevention, of cancer. This is truly an exciting time of exponential expansion of our scientific understanding of these diverse and often confusing diseases.

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