The Philadelphia Chromosome

Richard G. Lynch, MD
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MILESTONES

Nowell PC, Hungerford DA: **A minute chromosome in human chronic granulocytic leukemia.** *Science* 1960, 132:1497-1501

Peter C Nowell

At the 1960 Fall Meeting of the National Academy of Sciences, Peter Nowell and David Hungerford reported that in each of seven patients with chronic granulocytic leukemia that they had studied, the leukemia cells contained an abnormal small chromosome that was not present in normal cells or in the cells of other types of leukemia. The abstract of their presentation appeared in *Science*[1] and was followed by a more detailed publication[2] describing their findings in ten patients with chronic granulocytic leukemia.

The milestone research reported by Nowell and Hungerford in *Science* in 1960[1] identified for the first time a consistent chromosome abnormality in a human neoplasm. Through meticulous examination of metaphase chromosome preparations they observed that one of the four smallest acrocentric chromosomes was markedly reduced in size, by what appeared to be the loss of approximately half of its long arm. The consistent association of this abnormality with chronic granulocytic leukemia suggested to Nowell and Hungerford that this chromosome change might confer on the leukemia cells their neoplastic character. A pathogenic role for the chromosome abnormality was further implied by its presence in leukemia cells at the onset of disease and prior to any treatment, and by its persistence in leukemia cells of patients whose disease had been present for many years. Investigators in Edinburgh who designated the abnormal chromosome the Philadelphia chromosome (Ph) confirmed the findings of Nowell and Hungerford. Peter Nowell was then, and still is, an investigative pathologist in the Department of Pathology at the University of Pennsylvania, and David Hungerford was a cytogeneticist at The Institute for Cancer Research in Philadelphia. A critical aspect of their research was the comparison of the chromosomes in the patients' leukemia cells to the chromosomes in their normal cells. Although very labor-intensive, it was possible to visualize individual chromosomes in leukemia cells because these cells spontaneously divide when cultured *in vitro*, and in the presence of colchicine the mitoses are arrested in metaphase. Visualizing the chromosomes of the normal cells in the patients' blood samples could have presented a barrier to this research because normal blood leukocytes do not spontaneously divide when placed in cell culture. However, in another fundamental discovery, Nowell had observed that phytohemagglutinin (PHA) – a plant mucoprotein used to separate leukocytes from erythrocytes in the blood samples – had the property of being a powerful lymphocyte mitogen[3]. This discovery made it possible to prepare chromosomes from the normal, non-leukemia leukocytes present in the patients' blood.

The discovery of the Philadelphia chromosome by Nowell and Hungerford was strong evidence that linked a genetic abnormality with human cancer. Their discovery was a landmark in cancer research and proved to be a seminal event in the field of cancer cytogenetics. Many thousands of publications and hundreds of research projects from numerous laboratories around the world can trace their ancestry to the original findings described by Nowell and Hungerford in their classic paper. A tremendous interest in the area of human cancer cytogenetics continues unabated to the present day, and the growth of knowledge in this area has been very impressive. The technology available to examine human chromosomes in 1960 only allowed for the detection of gross abnormalities in chromosome morphology and number. Compared to the penetrating, sophisticated molecular analyses used by investigators today, those tools were rather primitive. The introduction of the quinicrine fluorescence/Giemsa banding technique in the 1970's was a major advance in cytogenetics and its application to the study of chronic granulocytic leukemia cells subsequently established that the Philadelphia chromosome was produced by a reciprocal translocation between chromosomes 22 and 9[4]. In this abnormality a truncated portion of the protooncogene *c-ABL* from chromosome 9 relocates to the *BCR* gene locus on chromosome 22 and a large portion of the long arm of chromosome 22 relocates to chromosome 9. This reciprocal translocation

has two important consequences. The first is that it results in a significant reduction in the size of chromosome 22, the alteration that allowed Nowell and Hungerford to detect the cytogenetic abnormality in chronic granulocytic leukemia cells. The second consequence, which was elucidated later, was that the translocation resulted in the fusion of two genes, *BCR* and *ABL1,* to form the hybrid oncogene *BCR-ABL.* It was subsequently shown that the fused *BCR-ABL* gene encoded a chimeric protein that has tyrosine kinase activity[5] and is leukemogenic[6]. The results of a recent clinical trial suggest that the pharmacological blockade of the BCR-ABL kinase may be of value in the treatment of chronic granulocytic leukemia[7].

The impressive growth of knowledge about the roles of genetic alterations in the pathogenesis of human leukemia and lymphoma that has taken place since the milestone discovery of Nowell and Hungerford has also revealed the enormous level of complexity involved in these processes. The degree of this complexity has significant implications for the treatment of these malignant neoplasms, a subject that has been discussed by Nowell[8].

References

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