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Tumor Suppressor Genes and Oncogenes in Cancer: Are the Present Techniques Meeting the Challenge?

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Oncogenes and tumor suppressor genes are genes involved in cell proliferation and differentiation. They play a crucial role in the initiation and progression of cancer. Some of these genes are found to be altered in human cancers, i.e., mutated, amplified, deleted, translocated, or abnormally regulated. Recently, the protein products of the genes have been purified, and antibodies against them have been developed. Studies of oncogenes and tumor suppressor genes at the DNA, mRNA, or protein level may reveal new ways for diagnosis, monitoring, prognosis and treatment of cancer. The ability of these newly discovered genes to diagnose cancer is theoretically better than the traditionally used tumor markers. This belief originates from the well-known fact that traditional tumor markers are not directly related to cancer initiation and progression but are merely abnormalities associated with increased cell number or with premature cell types (e.g. the oncofetal antigens). It is thus not surprising that virtually all known tumor markers are found in normal cells and their concentration increases in many non-malignant diseases. Organ-specific tumor markers do not exist either. Recently, the supposedly most organ specific tumor marker, prostate specific antigen, was found to be produced by 30 - 40 % of female breast tumors.

There are good indications that at least some oncogenes and tumor suppressor genes are directly involved in the pathogenesis of some cancers. It is thus reasonable to expect that such altered genes (mutated, amplified or deleted) could be used to diagnose cancer with absolute sensitivity and specificity. There are some major limitations with this approach. The source of the specimen to be tested is important. Only when the genetic alteration is present in all cells, as in the relatively small inherited cancer syndromes, that genetic material from peripheral blood leukocytes is adequate. Even in this case, when the mutation is scattered throughout the gene (as it happens with the BRCA-1 breast cancer gene or the p53 gene) considerable effort must be devoted to find the mutation. Fortunately, there are now indications that large scale automatic sequencing will efficiently address this problem in the near future.

Most cancers are associated with somatic genetic changes and their diagnosis requires the availability of cancer cells. These would be found in some cases in feces, urine, sputum or blood but the number of cancer cells may be so small, that extraordinarily sensitive and specific techniques must be used for their identification. Although the polymerase chain reaction is promising, its routine use is complicated by the potential for contamination and sometimes by equivocal results. Unfortunately, in most

cases, the identification of cancer cells is only possible when their number is large and when they have already spread to distant locations. Immune response against mutant proteins may have some potential for diagnosis as it will be discussed in detail during the presentation.

Cancer has been with mankind for thousands of years. Although the recent advances in molecular biology are impressive and the cloning of new genes, including cancer-associated genes, is increasing exponentially we do not as yet have reliable, non-invasive, biochemical methods for early cancer diagnosis. Clearly, small battles have been won but the war is far from over.