

Keynote Lecture 3

Oncogenes and tumor suppressor genes

Chairperson: N J Agnantis Greece

Genetic analysis of tumor development

E. Santos

Laboratory of Cellular and Molecular Biology National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

The genetic paradigm of cancer – that tumors arise as a consequence of the accumulation of mutations in genes controlling cell proliferation, differentiation or death – is now widely accepted. The purpose of this is lecture provide a review of current knowledge on the various types of cancer genes identified so far in different stages of tumor development. We will also address recent attempts to translate the available wealth of basic knowledge on tumor genes into clinical applications at the level of diagnostics, prognosis or even treatment of this disease.

Distinct classes of cancer genes have been operationally identified. Dominant oncogenes, initially identified by transfection experiments, constitute the first main group of human cancer genes identified since the early 1980s. The products of their precursor genes in normal cells – the protooncogenes – exert positive control over cell proliferation processes and their mutation in tumors confers them a dominant phenotype.

Analysis of somatic cell hybrids between neoplastic and normal cells as well as the study of inherited pediatric tumors gave rise to the identification of tumor suppressor genes. The products of these genes exert negative regulatory roles over cellular proliferation. Malignancy is associated with mutational inactivation of these genes, which causes loss of function and accounts for their recessive genetic behavior. In a “cancer-car” homology, oncogene activation would be akin to a jammed gas pedal and suppressor gene inactivation to loss of the brakes. A single mutated copy of a dominant oncogene is enough to trigger malignancy, whereas mutation of the two copies of suppressor genes is needed for the same purpose. Molecular and genetic analysis has proven that Knudson’s two-hit hypothesis is fundamentally correct (1). Various molecular studies have identified intragenic mutations, loss of chromosomal material (loss of heterozygosity or homozygous deletion), or even epigenetic mechanisms, such as abnormal methylation, as potential mechanisms leading to inactivation of the two copies of suppressor genes.

The study of inherited tumor susceptibility syndromes has contributed greatly to our current understanding of the molecular mechanisms of cancer (2, 3). Most of the tumor susceptibility genes initially identified (for example, p53, *Rb*, *VHL*, *APC*) tell within the category of classic suppressor genes. These genes directly regulate the growth of tumors by inhibiting growth or promoting death. Their inactivation contributes directly to neoplastic growth and they have been termed gatekeepers since they are supposed to function by preventing runaway growth. In contrast, many other

susceptibility genes (such as *XPB*, *ATM*, *MSH2*, *MLH1*) do not affect cell growth directly and only indirectly suppress neoplasia. Most members of this class of genes encode DNA repair proteins which function as caretakers of the integrity of the genome. Inactivation of caretaker genes results in greatly increased rates of mutation and is equivalent to chronic exposure to mutagens. Finally, the study of juvenile polyposis syndrome may have uncovered another group of indirectly acting cancer susceptibility genes, denominated landscapers because their initial activation may have occurred in the stromal tissue of the polyps, thus providing an “abnormal terrain” promoting neoplastic progression of the surrounding epithelial cells.

The mechanisms of mutational activation of the different cancer genes may be highly variable. It has been argued that an underlying genetic instability may be required for the generation of the multiple mutations occurring in cancer. There is now evidence that most cancers are indeed genetically unstable (4). In a small subset the instability is observed at the nucleotide level, resulting in base substitutions or deletions or insertions of a few nucleotides. In most other cases the instability is observed at the chromosome level, resulting in loss or gain of whole chromosomes or fragments thereof.

Functional analysis of the products of the various cancer genes has revealed fundamental roles in signal transduction pathways controlling cellular proliferation, differentiation, or even death (5). These studies have made it increasingly clear that progression of the normal cell cycle is the result of a balanced interaction among multiple regulators, codified by protooncogenes, suppressor genes, gatekeepers or caretakers. It is not surprising that functional alterations at the level of any of those multiple regulators may result in an unbalanced cell cycle and eventual neoplastic progression. Such a simplified context of functional analysis at the molecular level provides the conceptual framework that makes it possible to define cancer as a “genetic disease of the cell cycle”.

The recent remarkable progress in identifying genetic and molecular alterations in human tumor cells is starting to be exploited successfully at the clinical level. Thus, nucleic-acid-based markers of neoplastic progression can be used to detect cancer cells in a variety of clinical settings with unprecedented precision (6). Likewise, the new wealth of genomic information for both human and model organisms is being integrated with traditional genetic approaches to attack problems of anticancer drug discovery and characterization (7). Finally, current efforts to develop gene expression microarrays capable of producing large gene expression data sets specific to different clinical samples hold great promise to achieve the molecular fingerprinting of different cancer cell types and/or stages (8).

References

1. Jones PA, Laird PW. *Cancer epigenetics comes of age*. Nature Genetics 1999; 21: 163-167.

2. Kinzler KW, Vogelstein B. *Gatekeepers and caretakers*. Nature 1997; 386: 761-763.
3. Kinzler KW, Vogelstein B. *Landscaping the cancer terrain*. Science 1997; 280: 1036-1037.
4. Lengauer C, Kinzler KW, Vogelstein B. *Genetic instabilities in human cancers*. Nature 1998; 396: 643-649.
5. Hunter T. *Oncoprotein networks*. Cell 1997; 88: 333-346.
6. Sidranski D. *Nucleic acid-based methods for the detection of cancer*. Science 1997; 278: 1054-1058.
7. Hartwell LH, Szankasi P, Roberts CJ et al. *Integrating genetic approaches into the discovery of anticancer drugs*. Science 1997; 278: 1064-1068.
8. Cole KA, Krizman O, Emmert-Buck MR. *The genetics of cancer - a 3D model*. Nature Genetics 1999; 21: 38-41.