

“Medical Science, Medicinal Science” field

Achievement : For their pioneering work in conceptualizing a model of multi-step carcinogenesis and its application and impact on improving cancer diagnosis and therapeutics

Prof. Bert Vogelstein (USA)

Born: June 2, 1949 (Age: 71)
Professor, Johns Hopkins University School of Medicine

Dr. Robert A. Weinberg (USA)

Born: November 11, 1942 (Age: 78)
Member, Whitehead Institute for Biomedical Research
Professor, Massachusetts Institute of Technology (MIT)

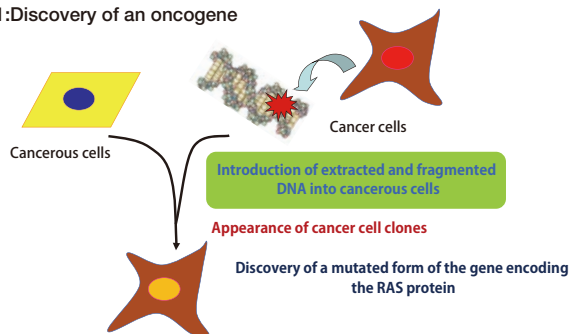
Summary: Discoveries of oncogenes and tumor suppressor genes and proposal/verification of the multi-step carcinogenesis model.

Dr. Weinberg discovered the presence of cellular genes, called proto-oncogenes, which can be converted to cancer-causing oncogenes by a mutation(s). He also contributed in the discovery of a gene, now called a tumor suppressor gene, that is required for the protection of cells to become cancer cells. Dr. Vogelstein independently searched for actual mutated genes in human cancer cells and discovered numerous new genes that are critical to the development of cancer. On the basis of these achievements, the concept of “multi-step carcinogenesis model” was established. Although many other investigators contributed to this field, Drs. Weinberg and Vogelstein stand out in that they continued their innovative research as the pioneers and leaders in corroborating this concept. In fact, Dr. Weinberg experimentally demonstrated the requirement of multiple oncogenes to convert normal cells into cancer cells, while Dr. Vogelstein verified the concept by molecular genetics combined with histopathology of large intestinal lesions, from which human colorectal cancers arise, to show the association of a series of mutations in cancer-associated genes. Thus, they revealed pivotal roles for certain human oncogenes and tumor suppressor genes in the propagation and suppression of numerous common human cancers. Their discoveries have also led to the opening of the field of cancer genomics, now an especially powerful force in discerning and developing mechanism-based human cancer diagnostics and therapeutics.

Dr. Weinberg’s achievements

Dr. Weinberg helped launch this new era of human cancer genes. In elegant and original research, he introduced extracted and fragmented DNA from cancer cells and then introduced the fragmented DNA into cancerous cells and found an appearance of cancer cell clones (Fig. 1). When he then analyzed the cancer cell-derived genes in these cells, he discovered a mutated form of the *RAS* gene. Normal *RAS* gene product is important for the promotion of cell growth and it is transiently activated by cell growth signals and then converted

Figure 1: Discovery of an oncogene



into an inactive state to prevent excessive cell growth. On the other hand, the product of the mutated *RAS* continues to remain in the active form; in analogy to car driving, the driver keeps stepping on the accelerator (Fig. 2).

This “oncogene” was simultaneously discovered by other groups, but Dr. Weinberg further advanced his study using primary cultured cells, which cannot be transformed by the mutant *RAS* gene alone. He then demonstrated that these primary cells become cancer cells by introducing multiple oncogenes. During this research, Dr. Weinberg also assumed the presence of genes the products of which suppress cancer cell development and greatly contributed to the discovery of *RB* gene, the first of so-called “tumor suppressor genes”; in analogy to car driving, the driver puts on the brakes. Thus, these studies lead to the establishment of a paradigm that cancer will arise by the appearance of oncogenes and disappearance of tumor suppressor genes (Fig. 3).

Dr. Vogelstein’s achievements

Dr. Vogelstein took a different approach, using methods of molecular genetics combined with histopathology of large intestinal lesions to show that a series of mutations in cancer-associated genes (*i.e.*, *APC*, *RAS*, *TP53*, and others) were associated with the progression from benign adenomas to increasingly aggressive colon adenocarcinomas, establishing a foundation of multi-step carcinogenesis model (Fig.5). In fact, Dr. Vogelstein was among the first to demonstrate that *TP53*, which was originally considered as an oncogene, is a tumor suppressor gene. His discoveries, in parallel with those of Dr. Weinberg, have also led to the opening of the field of cancer genomics, now an especially powerful force in discerning and developing mechanism-based human cancer diagnosis and therapeutics. On the basis of the series of discoveries, Dr. Vogelstein has authored conceptual cornerstone of modern cancer research, namely, the *Vogelgram*.

Figure 2: Functional difference between the normal and mutated *RAS* proteins

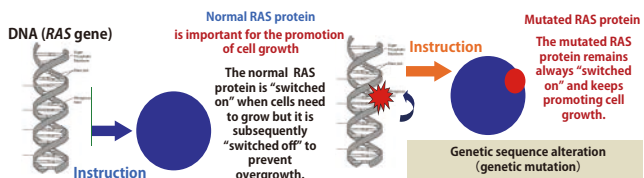


Figure 3: Development of cancer cell : Outline

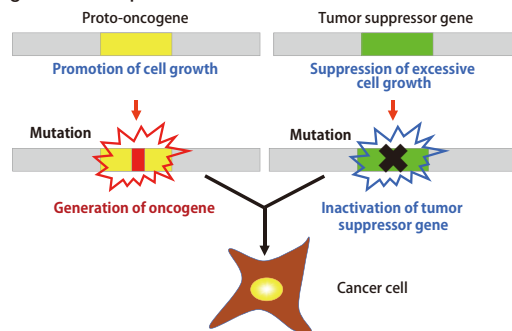
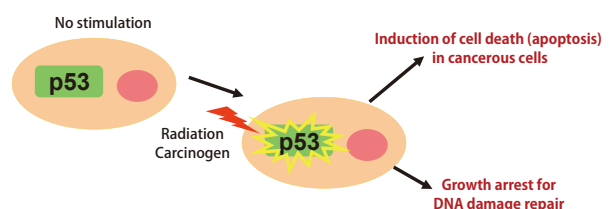


Figure 4: Action of normal tumor suppressor p53 (*TP53* gene product)

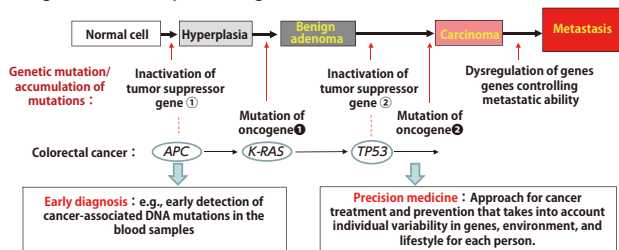


The ripple effects of the achievements by Drs. Weinberg and Vogelstein

The scientific and social contribution of the work by Drs. Weinberg and Vogelstein has been immeasurable to the cancer field. Their efforts have provided a paradigm of cancer progression that has shaped our view up through today. While this has produced important changes in how cancer is diagnosed and treated, the complexity of cancer evolution has proven much greater than any could have imagined. Drs. Weinberg and Vogelstein have published influential conceptual cornerstones articles of modern cancer research, namely, *Hallmarks of Cancer* by Dr. Weinberg, together with Dr. Douglas Hanahan (Fig. 6), and *Vogelgram* by Dr. Vogelstein (Fig. 5).

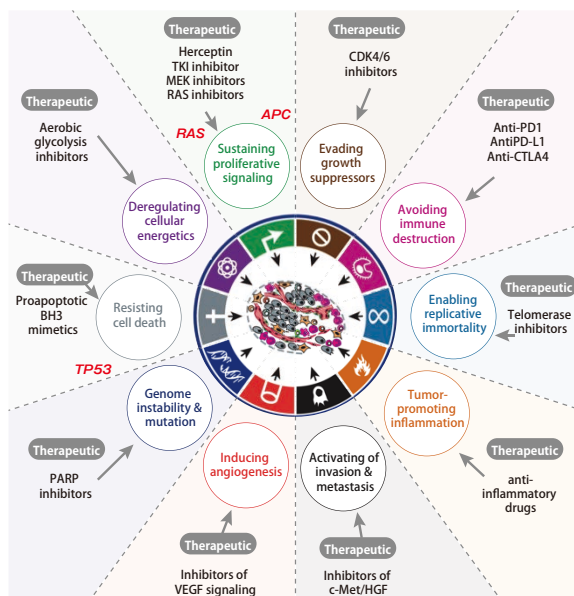
Overall, the paradigm set out by these two investigators has established principles that have enabled an understanding of the complexity of cancer, especially in providing a strong rationale for early cancer detection and intervention. Their accomplishments have served as the basis for many of the contemporary developments of targeted cancer therapies. Indeed, the notion of “precision medicine” in oncology has been synthesized from many of their ideas. Overall, their work has not only advanced basic cancer research, but also created the transformative field of cancer drug development that is improving the lives of many cancer patients.

Figure5:Multi-step carcinogenesis model



"Vogelgram" (modified from the original article of Fearon ER and Vogelstein B in Cell 61, 759-767, 1990)

Figure 6:The hallmarks of cancer and their therapeutic targeting



"Hallmarks of cancer" (modified from the original in Hanahan D and Weinberg RA, Cell 144, 646-674, 2011)