

This week's Citation Classic

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Huebner R J & Todaro G J. Oncogenes of RNA tumor viruses as determinants of cancer. *Proc. Nat. Acad. Sci. US* 64:1087-94, 1969. [Viral Carcinogenesis Branch, National Cancer Institute, National Institutes of Health. Bethesda, MD]

Sero-epidemiological and cell culture studies led us to the conclusion that vertebrate cells contained the genetic information for producing C-type RNA viruses. We also postulated that the viral information (the virogene) often included cellular oncogenes responsible for transformation and that the action of carcinogens, irradiation, and the normal aging process was also mediated by transforming proteins specified by the inherent oncogenes. [The SCI[®] indicates that this paper has been cited over 705 times since 1969.]

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"The viral oncogene theory was inescapable given the years of cumulative evidence culminating in the 1969 report in the *Proceedings of the National Academy of Sciences*. Actually, an earlier report¹ was given at an international conference held at the Abbaye de Royaumont in June 1969, where Andre Lwoff, as chairman, focused discussion on 'Les Oncogenes,' thus raising considerable controversy at the outset. This was appropriate since it was his germinal genetic theories, shared with Jacob and Monod, which helped formulate our concept that the proximal cause of cancer was mediated by endogenous transforming oncogenes residing within vertebrate cells. A number of earlier encounters with Sir McFarlane Burnet convinced me that he was right: the stochastic behavior of cancer in man could not be attributed to exogenous infectious viruses. This decision helped crystallize our view that cancer was the result of derepression of inherent species-specific endogenous oncogenes often linked in mice and chickens with endogenous oncornavirus. Genetic abnormalities or deficiencies, environmental carcinogens, and 'oncogenic' viruses were thus inducers of such oncogenes

"Another key factor was our observation that the endogenous leukemia and sarcoma viruses in chickens, mice, rats, and cats actually carried 'movable' oncogenes, since 'sarc' genes could be rescued from primary hosts and transmitted as transforming oncogenes to cultured cells of a wide variety of animal hosts, including human. Subsequently, it was demonstrated by rescue experiments that the transforming and tumor-inducing leukemia and sarcoma oncogenes more often than not existed on tumor cells independently of virogene expression, and were rescuable by viruses. The fact that the oncogenes could be transmitted to cells of the same and other susceptible species clearly indicated that transforming proteins specified by endogenous sarc and leuk oncogenes provided species-specific determinants responsible for neoplasia and transformation, while exogenous factors (environmental chemicals, radiation, DNA tumor viruses) served as inducers of the postulated oncogene sequences. Definitive evidence establishing the role(s) of the transforming proteins specified by sarc and leuk oncogenes was provided by subsequent molecular, immunological, and immunoprevention studies in experimental animals, particularly in mice, rats, cats, and chickens.

"The viral oncogene theory expressed a new concept in which it was postulated that all carcinogenesis (radiation, carcinogens, aging, etc.) was mediated through activation of an endogenous host cell gene present in every vertebrate cell. This opened the way for subsequent discoveries of the sarc, onc, and leuk proteins by molecular biologists

"Recently, it became apparent that the oncogene determinants of cancer represented also the required determinants for immunoprevention. Vaccines and IgG preparations incorporating immunity to sarc and leuk gene expressions have recently been used to prevent virtually all types of cancers in mice and rats, including cancers produced by chemicals and DNA tumor viruses.² These successful immunoprevention studies we believe provide excellent models for development of comparable prevention of cancer in man."

1. Huebner R J, Todaro G J, Sarma P, Hartley J W, Freeman A E, Peters R L, Whitmire C E, Meler H & Gilden R V. "Switched-off vertically transmitted C-type RNA tumor viruses as determinants of spontaneous and induced cancer: a new hypothesis of viral carcinogenesis. *Defectiveness, rescue and stimulation of oncogenic viruses. Second International Symposium on Tumor Viruses*. Paris: Editions du Centre National de la Recherche Scientifique. 1970. p. 33-57.
2. Huebner R J & Fish D C. Sarc and leuk oncogene-transforming proteins as antigenic determinants of cause and prevention of cancer in mice and rats. (Griffin A C & Shaw C R. eds.) *Carcinogens identification and mechanisms of action* New York: Raven Press. 1979. p. 277-98.