Infections Causing Human Cancers

Harald zur Hausen
Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280
69120 Heidelberg, Germany. E-mail: zurhausen [at] dkfz-heidelberg.de

Approximately 20% of the global cancer burden is directly or indirectly linked to infectious events. Three common human cancers have been linked to infections: hepatocellular carcinoma, linked to persistent *Hepatitis* B or C infections, cancer of the cervix, triggered by high risk *Papillomavirus*es, and gastric cancer, linked mainly to a bacterial infection, *Helicobacter pylori*.

Cancer induction by Hepatitis B or C viruses requires long periods of viral persistence commonly covering several decades. *Hepatitis B viruses* possess two genes that may contribute to carcinogenesis: the HBx gene and the surface protein HBsAg. HBx interferes with cellular repair mechanisms whereas HBsAg induces oxidative stress. *Hepatitis C* virus also seems to contribute to liver carcinogenesis indirectly. Here 3 genes, non-structural proteins NS3 and NS5A and the core protein led to oxidative stress within the infected cells and to mutational events. Specific types of human pathogenic papillomaviruses (HPV), most prominently HPVs 16 and 18 among several others, cause cancer of the cervix and a substantial percentage of cancers of other anogenital sites (cancer of the vulva, vagina, penile cancer, perianal and anal cancers). Their mechanism of action differs substantially from Hepatitis viruses: they commonly insert specific vical oncogenes (E6 and E7) into the host cell genome. Although function and expression of these genes is effectively controlled in proliferating cells by host cell proteins, failure of these host cell functions results eventually in malignant growth. The same *anogenital papillomavirus* types, again preferentially HPV 16, are responsible for ~25% of oral cancers and for the rare nailbed cancers.

Epstein-Barr virus (EBV) contributes to nasopharyngeal carcinomas, Burkitt's lymphomas, certain other B-cell lymphomas and to a subset of Hodgkin's disease. More recent data also point to a role of this virus in close to 10% of gastric cancers arising in the upper third of the stomach. Clear-cut evidence exists for a role of EBV in specific B cell lymphomas arising under conditions of immunosuppression. EBV acts in this condition as a direct carcinogen. The mechanistic contributions of EBV are less clear in Burkitt's lymphomas, in nasopharyngeal cancer and in Hodgkin's disease. Other infections have been linked to less common tumors: *Human Herpesvirus* type 8 to Kaposi's sarcomas, T-lymphotropic retrovirus type I to the endemic form of adult T-cell leukemia. Parasitic infections, contribute to bladder and rectal cancers or to cholangiocarcinomas.

The mechanisms by which infectious agents contribute to cancer development differ widely, permitting their classification as direct and indirect carcinogens. HIV infections, as example, act as indirect carcinogenes and induce immunosuppression resulting in other frequently virus-linked malignancies. Prevention of apoptosis (by specific human pathogenic papillomaviruses) emerges as another mode of indirect contribution to cancer development. Chronic inflammatory events, commonly observed in Hepatitis virus infections, in gastric infections with Helicobacter pylori, and in parasitic infections also contribute indirectly to cancer development.

CURRICULUM VITAE

Harald zur Hausen
German Cancer Research Institute

Harald zur Hausen was born on March 11, 1936 in Gelsenkirchen-Buer, Germany. He studied Medicine at the Universities of Bonn, Hamburg and Düsseldorf and received his M.D. in 1960. After his internship he worked as postdoc at the Institute of Microbiology in Düsseldorf, subsequently in the Virus Laboratories of the Children's Hospital in Philadelphia where he was later appointed as Assistant Professor. After a period of 3 years as a senior scientist at the Institute of Virology of the University of Würzburg, he was appointed in 1972 as Chairman and Professor of Virology at the University of Erlangen-Nürnberg. In 1977 he moved to a similar position to the University of Freiburg. From 1983 until 2003 he was appointed as Scientific Director of the Deutsches Krebsforschungszentrum (German Cancer Research Center) in Heidelberg.

He had and has a number of special appointments, among them being the Chairman of several Scientific Price-Committees, between 1989-1991 Chairman of the Association of National Research Centers (Großforschungseinrichtungen) in Germany and from 1993 to 1996 President of the Organization of European Cancer Centers (OECI).

He received a number of national and international awards, among them the Robert-Koch-Price, the Charles S. Mott Price of the General Motors Cancer Research Foundaton, the Federation of the European Cancer Societies Clinical Research Award, the Paul-Ehrlich-Ludwig Darmstätter-Price, the Jung-Price, Hamburg, the Charles Rudolphe Brupbacher Price, Zürich, the Prince Mahidol Award, Bangkok, the Raymond Bourgine Award, Paris. He received honorary doctorates from the Universities of Chicago, USA, Umeå, Sweden, Prague, Czech Republic, Salford, UK, Helsinki, Finland, and Erlangen-Nürnberg, Germany.

He is an elected member of various academies (LEOPOLDINA, Academia Europaea, Heidelberg Academy of Sciences, Polish Academy of Sciences, Venezuela National Academy of Medicine, American Philosophical Society, Institute of Medicine of the National Academy of Sciences (USA), and research organizations (EMBO, HUGO) and became an Honorary Member of a number of biomedical scientific societies. A large number of Special Lectures and Visiting Professorships, Memberships in Editorial Boards and active involvements in the organization of international meetings complement his curriculum. Since 2003 he is Vice-President of the German Academy for Natural Sciences and Medicine LEOPOLDINA in Halle.

Harald zur Hausen is author or co-author of presently 278 papers in international journals. He proposed the role of papillomaviruses in the etiology of cancer of the cervix in the early 1970th and proved their role 10 years later. He is the discoverer or co-discoverer of a larger number of novel virus types (among them HPV 6, 11, 16, 18 and many other HPV types, Adeno-Associated Virus type 5, Lymphotropic Polyoma Virus [LPV], African Green Monkey Epstein-Barr Virus, and recently a larger number of TT Virus genotypes). In addition, he was the first to discover latent EBV DNA in Burkitt's lymphoma and epithelial nasopharygeal carcinoma cells and developed an effective induction method for latent herpesviruses by phorbolesters.