Infectious Disease and Cancer

Joseph J. Mazza, MD, MACP

Abstract

With the recent advances in molecular biology and genetics over the past several decades, we have gradually uncovered the elusive cause of some of the malignant diseases that have been, and continue to be, a major factor in human mortality. Infectious disease agents, so ubiquitous in our environment, have now become the most credible link in our search for the cause of cancer. The number of malignancies associated with specific infectious disease agents continues to grow and now represents approximately 20% of all cancers. This perspective represents a brief summary of those cancers that have been associated with or caused by infectious disease agents. Hopefully, knowledge of this relationship can be translated into more effective means of treatment.

• • •

Infection from a variety of microorganisms must be considered as an important risk factor for cancer in humans; it is postulated that approximately 20% of cancers worldwide are linked to viruses, bacteria, and parasites.[1] Infectious disease agents are now recognized as a factor contributing to the cause of many chronic illnesses and may play an important role in malignant diseases. As we have continued to explore this possibility with recent molecular and genetic technology, ample data have become available that support the concept of viral agents being incorporated into the human genome, altering its composition and affecting its functioning genes and their products.

Viral nucleotide sequences discovered in the human genome have been inherited or passed on from lower species and preserved through the eons of the evolutionary process and may play an important beneficial (protective) role in host survival, constituting a necessary symbiotic relationship.[2-4] However, these incorporations may result in alterations of genes that encode for factors related to cell proliferation, differentiation, and transition from normal to abnormal, with the potential of becoming a malignant clone and destroying the host. Examples of these end results can be seen in the integration of human T-cell lymphotropic virus (HTLV) I & II into the human genome that lead to malignant proliferation and demise of the host (Table 1). Although the pathogenesis of malignant transformation is not completely understood and is likely a multistep process, infectious disease agents must be considered as possible initiating events in this process or a later promoting factor causing mutational alternations of a protoncogene.

Additionally, viruses and bacteria may also play an important role in the occurrence of malignancy by

Table 1. Examples of Infectious Disease Agents Linked to or Associated with Various Cancers

Infectious Agent	Disease
The Epstein-Barr virus (EBV) [5-17]	Non-Hodgkin's lymphoma
	Hodgkin's disease
	Burkitt's lymphoma (African)
	Nasopharyngeal carcinoma
Helicobacter pylori[18-21]	Lymphoma of the stomach (marginal-zone of mucosa associated lymphoid tissue type [MALT])
Campylobacter jejuni[22-23]	Lymphoma of the small intestine
Borrelia Burgdorferi[24-25]	Lymphoma (marginal-zone B-cell)
Simian virus 40[26-27]	Non-Hodgkin's lymphoma
Papilloma virus[28-31]	Cancer of the cervix
	Cancer of the anogenital region
Herpes virus-VIII[32-35]	Kaposi's sarcoma
	Multiple myeloma
HTLV-I & II[36-37]	Adult T-Cell Lymphocytic Leukemia/Lymphoma
Hepatitis B virus[38-39]	Hepatocellular carcinoma
Hepatitis C virus (HCV)[40-41]	Hepatocellular carcinoma
	Splenic lymphoma with villous lymphocytes
Cytomegalovirus (CMV)[42]	Glioblastoma of the central nervous system
Xenotropic murine leukemia virus-related virus (XMRV)[43-44]	Familial prostate cancer

HTLV, human T-cell lymphotropic virus

Author Affiliation: Department of Hematology/Oncology, Marshfield Clinic Research Foundation, Marshfield, Wis.
Corresponding Author: Joseph J. Mazza, MD, Department of Hematology/Oncology, Marshfield Clinic Research Foundation, 1000 N Oak Ave, Marshfield, WI 54449; phone 715.389.7634; fax 715.389.3808; e-mail mazzaj@mfldclin.edu.

altering the microenvironment of the infected tissue, allowing normal host cells/tissue to transition into a malignant clone with unchecked proliferation and invasive capability. These environmental changes are often associated with a chronic illness and may persist for years before a malignant clone arises from the milieu of infected cells.

Recently, we have come to appreciate the rapidly expanding spectrum of genetic abnormalities, eg, the array of translocations and deletions seen in patients with myelodysplasia, leukemia, lymphomas, and other malignant tumors. Conceivably, these cytogenetic abnormalities that result in abnormal gene products may be the result of viral genome sequences that have been incorporated into and/or damaged the deoxyribonucleic acid (DNA) of the host's genome, leading to or initiating the evolution of an abnormal or malignant clone. The gene products from these altered genes are believed to be important cytokines and growth factors that are over-expressed and provide the microenvironment necessary for abnormal clonal transformation, ie, metaplasia and proliferation. Some examples of these products that influence clonal proliferation include tyrosine kinases that act as growth factors of hematopoietic cells, interleukin 6 that appears to be a growth factor for myeloma cell, etc (Table 1).

Unrepaired alterations to the DNA are essential first steps in the process of malignant transformation and can result from over expression of certain genes causing inactivation of important suppressor genes that guard against the development of this transformation, cell proliferation, and clonal expansion.

Over the past several decades, molecular and genetic technology (ie, microarray, gene mining of the human genome, epigenetics, comparative genomics, etc) have provided tools and methods of detecting nucleotide sequences that are genetic representatives of a viral genome.

Exploitation of polymerase chain reaction (PCR) has provided a sensitive and accurate means to detect viral sequences that perhaps are contributing factors in the development of various cancers. In addition, extensive catalogs of gene sequences or genetic probes of infectious agents have been commercialized and made available to investigators throughout the world. Microarray plates containing numerous nucleotide sequences for genetic probes have been developed and are being used to detect the presence of microorganisms in various tissues from individuals suffering from a variety of chronic illnesses. The microarray technique allows the investigator to make available thousands of these genetic probes on a small microcompartmentalized plate on which the genetic information from an infected cell can bind to a complimentary genetic probe on the plate.

Summary

Viruses that can incorporate themselves into our genome, bacteria that cause chronic infection, and microorganisms that alter the microenvironment of tissues appear to play an important role in the evolution of malignant clones of cells and have been implicated in a number of cancers—the list continues to grow. The frequency of papilloma virus found in cervical cancer, one of the most frequently occurring cancers in women, the Epstein Barr Virus occurring in Burkitt's Lymphoma (African), and the association of Hepatitis C virus with hepatocellular cancer are a testament to a cause and effect relationship of these agents. Although a direct cause-and-effect relationship cannot be made for most of these agents, circumstantial evidence has enhanced our quest to better understand this transformation via DNA alteration and gene function resulting from host infections. The role of cytokines, growth factors, tumor suppressor genes, genetic mutations, deletions, and hyper- and hypodiploidy all are part of the complex network that has been implicated in this biological process leading to cancer. Additionally, external environmental factors, as inducers of genetic alterations leading to a microenvironment conducive to metaplasia and the proliferation of a malignant clone, also remain prime suspects. Hopefully, with a deeper understanding of these factors, opportunities will continue to emerge that will lead to therapeutic interventions that target important components of this process.

References

1. Zur Hausen H. The search for infectious causes of cancer: where and why. *Virology.* 2009;392:1-10.
2. Relman DA. The human body as microbial observatory. *Nat Genet.* 2002;30:131-133.
3. Bannert N, Kurth R. Retroelements and the human genome: new perspectives on an old relation. *Proc Natl Acad Sci USA.* 2004;101:14572-14579.
4. Conley AB, Piriyapongsa J, Jordan IK. Retroviral promoters in the human genome. *Bioinformatics.* 2008;24:1563-1567.
5. Thorley-Lawson DA, Gross A. Persistence of the Epstein-Barr virus and the origins of associated lymphomas. *N Engl J Med.* 2004;350:1328-1337.
6. Souza TA, Stollar BD, Sullivan JL, et al. Peripheral B cells latently infected with Epstein-Barr virus display molecular hallmarks of classical antigen-selected memory B cells. *Proc Natl Acad Sci USA.* 2005;102:18093-18098.
7. Macsween KF, Crawford DH. Epstein-Barr virus-recent advances. *Lancet Infect Dis.* 2003;3:131-140.
8. Cohen JI. Benign and malignant Epstein-Barr virus-associated B-cell lymphoproliferative diseases. *Semin Hematol.* 2003;40:116-123.

9. Fang W, Nath KA, Mackey MF, et al. CD40 inhibits B cell apoptosis by upregulating bcl-xL expression and blocking oxidant accumulation. *Am J Physiol.* 1997;272:C950-C956.
10. Brousset P, Schlaifer D, Meggetto F, et al. Persistence of the same viral strain in early and late relapses of Epstein-Barr virus-associated Hodgkin's disease. *Blood.* 1994;84:2447-2451.
11. Niedobitek G, Kremmer E, Herbst H, et al. Immunohistochemical detection of the Epstein-Barr virus-encoded latent membrane protein 2A in Hodgkin's disease and infectious mononucleosis. *Blood.* 1997;90:1664-1672.
12. Pallesen G, Hamilton-Dutoit SJ, Rowe M, et al. Expression of Epstein-Barr virus latent gene products in tumour cells of Hodgkin's disease. *Lancet.* 1991;337:320-322.
13. Su IJ, Chen JY. The role of Epstein-Barr virus in lymphoid malignancies. *Crit Rev Oncol Hematol.* 1997;26:25-41.
14. Knecht H, Berger C, al-Homsi AS, et al. Epstein-Barr virus oncogenesis. *Crit Rev Oncol Hematol.* 1997;26:117-135.
15. Kieff ED, Rickinson AB. Epstein Barr Virus and its Replication. In: Knipe DM, Howley PM, eds. *Field's Virology.* 5th ed. Philadelphia, PA: Lippincott, Williams and Wilkins;2007:1-120.
16. Hawkins EP, Krischer JP, Smith BE, et al. Nasopharyngeal carcinoma in children—a retrospective review and demonstration of Epstein-Barr viral genomes in tumor cell cytoplasm: a report of the Pediatric Oncology Group. *Hum Pathol*. 1990;21:805-810.
17. Vasef MA, Ferlito A, Weiss LM. Nasopharyngeal carcinoma, with emphasis on its relationship to Epstein-Barr virus. *Ann Otol Rhinol Laryngol.* 1997;106:348-356.
18. Cover TL, Blaser MJ. Helicobacter pylori in health and disease. *Gastroenterology.* 2009;136:1863-1873.
19. Proença-Modena JL, Acrani GO, Brocchi M. Helicobacter pylori: phenotypes, genotypes and virulence genes. *Future Microbiol.* 2009;4:223-240.
20. Kandulski A, Selgrad M, Malfertheiner P. Helicobacter pylori infection: a clinical overview. *Dig Liver Dis.* 2008;40:619-626.
21. Psyrri A, Papageorgiou S, Economopoulos T. Primary extranodal lymphomas of stomach: clinical presentation, diagnostic pitfalls and management. *Ann Oncol.* 2008;19:1992-1999.
22. Al-Saleem T, Al-Mondhiry H. Immunoproliferative small intestinal disease (IPSID): a model for mature B-cell neoplasms. *Blood.* 2005;105:2274-2280.
23. Peek RM Jr. Intestinal malignancy and campylobacter jejuni. *Gastroenterology.* 2004;127:1266-1267.
24. Ferreri AJ, Ernberg I, Copie-Bergman C. Infectious agents and lymphoma development: molecular and clinical aspects. *J Intern Med.* 2009;265:421-438.
25. Du MQ. MALT lymphoma: recent advances in aetiology and molecular genetics. *J Clin Exp Hematop.* 2007;47:31-42.
26. Shah KV. SV40 and human cancer: a review of recent data. *Int J Cancer.* 2007;120:215-223.
27. Vilchez RA. Limitations of epidemiological and serologic studies addressing simian virus 40 and non-Hodgkin's lymphoma. *Cancer Invest.* 2006;24:333-336.

28. Ramos MC, Pizarro De Lorenzo BH, Michelin MA, et al. High-grade cervical intraepithelial neoplasia, human papillomavirus and factors connected with recurrence following surgical treatment. *Clin Exp Obstet Gynecol.* 2008;35:242-247.
29. Dunne EF, Datta SD, Markowitz L. A review of prophylactic human papillomavirus vaccines: recommendations and monitoring in the US. *Cancer.* 2008;113:2995-3003.
30. De Vuyst H, Lillo F, Broutet N, et al. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. *Eur J Cancer Prev.* 2008;17:545-554.
31. Thomison J 3rd, Thomas LK, Shroyer KR. Human papillomavirus: molecular and cytologic/histologic aspects related to cervical intraepithelial neoplasia and carcinoma. *Hum Pathol.* 2008;39:154-166.
32. Ma HJ, Sjak-Shie NN, Vescio RA, et al. Human herpesvirus 8 open reading frame 26 and open reading frame 65 sequences from multiple myeloma patients: a shared pattern not found in Kaposi's sarcoma or primary effusion lymphoma. *Clin Cancer Res.* 2000;6:4226-4233.
33. Beksac M, Ma M, Akyerli C, et al. Frequent demonstration of human herpesvirus 8 (HHV-8) in bone marrow biopsy samples from Turkish patients with multiple myeloma (MM). *Leukemia.* 2001;15:1268-1273.
34. Sjak-Shie NN, Vescio RA, Berenson JR. HHV-8 infection and multiple myeloma. *J Leukoc Biol.* 1999;66:357-360.
35. Sjak-Shie NN, Vescio RA, Berenson JR. The role of human herpesvirus-8 in the pathogenesis of multiple myeloma. *Hematol Oncol Clin N Am.* 1999;13:1159-1167.
36. Uchiyama T. Human T cell leukemia virus type I (HTLV-I) and human diseases. *Ann Rev Immunol.* 1997;15:15-37.
37. Mueller N, Tachibana N, Stuver SO, et al. Epidemiologic perspectives of HTLV-I. In: Blattner WA, ed. *Human Retrovirology: HTLV.* New York, NY: Raven Press; 1990:281-293.
38. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer.* 1988;61:1942-1956.
39. Alward WL, McMahon BJ, Hall DB, et al. The long-term serological course of asymptomatic hepatitis B virus carriers and the development of primary hepatocellular carcinoma. *J Infect Dis.* 1985;151:604-609.
40. Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med.* 2001;345:41-52.
41. Kaklamani E, Trichopoulos D, Tzonou A, et al. Hepatitis B and C viruses and their interaction in the origin of hepatocellular carcinoma. *JAMA.* 1991;265:1974-1976.
42. Cobbs CS, Soroceanu L, Denham S, et al. Modulation of oncogenic phenotype in human glioma cells by cytomegalovirus IE1-mediated mitogenicity. *Cancer Res.* 2008;68:724-730.
43. Urisman A, Molinaro RJ, Fischer N, et al. Identification of a novel gammaretrovirus in prostate tumors of patients homozygous for R462Q RNASEL variant. *PLoS Pathog.* 2006;2:e25.
44. Dong B, Kim S, Hong S, et al. An infectious retrovirus susceptible to an IFN antiviral pathway from human prostate tumors. *Proc Natl Acad Sci USA.* 2007;104:1655-1660.

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

Visit www.wmjonline.org to learn more.