Infectious Disease and Cancer

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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. 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 role in malignant transformation. 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 transformation 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 protooncogene.

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

<p>| Table 1. Examples of Infectious Disease Agents Linked to or Associated with Various Cancers |
|----------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Disease</th>
</tr>
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<tbody>
<tr>
<td>The Epstein-Barr virus (EBV)</td>
<td>Non-Hodgkin’s lymphoma</td>
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<tr>
<td></td>
<td>Hodgkin’s disease</td>
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<td></td>
<td>Burkitt’s lymphoma (African)</td>
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<td>Helicobacter pylori</td>
<td>Nasopharyngeal carcinoma</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>Lymphoma of the stomach (marginal-</td>
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<tr>
<td></td>
<td>zone of mucosa associated lymphoid</td>
</tr>
<tr>
<td></td>
<td>tissue type (MALT)</td>
</tr>
<tr>
<td>Borrelia Burgdorferi</td>
<td>Lymphoma of the small intestine</td>
</tr>
<tr>
<td>Simian virus</td>
<td>Lymphoma (marginal-zone B-cell)</td>
</tr>
<tr>
<td>Papilloma virus</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Herpes virus-VIII</td>
<td>Cancer of the cervix</td>
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<tr>
<td>HTLV-I &amp; II</td>
<td>Cancer of the anogenital region</td>
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<tr>
<td>Hepatitis B virus</td>
<td>Kaposi’s sarcoma</td>
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<tr>
<td>Hepatitis C virus (HCV)</td>
<td>Multiple myeloma</td>
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<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Adult T-Cell Lymphocytic Leukemia/Lymphoma</td>
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<tr>
<td>Xenotropic murine leukemia</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>virus-related virus (XMRV)</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HTLV, human T-cell lymphotropic virus</td>
<td>Splenic lymphoma with villous lymphocytes</td>
</tr>
<tr>
<td></td>
<td>Glioblastoma of the central nervous system</td>
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<tr>
<td></td>
<td>Familial prostate cancer</td>
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</tbody>
</table>
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, e.g., 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, i.e., 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 cells, interleukin 6 that appears to be a growth factor for myeloma cells, 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 (i.e., 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 micro-compartmentalized 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**


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