The Slow Dance of Infection, Inflammation, and Cancer

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Chronic inflammation as a contributing cause of cancer has been recognized for over a century, yet the association of an infectious agent with cancer has been a more controversial subject. Sunday's ASH-ASCO Joint Symposium will describe some of the molecular mechanisms of *Helicobacter pylori* infection and inflammation in gastric cancer development and will elucidate potential roles for viral infection and inflammation in the etiology of prostate and oropharyngeal cancers.

Infection with *H. pylori* has convincingly been shown to be a causative event for gastric cancer. Development of chronic inflammation, however, appears to be a prerequisite. The severity of the inflammation caused by *H. pylori* depends on multiple factors including virulence, genetic susceptibility, environmental factors (especially diet), and age of infection, which explains why only 1 percent or less of those infected will actually develop gastric cancer. Up to 15 percent of human cancers have been linked to an infectious agent, with chronic inflammation being implicated in the majority.

The inflammatory process, however, may also have a tumor suppressive effect with tumor-infiltrating leukocytes secreting cytokines that both promote and inhibit cellular proliferation in the tumor and the microenvironment. It appears that an imbalance in these effects allows for tumor progression. As Dr. Francis Megraud will describe, *H. pylori* strains differ in their ability to activate the NF-κB pro-inflammatory pathway. The bacterium also can directly alter cellular structure and proliferative ability by interacting with the Src kinase pathway. Oxidative stress associated with inflammation most likely plays a role in neoplastic development by damaging DNA-repair enzymes and proteome function. Gene mutations and epigenetic changes have all been implicated in malignant transformation.

Viral infection has been associated with other epithelial cancers. Human papillomavirus (HPV) infection has been detected in about 26 percent of all head and neck squamous-cell carcinomas. Dr. Maura Gillison will describe results of a case-control study of patients with newly diagnosed oropharyngeal squamous-cell carcinoma, a subset for which molecular evidence of HPV association has been the most convincing. The epidemiology has been less consistent, however. This study included detailed information on the demographics, medical history, sexual behavior, history of smoking and alcohol use, and oral hygiene practice, together with detailed molecular and serological analyses. Dr. Eric Klein will present exciting data on the identification of a new gamma-retrovirus, XMRV, which was identified in patients with prostate cancer who harbor a common polymorphic variant in the gene *RNASEL*. This gene is critical for the regulation of the antiviral activity of interferons. The same variant had previously been identified as a risk factor for development of prostate cancer, and, given its role in viral infection, the hunt for a virus was initiated.

The search for pathogens as etiologic agents of cancer has already passed through several rounds of resurgence and disappointment. This cycle may now be permanently broken by the rapid pace of technologic revolution.