Kaposi's Sarcoma and Interleukin-6

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IL-6 Gene

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that also has an important role in immunity. IL-6 induces growth and terminal differentiation of B cells; secretion of immunoglobulins; differentiation and activation of T cells and macrophages; and the induction of acute-phase response proteins (1). The gene for IL-6 is located on chromosome 7p21 (2). Many types of cells, including macrophages, T cells, fibroblasts, and endothelial cells, produce IL-6 in response to stimuli such as bacteria, viruses, and other cytokines, particularly IL-1 and tumor necrosis factor, alpha (TNF).

Gene Variants

The 5' flanking region of the *IL-6* gene is important in the regulation of its expression. Recently, a G/C polymorphism was detected at position -174 of the promoter region (3). This same study found the frequency of the C allele in a group of 383 asymptomatic Caucasian men and women to be 0.403 (95% CI, 0.37-0.44) (3).

Disease Burden

In comparison with the G allele, the C allelic variant has been associated with

suppressed gene transcription, and this polymorphic difference in IL-6 expression appears to be clinically important. The CC genotype is significantly underrepresented in persons with systemic-onset juvenile chronic arthritis (OR=0.34 [95% CI, 0.12-0.98]) (3). Systemic-onset juvenile chronic arthritis is an inflammatory disease whose signs and symptoms are the consequence of a vigorous acute-phase reaction primarily mediated by IL-6. On the other hand, the C allele has been associated with delayed initial onset of the sporadic form of Alzheimer's disease (OR=0.60 [95% CI, 0.38-0.94]) (2). IL-6 has increased central nervous system activity in patients with Alzheimer's disease, and an alteration of the immune response with C allelic inheritance may retard onset of the disease.

The importance of IL-6 in the pathogenesis of Kaposi's sarcoma (KS) is supported by substantial in vitro evidence, including the observation that the cytokine stimulates KS spindle-cell culture growth(4). In a recent study that compared 115 HIV-infected men who had KS with a control group of 126 deceased HIV-infected men who did not have KS, the CC genotype, associated with decreased transcription of the *IL-6* gene, was seen significantly less often in patients with KS than in controls (OR=0.35 [95% CI, 0.14-0.79]) (5). Furthermore, men homozygous for the G allele, associated with increased production of IL-6, were overrepresented among patients with KS (OR=2.11 [95% CI, 1.2-3.7]).

Interactions

The etiology of KS is complex, but infection with human herpesvirus 8 (HHV-8) appears to be the primary and necessary event for development of the tumor (6). The sequence of the HHV-8 genome suggests several ways the virus might promote uncontrolled cellular proliferation. The virus encodes for several genes, incorporated from its human host, that are homologous to human oncoproteins, including a cyclin that regulates the G1-to-S phase of the cell cycle, and a Bcl-2 like protein that prevents apoptosis (6). In addition, HHV-8 encodes for functional chemokines that may promote angiogenesis and inhibit immune type I helper-T-cell responses. Early in the development of a KS lesion, large numbers of inflammatory cells are recruited to the site, and their production of pro-inflammatory cytokines such as IL-6 and TNF-alpha are thought to promote the angioproliferative inflammation that characterizes the disease.

However, HHV-8 infection alone is not sufficient for the development of KS, and epidemiologic evidence supports the contribution of other environmental, hormonal, and genetic cofactors in the pathogenesis of the condition. For instance, co-infection with HIV dramatically increases the risk for development of KS, as does the immunosuppressive therapy required by organ transplant patients. Because KS is more prevalent in men than women, sex hormones have also been postulated to act as cofactors in the pathogenesis of the disease (7).

Laboratory Tests

The association between an *IL-6* promoter polymorphism (G-174C), increased IL-6 production, and subsequent increased risk for the development of KS in HIV-infected men is a recent observation, and no commercially available molecular diagnostic test exists to detect the alleles. Serum levels of IL-6 can be measured reliably with a commercially available enzyme-linked immunoassay (ELISA), but a nested case-control study found that HIV-infected persons with increased IL-6 serum levels alone were not at increased risk for KS (8). Serum IL-6 levels may not accurately reflect IL-6 spindle-cell response in the microenvironment of the lesion.

Population Testing

Detection of the *IL-6* gene G/C polymorphism in HIV infected populations may prove clinically useful. KS is the most common AIDS-associated cancer in the United States, and persons identified to be at a particularly high risk for KS might be offered prophylactic antiviral therapy to inhibit the replication of HHV-8. In vitro susceptibility studies suggest that HHV-8 is resistant to acyclovir and penciclovir but sensitive to ganciclovir and foscarnet (9). Individuals considered to be at a lower risk for the development of KS might be spared the potential toxicities associated with current antiviral therapy. High-risk persons may one day also be offered immune therapy capable of decreasing the production of IL-6. Interestingly, the case-control study outlined above that detected the association between an *IL-6* promoter polymorphism and the development of KS also discerned a significant relation between the GG genotype and the prevalence of

HHV-8 infection (5). However, delineating the relation between this genotype and susceptibility to the acquisition of HHV-8 in HIV-infected men awaits the completion of prospective investigations.

References

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Internet sites

American Cancer Society: http://www.cancer.org

Kaposi's Sarcoma Support Group:
http://www.oncolink.upenn.edu/disease/Kaposi

National Cancer Institute:
http://www.nci.nih.gov/cancer_information/cancer_type/aids_related_malignancies