cervical carcinoma [6]. We would like to add some interesting details concerning the connection between IL-1RA gene polymorphism and cancer.

Witkin et al. [1] mentioned that the concentration of IL-1RA in the serum of patients with gynecologic cancers is elevated in comparison with that in patients with benign diseases and with that in healthy women. This observation is based on an article by Fujiiwaki et al. [7]. It should be noted that only 15 patients with solid tumors were enrolled in that study: 7 patients with cervical cancer, 6 with endometrial cancer, and only 2 with ovarian cancer.

It is known that gene polymorphisms can cause changes in the expression of proteins [8]. Therefore, a polymorphism in the IL-1RA gene may have a substantial impact on the IL-1 cytokine system. For instance, the study of Unfried et al. [9] demonstrated a significant association between the allele 2 polymorphism of the IL-1RA gene and recurrent idiopathic miscarriage. Furthermore, El-Omar et al. [10] and Machado et al. [11] have observed an association between IL-1RA and gastric cancer.

Because few data are available on the connection between IL-1RA and cervical cancer, we conducted a prospective case-control study to investigate the relationship between polymorphisms in the gene encoding for the IL-1RA and the clinical characteristics of patients with cervical cancer. Blood samples were analyzed, and DNA was extracted. The genomic DNA fragments were amplified by PCR.

One hundred thirteen women with cervical cancer and 107 female control subjects with benign disorders were enrolled. Because germline mutations do not fluctuate with age, the age of control subjects was not specified; however, only women >47 years old were included in the control group. The median age of the patients with cervical cancer was 46 years (range, 25–80 years). Of the 220 women included in our study, 58.4% were in stage T1 or T2, and 41.6% were in stage T3 or T4. The frequency of the IL-1RA 1/2 genotype in the study group was statistically significantly different from that in the control group with respect to allele 2 heterozygosity (24.8% vs. 13.1%, respectively; \( P = .04 \)).

No statistically significant differences were observed between the frequency of the IL-1RA 1/3 genotype among patients with cervical cancer and the frequency in the control group (4.4% vs. 3.7%) or in the frequencies of the homozygous allele 2. Only 1 woman with cervical cancer was identified as homozygous for allele 3, and an additional 9 patients were identified as homozygous for allele 2. In the control group, 3 women were heterozygous for allele 2/3. No statistically significant correlations were observed between IL-1RA 1/2 polymorphism and tumor stage \( (P = .5) \), grade of tumor differentiation \( (P = .4) \), recurrence status \( (P = .5) \), and age at treatment \( (P = .5) \).

These data support the claim that allele 2 of the gene encoding for IL-1RA plays a role as a genetic determinant of whether an individual will develop cancer with solid tumors. Further prospective studies are warranted to clarify the role of the IL-1RA gene in the pathophysiology of cancer.

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References

Interleukin-1 Receptor Antagonist Gene Polymorphism, Infectious Burden, and Coronary Artery Disease

Sir—We read with great interest the review by Witkin et al. [1], which reported that persons who are homozygous for allele 2 of the IL-1 receptor antagonist (IL-1RA) gene have a more prolonged and more severe proinflammatory immune response than do persons with other IL-1RA genotypes. Thus, being homozygous for allele 2 of the IL-1RA gene might be detrimental for subjects with chronic inflammatory conditions and might also be associated with coronary artery disease (CAD).

There is increasing evidence that inflammation and, possibly, infection play an important role in atherogenesis [2–4]. The hypothesis that infectious agents may
contribute to atherogenesis is supported by the results of several epidemiologic studies, which suggest that Helicobacter pylori [5], cytomegalovirus (CMV) [6], herpes simplex virus (HSV) [7], and Chlamydia pneumoniae [8] may have atherogenic effects. However, existing epidemiologic data about the association of some of these pathogens with atherosclerosis are conflicting [9]. Moreover, recently published data [10] support the hypothesis that atherosclerosis has an immunopathological component; these data render it improbable that a single infectious agent should assume particular importance in the initiation or progression of atherogenesis.

Our data for 218 consecutive patients (119 men and 99 women; mean age, 64.6 years [range, 29–83 years]) who underwent coronary angiography support the hypothesis of Witkin et al. [1], that "triggers" such as IL-1RA gene polymorphisms or additional exposure to other pathogens could influence the effect of infectious agents on the development of CAD. Blood samples obtained from all subjects were tested for serologic markers of 6 infectious agents (C. pneumoniae, hepatitis A virus, H. pylori, CMV, and influenza virus types A and B). We examined the possible association between seropositivity for a particular microbial agent and angiographically proven coronary artery disease (defined as ≥1 coronary artery with stenosis >50%-diameter).

Analysis of serologic markers for all 6 microbial agents demonstrated that seropositivity for a single pathogen was not a predictor of risk for CAD. In contrast, the number of infectious pathogens to which individuals have been exposed (i.e., the "infectious burden") correlated with the prevalence of CAD. A total of 48.8% of patients with CAD and 31.2% of patients without CAD tested positive for ≥4 of the 6 serologic markers (P = .02); 21.3% of patients with CAD and 9% of patients without CAD tested positive for ≥5 of the 6 serologic markers (P = .03). Therefore, our data support the hypothesis of Witkin et al. [1] that some "triggers" such as cytokine-receptor gene polymorphisms or additional exposure to other pathogens could influence a patient’s susceptibility to the atherogenic effect of infection with a particular pathogen.

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References

Candidemia in the Surgical Intensive Care Unit

Sir—We read with great interest the article by Blumberg et al. [1] that reported the results of a multicenter US study of fungemia in the surgical intensive care unit (ICU), in which risk factors and outcomes for 42 candidemic patients were analyzed. In our opinion, there were at least 2 surprising and interesting results: (1) the absence of colonization as a predictor of invasive infection and (2) the protective role of previous antifungal therapy (prophylaxis). We retrospectively analyzed data from 75 cases of fungemia that were seen in 4 surgical ICUs of university hospitals in Slovak Republic in 1992–2002. Only 47 (64%) of 75 episodes were caused by Candida albicans, in contrast to the results of the study by Blumberg et al. [1], in which fewer than one-half of strains tested in vitro were identified as C. albicans (16 of 35 strains). The second most common strain was C. glabrata, followed by C. tropicalis. In our study, C. glabrata was responsible for only 6.7% cases of fungemia, which underlines the differences in the etiology of fungemia in patients with and without cancer between Europe and the United States [2, 3]. Similarly, a history of colonization with Candida was not a predictor of fungemia in our group (only 3.3% of fungemic patients in the surgical ICU were colonized).

With regard to the use of prior antifungal therapy or prophylaxis, 16.7% of our patients had received fluconazole or amphotericin B 3–5 days before the onset of fungemia. However, we did not observe a statistically significant difference in mortality between patients who received prior treatment and those who did not (14.7% vs. 20%), despite the trend (as was observed in Blumberg’s group [1]) toward lower mortality among patients with prior receipt of antifungals.

Finally, we would like to know the overall and attributable mortality among patients from whom data were analyzed in this valuable study. In our cohort of 75...