Researchers Attempting To Define Role of Cytokines in Cancer Risk

Earlier this year, a team of researchers from Austria found in a case–control study that women who produced more of the cytokine interleukin 10 (IL-10) due to a genetic variation or polymorphism had a lower incidence of breast cancer.

“The mechanism remains to be determined but may include antiangiogenic functions of IL-10,” said study leader Uwe Langsenlehner, M.D., of the Medical University of Graz, Austria. “If this result can be confirmed in additional studies, determination of IL-10 genotypes may help give a more precise individual breast cancer risk profile.” This research, published in March in *Breast Cancer Research and Treatment*, is one of a growing number of studies that are helping to define how cytokine polymorphisms affect cancer risk, initiation, and progression.

IL-10 is one of more than 300–400 known cytokines produced by the immune system that are mediators of immunity, infection, and inflammation, said Joost Oppenheim, M.D., chief of molecular immunology in the Division of Basic Sciences at the National Cancer Institute. “Certain cytokines [such as tumor necrosis factor α (TNF-α) and IL-6] may promote cancer growth and spreading, stimulate cells to survive longer, are proangiogenic, encourage inflammation, and cause free radical damage of DNA and instability,” he said. Others, such as IL-2, granulocyte–macrophage colony-stimulating factor (GM-CSF), and interferons, inhibit cancer growth and spreading by stimulating other immune cells, such as T cells and natural killer cells. Animal models show that IL-10 can have immunosuppressive activity, Oppenheim said. “Many of the cytokines such as TNFα, IL-10, IL-1, and IL-6 have multiple biological roles, based on the fact that their receptors are expressed by diverse cell populations, which may result in apparently opposing effects,” Oppenheim added.

Since the early 1990s, researchers have tested recombinant cytokines, including IL-2, GM-CSF, and interferon, as local and systemic immunotherapies for cancer, in combination with chemotherapy in gene transfer experiments, and in vaccines—with limited success. These cytokines have also been studied for their potential antitumor properties since recombinant cytokines became available in sufficient quantities more than 20 years ago, starting with interferons and IL-2, said Oppenheim. Only in the past few years have researchers begun focusing on the role that endogenous cytokines may play in increasing cancer risk.

Langsenlehner’s study adds to other research that suggests that low IL-10 levels are associated with risk for prostate, cervical, and noncardia gastric cancers, melanoma, and lymphoma. However, the role of IL-10 in cancer remains ambiguous; other studies show that high levels of IL-10 may actually be a risk factor for other cancers, including cervical, cardiogenic, and ovarian cancers and myeloma. “The dual biological function of IL-10 as an anti-inflammatory (potentially cancer-promoting) and antiangiogenic (potentially cancer-inhibiting) agent reflects the apparently conflicting data,” Langsenlehner noted.

Many other cytokine polymorphisms are being studied for their relationship to cancer risk. High levels of the proinflammatory cytokine IL-1β may be associated with an increased risk of gastric cancer, and high levels of IL-6 may be associated with an increased risk of young-adult Hodgkin lymphoma. Whether any of these associations are causal, however, is an open question. High levels of certain cytokines have also been found in the blood of patients with certain cancers and may be associated with poor
prognoses, but again, rigorous studies to establish the true nature of the relationship haven’t been done. Also, in established cancers, expression of particular cytokines is likely to be different from that in normal patients.

**Cytokines in the Microenvironment**

From her studies of cytokines, Frances Balkwill, Ph.D., professor of cancer biology at Cancer Research U.K.’s Translational Research Laboratory in London, concluded that certain cytokines are actually cancer-modifying genes. In human ovarian cancer, she found that the cytokine network is rich in proinflammatory cytokines, growth factors, and chemokines and that TNF-α in particular plays a central role in the microenvironment—in stromal development and regulation of matrix metalloproteinases required for tissue invasion.

Just as using TNF-α-blocking monoclonal antibodies to treat rheumatoid arthritis has had some success, so Balkwill believes they could work with other agents to treat cancer. There are more than a dozen trials under way now in a range of cancers with TNF-α-blocking antibodies, she noted. Oppenheim said that although he had doubts this approach would be effective in cancer, he hadn’t believed that they would work in arthritis, either. “I could be wrong again,” he said.

Blocking certain cytokines such as TNF-α and IL-10 is not simple, as they each have multiple immunomodulatory effects. Not all cytokines have just one role, either; some, such as IL-10 and TNF-α, may have tumor-promoting or -inhibiting effects at different concentrations and in different environments. Oppenheim called this the “ying-yang effect” of cytokines. Balkwill agrees. “It’s a question of balance: A lot can kill a tumor, a little may have the opposite effect, and vice versa,” Balkwill said.

“In the context of breast cancer risk, IL-10 may act as a double-edged sword: On the one hand, high levels could facilitate development of cancer by supporting tumor escape from the immune response (a known effect), and on the other hand, IL-10’s antiangiogenic effects could prevent or reduce tumor growth and metastasis,” Langsenlehner said. “It may depend on the biology of each cancer and the microenvironment whether the anti-inflammatory mechanism—tumor escape—of IL-10 is stronger than the antiangiogenic effect, or the reverse,” he said.

Cytokines and the effect of cytokine polymorphisms on the development and progression of cancer cannot be considered in isolation because of complex interactions between them, according to Langsenlehner. For example, TNF-α is downregulated by IL-10 and by the crosstalk of many other cytokines. “This also makes it difficult to establish the precise mechanism of IL-10 action,” Langsenlehner said. Other studies indicate that IL-10 can indirectly inhibit proinflammatory cytokine production by both T and natural killer cells, and suppress antitumor responses.

**Pathogen Connection?**

It is well known that infection with *Helicobacter pylori* or some human papillomaviruses can cause gastric cancer or cervical cancer, respectively, but why one infected person progresses to cancer and another does not is not yet understood. One contributing factor could be an individual’s genetic cytokine profile. In a recent review, Glenn Dranoff, M.D., of the Dana-Farber Cancer Institute in Boston, pointed out that pathogens can stimulate chronic cytokine expression, which in turn can create chronic inflammation, which can set off a cascade of cytokines that pushes chronic infection toward cellular transformations that lead to cancer in some individuals. Individual cytokine profiles could be the missing link between infection and cancer in some people.

For example, one study of 146 Zimbabwean women found that patients with cervical cancer were more likely than those without the disease to carry a polymorphism for enhanced IL-10 production. No women in the healthy study arm were high-producers of IL-10. Some researchers have hypothesized that higher levels of IL-10 promote HPV growth, viral replication, and malignant transformation of infected cells in women infected with the virus—a possible explanation of why some women with HPV get cervical cancer while others do not. Again, since cytokines do not work in isolation, it will be important to study the relationship of IL-10 to other cytokines in cervical cancer patients.

The research of Emad El-Omar, M.D., of the University of Aberdeen’s Department of Medicine and Therapeutics in Scotland, illustrates how host genetic profiles affect the development of gastric cancer. “Being a gastroenterologist, I thought that cytokine levels of proinflammatory cytokines might help explain why one patient with high acid production and *H. pylori* infection gets gastric cancer but another develops an ulcer,” he said. Half the world is infected with *H. pylori*, but relatively few get gastric cancer; genetics—cytokine polymorphisms—may help explain individual risk.

In one study, he found that a high-producing proinflammatory cytokine polymorphism genotype of IL-1β increased the risk of one type of gastric cancer by producing low-acid secretion in the presence of *H. pylori* infection. He later identified four proinflammatory polymorphisms of three additional genes (IL-1 receptor antagonist, IL-10, and TNF-α) and found that each further increased the risk of gastric tumors; individuals with two of the genes had more risk than those with one, and those with all four proinflammatory genotypes had the highest risk of gastric cancer.

“The association of these polymorphisms with gastric cancer requires the presence of *H. pylori* and may be most important early in the disease process,” he said.

“Cytokine gene polymorphisms represent one component of a complex interplay among the host, pathogen, and environmental factors involved in
gastric carcinogenesis,” El-Omar added. The risk of gastric cancer is greatest in those with both bacterial and high-risk host genotypes, he found.

“Some dismiss the possibility that cytokine polymorphisms impact cancer risk,” said El-Omar. But he and a growing number of researchers believe that they can help explain why certain individuals are at greater risk of sporadic cancers than others with seemingly similar risk factors. Rather than a strict genetic mutation view of cancer, cytokine polymorphisms, together with environmental factors and epigenetic changes due to environmental factors, can help explain cancer risk, said Oppenheim.

It may be more difficult to ascertain a causal connection between cancer and cytokine polymorphisms such as TNF-α and IL-10 because of their dual biological functions. “It depends on the biology of each cancer and its microenvironment—whether the anti-inflammatory, or tumor escape, mechanism of IL-10 or the antiangiogenic, antiproliferative effect is stronger,” said Langsenlehner.

—Vicki Brower