Cancer and Arthritis Share Underlying Processes

Although arthritis and cancer are different diseases, some of the underlying processes that contribute to the disorders of joints and connective tissue that characterize arthritis also affect cancer development and metastasis. And the immune system appears to play an overseer’s role in both diseases.

It is this interconnectedness that makes some scientists optimistic that recent discoveries will lead to new treatment approaches for patients with these and other conditions. New insights into the molecular underpinnings of arthritis and cancer bolster evidence that health involves an exquisite balance among the body’s systems and that if something interferes with that balance in a significant way, a chain reaction occurs whose consequences can be grave.

“I think everything interdigitates,” said Rodger Winn, M.D., chief of community oncology at the University of Texas M. D. Anderson Cancer Center, Houston.

Inflammation and Proliferation

One overlapping area in cancer and arthritis research involves a group of pharmaceuticals that are big business in arthritis. The non-steroidal anti-inflammatory drugs (NSAIDs) provide relief to some 30 million people worldwide who suffer the pain and discomfort of inflamed joints and other conditions.

In addition, epidemiological studies in recent years have shown that regular users of NSAIDs also have lower than average colorectal cancer rates, raising the possibility of using NSAIDs as chemopreventive agents.

However, researchers at Stanford University School of Medicine, Palo Alto, Calif., found that NSAID-related gastrointestinal complications lead to an estimated 16,500 deaths annually — more than asthma, malignant melanoma, and cervical cancer combined. Knowing this has made the idea of using NSAIDs for cancer chemoprevention considerably less attractive.

Research into the enzyme system that underlies some of the inflammatory processes of arthritis and tumor growth has led to new pharmaceutical approaches to treatment and prevention of both diseases that seem to be more selective in their actions than NSAIDs.

For example, prostaglandins, fatty acids that affect cell function in every organ system, are produced in cells lining the joint capsule, where inflammation and proliferation take place in rheumatoid arthritis and osteoarthritis. And, these molecules appear to be important in cancer development because they affect cell division, cellular adhesion, immune surveillance, and apoptosis.

Prostaglandins are synthesized by two different forms of cyclooxygenase, enzymes designated COX-1 and COX-2. Both enzymes are involved in functions of cartilage cells and cells of the joint lining. But COX-1 is necessary for a healthy gastrointestinal tract and good kidney function, while COX-2 is induced during tissue injury and leads to inflammation and pain.

The enzymes are also found in tumor tissue, particularly colon tumors. COX-2 is particularly active, leading to increased prostaglandin production in transformed cells and tumors. Overexpression of COX-2 increases invasiveness and resistance to apoptosis.

COX-2 Inhibitors

Based on experience with arthritis, researchers at several drug companies have developed compounds that selectively inhibit COX-2 and apparently cause none of the gastrointestinal side effects that would occur if COX-1 were also inhibited. At least two are in late stages of clinical testing.

Cancer researchers are borrowing the drugs for trials in their own labs and have found that so far, studies in animals offer reason for optimism. Andrew J. Dannenberg, M.D., a gastroenterologist and director of clinical programs at Strang Cancer Prevention Center in New York, pointed out that COX-2 inhibitors reduced formation of intestinal tumors in lab rats and mice by 87% in some experiments.

Researchers speculate that the drugs could present an elegant alternative to the surgical policing of precancerous polyps, currently the standard approach for at-risk patients. “It seems to me really crude that in 1998 we say to someone, ‘Come back in 3 years and I’ll see if you’ve grown another one, and we’ll take it out,’” Dannenberg said.

Patrick Lynch, M.D., chief of the endoscopy unit at M. D. Anderson, is
working on two chemoprevention trials. The first will look at regression in familial polyposis using Searle's COX-2 inhibitor, celecoxib. The other study will look at the drug's effects on biomarkers and development of adenoma in patients with non-hereditary polyposis. Treatment studies are proceeding as well.

Raymond N. DuBois, M.D., Ph.D., professor of medicine and cellular biology at Vanderbilt University, Nashville, Tenn., said administration of a COX-2 inhibitor arrested growth even in advanced tumors in lab animals and in a few cases caused regression. "When we stopped the treatment, the tumors didn't start growing again," he said.

DuBois and colleagues are testing COX-2 inhibitors now in patients with colon cancer, but remain cautious about potential results. "We've been fooled before with animal results that didn't hold up in people," DuBois said.

Ultimately, if the drugs work, researchers agree it is unlikely they will be used widely as this would be neither practical nor cost-effective. A more likely scenario would be their use in patients at high risk for colon cancer — those with a strong family history of colorectal disease, a prior tumor, or longstanding inflammatory bowel disease.

TIMP Family

Lance Liotta, M.D., Ph.D., chief of the National Cancer Institute's Laboratory of Pathology, is focusing on how tumor cells commit breaking and entering — that is, how migrating cells are able to penetrate a cell cluster far distant from their origins, and take hold to multiply. Could the process they use be similar to that taking place during arthritic damage to joints, joint linings, and other tissues?

"It's a hypothesis we made many, many years ago," said Liotta.

A Careful Balance

Recent results are beginning to validate the theory. Liotta's lab is focusing on metalloproteinases (MMPs) and their brakes, tissue inhibitors of metalloproteinases (TIMPs). Under normal circumstances, these substances function in well-calibrated balance to maintain tissue integrity.

MMPs work close to cells to degrade the extracellular matrix and cell surface proteins to permit many processes, including growth, tissue repair, and matrix remodeling. The balance between MMPs and TIMPs goes awry in several ways when arthritic conditions begin: For instance, MMP levels have been found to be unusually high in joints of patients with osteoarthritis and rheumatoid arthritis.

MMPs aid metastasis not only by breaking down the matrix surrounding cells, but by actively participating in tumor cell migration, attachment, and growth, according to Liotta. Whether or not MMP activity is increased in tumor cells may help determine their potential to spread.

"We've identified 20 MMPs now, which really makes the whole thing complicated," said William Stetler-Stevenson, M.D., Ph.D., a senior investigator in Liotta's lab.

As for TIMPs, research has uncovered a variety of functions that may prove useful in cancer treatment. For instance, TIMP-1, when overexpressed, confers a growth advantage to breast carcinoma cells. Would control of TIMP-1 inhibit tumor development?

TIMPs 2 through 4 have inhibitory effects that may also stifle tumor cell invasion and proliferation. Several drugs aimed at regulating the MMP-TIMP system are in development, but so far they are not as powerful as traditional cytotoxic therapy, Stetler-Stevenson said.

"That doesn't mean they might not be therapeutic; they might just be more subtle," he said. "They might limit disease progression, rather than cause outright reversal."

Ultimate Connection

While connections between COXs, TIMPs, arthritis, and cancer have produced impressive fodder for investigation, researchers treating other autoimmune diseases have found connections to cancer that strengthen the idea that genetic control of the immune system is involved in all these processes.

"Once we understand these processes better, there may be commonalities in approaches" to cancer and autoimmune diseases, said Patrick Beatty, M.D., of the University of Utah, Salt Lake City.

—Jan Ziegler