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Body heat

Inflammation has been linked to diseases from Alzheimer's to cancer, and the list just keeps swelling

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Inflammation isn't pretty. And it often hurts.

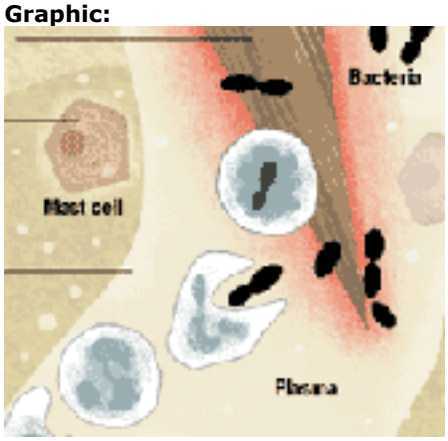
But the tell-tale swelling and ache, the redness and heat are signs that our bodies are fighting back against microbial invaders that might otherwise harm or kill us. Inflammation is our first line of defense and sometimes, it now seems, our worst enemy.

In multiple sclerosis, lupus and rheumatoid arthritis, the body turns upon itself with often catastrophic results. But the danger is not limited to these classic inflammatory diseases. Increasingly, scientists are linking inflammation to an expanding list of disparate and sometimes surprising diseases, from Alzheimer's, autism and asthma to cirrhosis, cardiovascular disease and cancer.

CRISTINA MARTINEZ / Union-Tribune

"We're converging toward what I believe may eventually be a unifying hypothesis of human disease," said Michael Karin, a professor of pharmacology and molecular biologist at UCSD. "I think we will find that inflammation and infection will account for 90 percent of human misery."

Graphic:



Good thing gone wrong

The evidence is compelling. For example, the Women's Health Study, a landmark research program involving almost 28,000 women, has found that women with the highest measures of inflammation in their blood face a seven-fold increased risk of heart attack or stroke. Sufferers of inflammatory bowel disease have a five-to seven-fold higher incidence of developing colon cancer. And studies have shown that people who take anti-inflammatory drugs seem to get Alzheimer's disease later in life than those who do not.

"Inflammation may be driving a lot of what we're seeing, in a lot of different diseases. It may be that the things that cause these diseases are related to inflammation," said Dr. Barrett Rollins, chief science officer at the Dana-Farber Cancer Institute in Boston.

"But that being said, there are still a lot of things we need to learn."

Basic biology

The basics, though, are pretty well-known. Inflammation is the body's biggest weapon, the biological equivalent of shock and awe. It is meant to overwhelm and destroy an enemy – regardless of collateral damage – in an effort to secure quick and total victory. The fundamental process is the same whether you're sneezed upon by someone with a cold, inhale a snoutful of allergenic pollen or cut your finger.

For illustration purposes, let's say the last happens, triggering a cascade of events known collectively as innate immunity.

Sentries called mast cells in the injured finger (they're stationed everywhere) detect the presence of pathogens and sound the alarm, secreting proteins called cytokines to summon help and histamines to make nearby capillaries suddenly porous. The leaky blood vessels flood the wounded area with plasma, producing swelling and discomfort, but also isolating pathogens from the rest of the body and slowing their spread.

Soon, the body's immunological warriors, a class of white blood cells called phagocytes, arrive. They are meat-eaters. Their job is to engulf and digest foreign material, including dead and dying cells.

As the phagocytes work, they secrete more cytokines, summoning more reinforcements and provoking greater and sharper symptoms of inflammation. Their fight will rage on until there is nothing left to kill or eat.

Under normal circumstances, said Geert Schmid-Schoenbein, a UCSD professor of bioengineering, "once the infection is cleared up, inflammation goes away." The phagocytes die. The wound heals. Tissues return to normal.

Only sometimes the process doesn't stop. Sometimes inflammation smolders like a fire within. It becomes chronic, though its consequences might not be immediately noticed or felt. Why this happens is not fully understood, but the tally of known or suspected causes of chronic inflammation is long and growing.

Some people appear to be genetically predisposed to chronic inflammation. Obesity is a huge factor. Fat cells, researchers have discovered, produce and spew their own pro-inflammatory cytokines. The fatter you are, say scientists, the bigger the threat of chronic inflammation.

Bacteria and viruses provoke an inflammatory response, and when they linger in conditions like gum disease and stomach ulcers, they foster a chronic inflamed state, even though the sufferer may initially feel no ill effect.

Numerous environmental and external stimuli have been linked to chronic inflammation. Among them: asbestos, smoking, coffee, alcohol, birth control pills, some medical treatments such as hormone replacement therapy, even prolonged or recurrent bouts of anger, hostility and depression.

"Every time we look for signs of inflammation, we find them," said Schmid-Schoenbein. "Even in apparently young, healthy, asymptomatic college students who consume tobacco products."

It has only been in the last decade – and most keenly in just the last few years – that researchers have begun to identify chemical biomarkers that signal inflammation even when symptoms are not present or obvious.

These biomarkers tend to be the working elements and products of inflammation: the various proteins, chemicals and cells that, in a normal, healthy state, are present only in modest amounts, if at all.

The current poster child of inflammatory biomarkers is C-reactive protein, a tool of the inflammatory process thought to help white blood cells bind to foreign and damaged cells. Higher-than-normal levels of CRP, however, have been connected to a number of diverse diseases and conditions.

For example, men with the highest levels of CRP have a three-fold increased risk of heart attack and a two-fold increased risk of stroke compared to men with the lowest levels. Obese people have elevated levels of CRP, as do people suffering from macular degeneration, an age-related condition in which central vision gradually declines, often leading to blindness.

"CRP levels always go up with inflammation," said Ken Buechler, president of Biosite, a San Diego-based company that creates diagnostic tools to quickly measure biomarkers like CRP. "It's non-specific to a disease. CRP rises whether it's a stroke or sepsis (the presence of pathogens in the blood)."

The question is whether elevated CRP causes disease or simply reflects a diseased condition. Researchers don't yet know. It may be a combination of both, depending upon the disease.

A hand in many things

More and more, researchers suspect inflammation is at work in heart attacks. In one widely held scenario, white blood cells attempting to clear away arterial plaques of cholesterol inadvertently damage healthy tissues as well. This escalates the inflammatory process until one or more plaques burst, blocking an artery and causing either a heart attack or stroke.

"It's a host of factors," said Rollins. "High cholesterol predisposes people to hardening of the arteries, but inflammation plays a role and seems to make things worse."

Likewise with Type 2 diabetes, which afflicts almost 16 million Americans. The disease is characterized by the inability to produce, use or regulate insulin, a hormone that transports sugars from the blood into cells for energy. Obesity is the biggest risk factor for developing diabetes, and here, too, inflammation plays a villainous role.

Dr. Steve Shoelson, of the Joslin Diabetes Center in Boston, has found that obese people accumulate fat in their livers. Excessive levels of fat cause a protein in the liver called NF-kB to be activated. NF-kB turns out to be a kind of master switch for starting the inflammatory response.

Shoelson thinks the resulting chronic inflammation disrupts the body's ability to process insulin, leading to diabetes. In experiments, Shoelson has activated the gene that produces NF-kB in mice, triggering inflammation. Though the mice are lean and apparently healthy, they display symptoms of diabetes.

Some forms of cancer are clearly exacerbated, if not caused outright, by inflammation. For example, in gastroesophageal reflux disease, the lining of the esophagus is routinely doused with stomach acid, causing inflammation and heightening the risk of esophageal cancer.

One of the products of inflammation is oxygen-free radicals – unstable and highly reactive molecules that damage or destroy anything they touch, friend or foe.

Some researchers have speculated that free-radical damage to healthy cells and their DNA sometimes results in cancerous mutations. The resulting tumors are then fed and nurtured by inflammatory growth factors intended to spur wound repair.

Similar explanations are proposed for neurological disorders such as Alzheimer's and autism. Biochemist Jeffrey W. Kelly and colleagues at the Scripps Research Institute in La Jolla, for example, have hypothesized that inflammation could disrupt normal neuron activity, causing amyloid beta proteins in the brain to misfold. Such plaques have been strongly linked to the development of Alzheimer's.

A study published last year by researchers at the Johns Hopkins University School of Medicine reported the first direct evidence linking brain inflammation to autism. They examined brain tissue from 11 people with autism who had died of accidents or injuries. They found that, compared to normal brains, the autistic brains contained abnormal patterns of cytokines and chemokines – indicators of inflammation. Samples of cerebrospinal fluid taken from six living children with autism showed elevated levels of cytokines.

Whether the inflammation causes or contributes to autism or is the result of the brain attempting to fend off some other damaging process remains to be determined.

Promise in the problem

Revelations of inflammation's links to many diseases have opened up new possibilities for drug therapies and treatments. New drugs are in development, and approved drugs are being given new jobs.

Statins, for example, are used to lower cholesterol and reduce inflammation. They are being tested for their efficacy in treating Alzheimer's disease and sickle-cell anemia, in which red blood cells become misshapen and cause painful clots.

And then there's aspirin, which is now widely prescribed in small, daily doses for people at risk of cardiovascular disease.

But aspirin has its drawbacks, including side effects such as internal bleeding when used in large doses over extended periods.

Shoelson will soon launch long-term clinical trials on an alternative that avoids aspirin's shortcomings. Salsalate is an aspirin-like drug already approved for treating arthritis and related inflammatory conditions. Preliminary studies have shown that it improves insulin sensitivity and lowers blood glucose and lipids after just two weeks of use. Shoelson and colleagues think it may help prevent diabetes.

"We are trying to determine if the drug may help in people who do not yet have diabetes, but are overweight and at risk to develop disease," said Dr. Allison Goldfine, of the Joslin Clinical Research section and, like Shoelson, a Harvard professor.

Other researchers are investigating the use of COX-2 inhibitors, anti-inflammatory drugs like Vioxx, Celebrex and Bextra. The problem with these pharmaceuticals, of course, is that they may create other problems. Merck withdrew Vioxx from the market last year after it was linked to increased risk of heart attack and stroke. An FDA panel has since ruled that Vioxx can be sold with a stronger warning label.

"Everything is a balancing act of risks and benefits," said Rollins. "COX-2 inhibitors may be beneficial for preventing colon cancer, but at the increased risk of cardiovascular disease."

At UCSD, Schmid-Schoenbein has focused on shock with Tony Hugli, of Torrey Pines Institute for Molecular Studies, and David Hoyt, of UCSD. A major cause of death in hospital emergency rooms, shock can cause massive, rapid organ failure when the body suffers inadequate blood flow, often due to severe trauma. In shock, when blood flow drops dangerously low, digestive enzymes escape into the wall of the intestine, peritoneal cavity, lymphatic system and bloodstream, where they break down tissues, causing organs to fail.

Understanding this sequence of events, said Schmid-Schoenbein, means doctors can now search for ways to preserve the intestinal barrier, perhaps by introducing drugs to inhibit or block digestive enzymes.

Better remedies, though, will take time, researchers caution. Inflammation is a tricky business.

"When you block some of the inflammatory reactions, you're also blocking part of the repair process," said Schmid-Schoenbein.