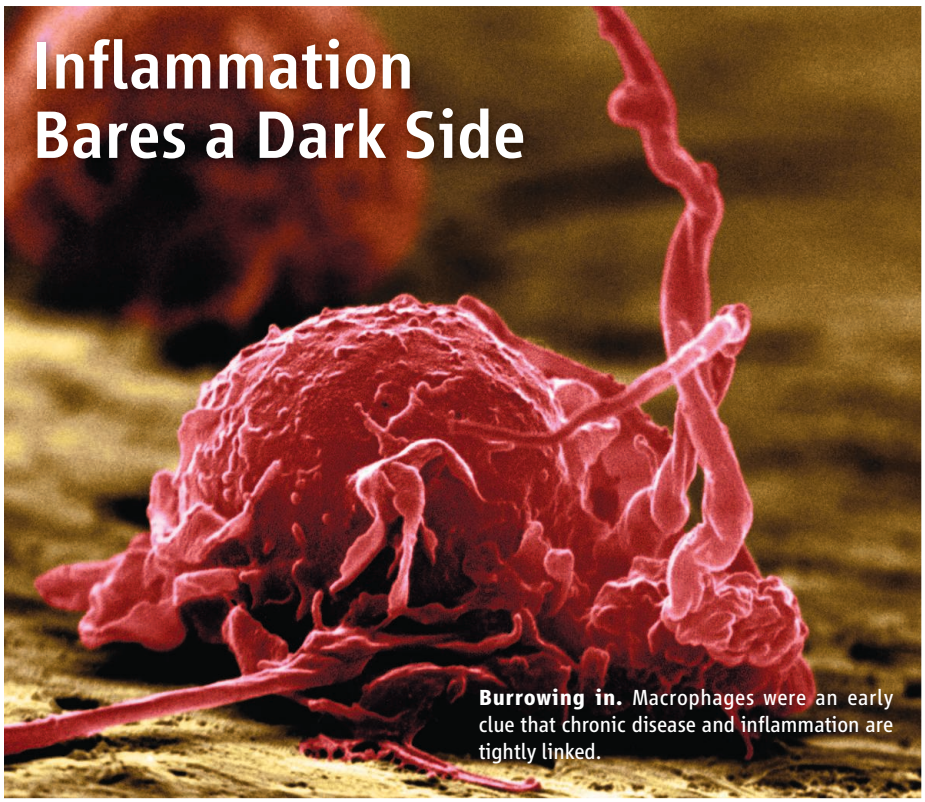
Inflammation Bares a Dark Side



Burrowing in. Macrophages were an early clue that chronic disease and inflammation are tightly linked.

NOT LONG AGO, INFLAMMATION HAD A CLEAR role: It was a sidekick to the body's healers, briefly setting in as immune cells rebuilt tissue damaged by trauma or infection. Today, that's an afterthought. Inflammation has hit the big time. Over the past decade, it has become widely accepted that inflammation is a driving force behind chronic diseases that will kill nearly all of us. Cancer. Diabetes and obesity. Alzheimer's disease. Atherosclerosis. Here, inflammation wears a grim mask, shedding its redeeming features and making sick people sicker.

When a kitchen knife slips while you're chopping vegetables, the body reacts swiftly. White blood cells swoop in and sterilize the injury, and the tissue-repair effort begins. This inflammatory response does have its downsides, causing swelling, redness, and pain. (Indeed, "inflammation" derives from the Latin verb *inflammare*, which means to set on fire.) But there's no question that acute inflammation is a net positive, a response to trauma that evolved millennia ago to keep us alive and healthy.

A darker story began to emerge in the 1990s. Researchers peering at apparently unrelated diseases noticed that immune cells congregate at disease sites. Atherosclerosis, in which fatty plaques build up in the arteries, was among the first to make the list. In the 1980s, the late Russell Ross of the University of Washington, Seattle, saw macrophages in atherosclerotic tissue; these white blood cells are a hallmark of inflammation. Slowly, as more people parsed arterial tissue, more came to agree that an inflammatory response was under way. There were T cells. There was interferon-γ, which the immune system produces as part of its inflammatory efforts. Also in the mix were gene variants identified by the Icelandic company deCODE that predispose people to heart attacks by fueling inflammation in plaques. And then this April, researchers used a new microscopic technique to describe, in *Nature*, tiny crystals of cholesterol in arteries that induce inflammation at the earliest stages of disease in mice.

Other conditions unrolled parallel story lines. In 1993, a group at Harvard University found that fat tissue in obese mice was churning out a classic inflammatory protein. Ten years later, back-to-back papers showed a correlation between macrophage infiltration of fat tissue in rodents and people and how obese they were. Newcomers to the inflammatory story include neurodegenerative diseases such as Alzheimer's and Parkinson's. Here, it's murkier whether inflammation is perpetuating disease or just along for the ride.

In most chronic illnesses for which inflammation has been fingered, it appears to drive ill health but not initiate it. In cancer, for example, papers published over the past decade suggest that tumors and inflammation dance together toward disaster: Tumors distort healthy tissue, setting off tissue repair, which in turn promotes cell proliferation and blood vessel growth, helping cancers expand. And although it's genetic mutations in tumor cells that initiate cancer, there's evidence that inflammation in surrounding tissue helps coax those cells along.

In cancer, inflammation shows up at least partly for the same reasons it normally does: tissue injury. Elsewhere, its appearance is more mysterious. In neurodegenerative conditions, for example, there's some tissue damage from loss of neurons, which could prod inflammation—but there's evidence, too, that inflammation is helping kill neurons. Inflammation also seems to promote two components of type 2 diabetes: insulin resistance and the death of pancreatic beta cells that produce insulin.

When it comes to obesity, it's unclear why inflammation permeates fat tissue. But theories are percolating. One cites a misguided immune response: Fat cells in obese individuals are not metabolically normal, and the immune system perceives them as needing help and sends macrophages to the rescue, even though they only do harm.

The surest way to prove that inflammation is driving any disease is by blocking it and testing whether that helps, and experiments are under way. In 2007, Marc Donath of University Hospital of Zurich in Switzerland and his colleagues described results from a clinical trial of type 2 diabetes that had once been dismissed as crazy. Seventy patients received either a placebo or anakinra, a drug used occasionally to treat rheumatoid arthritis that blocks interleukin-1. IL-1 is a proinflammatory cytokine, a protein that promotes inflammation; it's been found in beta cells from people with type 2 diabetes. In Donath's small study, published in *The New England Journal of Medicine*, the drug helped control the disease. Anakinra is not a good option for long-term diabetes treatment, so several companies are racing to develop alternatives.

Mediating inflammation in chronic diseases is a new frontier, its success still uncertain. But after inflammation eluded them for so long, researchers are chasing lead after lead, trying to stay a step ahead and discern when its fires need putting out.

–JENNIFER COUZIN-FRANKEL

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