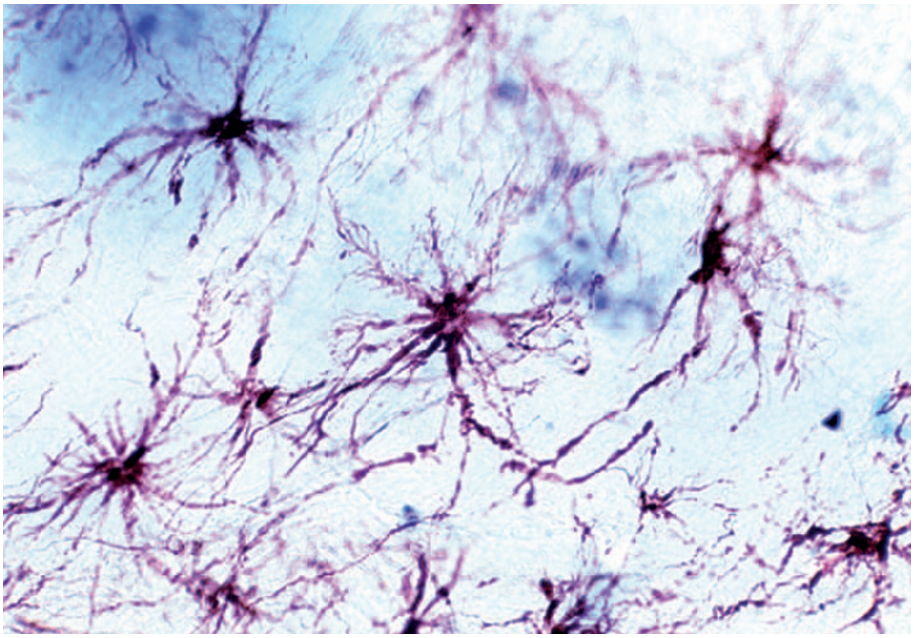

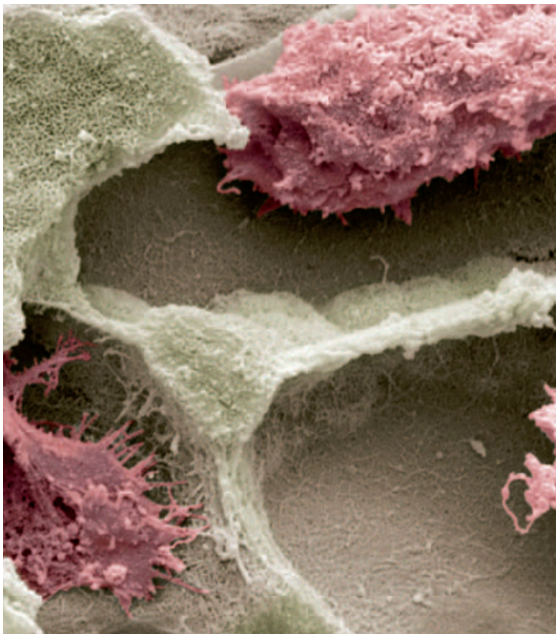

Osteoblasts (purple) are cells that form bones in healthy individuals (left). Myeloma promotes the activity of osteoclasts (right), which cause bone degradation.

AETIOLOGY

The path to disease

Multiple myeloma begins with a benign condition before progression to full-blown cancer, and work is underway to uncover the origins of both.

BY CYNTHIA GRABER

Multiple myeloma takes root years before any symptoms appear. Some plasma cells avoid the normal checks in the bone marrow and begin to clone themselves and proliferate, a condition known as 'monoclonal gammopathy of undetermined significance' (MGUS), which can persist for years or even decades. It might begin to weaken bones and cause some protein deposits on organs, but the patient typically never feels a thing. In multiple myeloma, however, these same monoclonal plasma cells explode in numbers and become malignant, causing anaemia, bone destruction and kidney failure.

Only about 1% of people with MGUS develop full-blown multiple myeloma each year. But several questions remain, with implications for early intervention and treatment. Most importantly, what causes MGUS to develop in the first place? And what is it that catapults the quiescent MGUS cells into the deadly disease of multiple myeloma?

THE ORIGINAL CAUSE

The origins of MGUS are mysterious, although researchers have been able to tease out a variety of risk factors. Men seem to be at higher risk than women. Individuals whose immune systems have been suppressed by autoimmune diseases seem to develop the disease at greater numbers, as do people over the age of 50. Some of these trends may be due to the body's heightened effort (in the case of diseases) or long-term struggle (in the case of age) to produce cells to fight infection, until finally one mutates and proliferates. "If you are older, the plasma cells are more likely to be responding to antigenic stimulation [such as an infection] all the time," explains haematologist Vincent Rajkumar, a multiple myeloma specialist at the Mayo Clinic in Rochester, Minnesota, "and at some point a mistake is going to happen."

Another likely cause is genetics. There is a greater risk of developing MGUS if an immediate family member has the disease, although it is not clear whether this is due to genetics, the environment or a combination of the two. And several studies have shown that African-Americans contract MGUS at roughly twice the rate as Caucasians, after adjusting for potential socio-economic and environmental effects.

Environmental connections are also suspected in both MGUS and multiple myeloma. A few years after the attacks on 11 September 2001, researchers tasked with evaluating the health impacts of the fires and dust from the World Trade Center alerted the public that a number of first responders had contracted multiple myeloma. A statistically significant link to the event has not held up over time, however. Despite this lack of a convincing connection, epidemiological studies have focused on whether there is a link with specific chemicals, or classes of chemicals. Some studies suggest that firefighters generally seem to contract multiple myeloma at higher rates, and farm workers may too.

According to a Mayo Clinic review published in 2010, the incidence of MGUS rises with increased pesticide exposure. Rajkumar, one of the review's authors, highlights exposure to benzene, petrochemicals and pesticides as factors that have been shown to place people at higher risk, suggesting that these chemicals may lead to DNA mutations that could convert normal plasma cells into malignant ones.

But W. Michael Kuehl, who studies the causes of multiple myeloma at the National Cancer Institute (NCI) in Bethesda, Maryland, maintains that the environmental triggers have not yet been proven. "It's very hard to make sure that the control group and the 'at risk' group are exactly the same" in epidemiological studies, he says.

Brian Durie, a myeloma specialist at the Cedars-Sinai Outpatient Cancer Center in Los Angeles, California, thinks the environmental impact may be significant, particularly for certain classes of herbicides and pesticides. "There are

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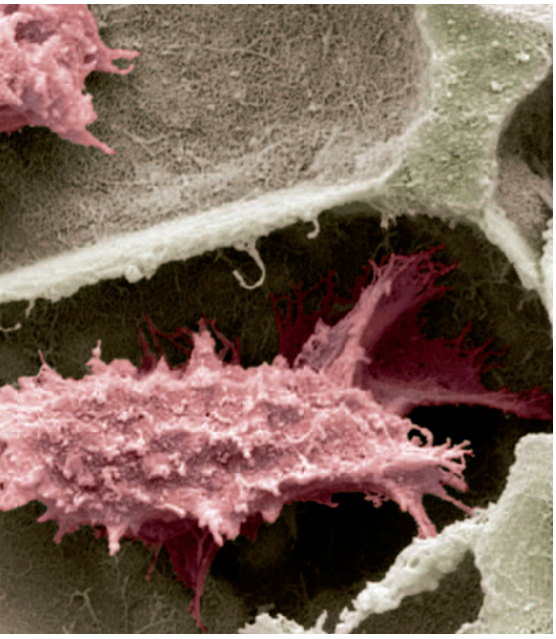

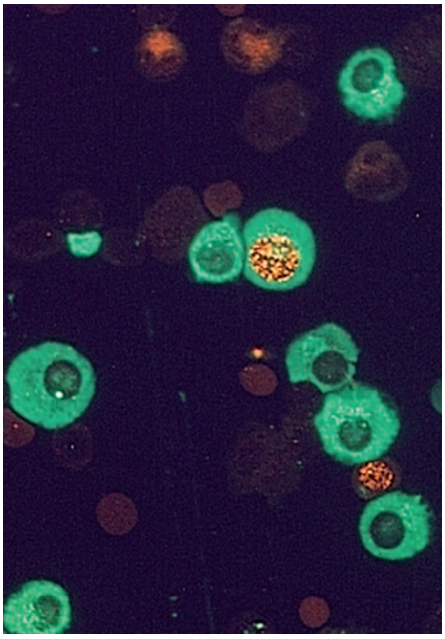

Right, red staining in the plasma cells shows that myeloma has developed.

JEAN-CLAUDE REVY, ISM/SCIENCE PHOTO LIBRARY / CNRI/SCIENCE PHOTO LIBRARY / S. VINCENT RAJKUMAR, MAYO CLINIC

an increasing number of links between these specific chemicals and myeloma," says Durie, who is also chairman of the International Myeloma Foundation in North Hollywood.

BECOMING MALIGNANT

Rajkumar likens MGUS to a polyp that has yet to develop into colon cancer. "It stays quiet," he says, "unless it gets a second hit, at which point it becomes malignant colon cancer. Similarly, MGUS then becomes myeloma. That second hit — why it happens, who gets it — that's also unknown." It may be, he suggests, a combination of genetics and environmental impact.

The effects of MGUS and multiple myeloma are vastly different, but the cells look similar. Although the cells in advanced myeloma have mutations not found in MGUS cells, a researcher given a cell would be hard pressed to determine which sort it is.

Some of the differences lie in the bone marrow and the bone — the tumour's microenvironment (see 'Neighbourhood watch', page S48). This environment had previously limited the cell's ability to proliferate, but suddenly, either through changes in the cells themselves or changes in the bone and marrow, that microenvironment starts contributing to a cell's unchecked growth.

In a healthy individual, the activities of bone-creating osteoblasts and bone-absorbing osteoclasts are balanced. The signals from myeloma's plasma cells, however, inhibit the growth of osteoblasts and stimulate the growth and activity of osteoclasts (see 'Structural support', page S56). As a result, bone destruction races ahead of bone creation. David Roodman, director of the Multiple Myeloma Center at the University of Pittsburgh Cancer Institute in Pennsylvania, who has conducted extensive research on the tumour's microenvironment, says that osteoclasts also provide several growth factors for the tumour cells. So as well as weakening the bone, the osteoclasts help the tumour cells multiply.

The myeloma cells also develop modifications that help them survive outside the niche in which they were formed. "We don't know whether it's a change in the plasma cell or a change in the microenvironment" that triggers these adaptations, says Roodman. Either way, he says, the implication is that treatments to control the tumour's growth could be targeted to the microenvironment as well as the tumour.

Several different genetic mutations can lead to the same result: mutated, proliferating plasma cells. Genes in plasma cells constantly rearrange themselves so they can respond to a variety of threats by creating appropriate antibodies; the diversity of that rearrangement, and thus the diversity of the antibodies, helps us fight infections and diseases. But in multiple myeloma, this genetic rearrangement leads to one or several unwanted mutations, setting off a chain reaction that results in the cells overexpressing and creating unchecked clones.

Several different mutations can lead to the same result: mutated, proliferating plasma cells.

In addition, the *DKK1* gene may aid the destruction of osteoblasts and the proliferation of osteoclasts, although the mechanism for the activation of the gene is unknown. The DKK1 protein produced by the gene seems to trigger events that prevent bone reconstruction and drive bone destruction. This link, discovered in 2003 by researchers at the University of Arkansas for Medical Sciences (UAMS) in Little Rock, demonstrates that multiple myeloma cells produce DKK1. John Shaughnessy, director of basic research at the Myeloma Institute for Research and Therapy at UAMS, and the study's lead researcher, says there is a positive feedback loop at work: DKK1 may support the growth of more myeloma cells through increased production of osteoclasts. Indeed, Shaughnessy's group has shown that elevated levels of DKK1 expression within MGUS plasma cells are predictive of conversion to multiple myeloma. Shaughnessy is particularly excited about the development of a drug, now in phase II clinical trials, to mop up DKK1. He is optimistic that the drug will not cause serious side effects, because although DKK1 is important for embryonic development, it plays no significant role in adult biology.

ON THE MAP

Researchers have been narrowing down which aspects of MGUS make it more likely to undergo a second series of mutations to become multiple myeloma. For instance, the precancerous cells are no longer normal plasma cells, so the antibodies they create are not the same as those produced by a normal cell. The mix of 'heavy chain' proteins to 'light chain' proteins is out of proportion, with more light proteins being excreted into the blood. Understanding such changes and determining which of them are more likely to lead to myeloma will help doctors and researchers figure out which patients are most at risk.

There is still a great deal of information to be collected, says Ola Landgren, who heads multiple myeloma research at the NCI. His lab is enrolling 250 patients with either MGUS or smouldering myeloma, and plans to follow them for at least five years. Landgren says his team will be able to evaluate the differences between the end of the study and the beginning, for those who progressed to disease and those who didn't, through a variety of assays including sequencing and gene expression. It amounts to "a lot of fishing to try to build a map", he says.

Research is underway to help researchers understand the origins of the disease and home in on the specific cellular pathways involved. Epidemiological studies should help them understand who is more susceptible to MGUS in the first place. If we know why people get it, says Rajkumar, "we can try to do something about it" (see 'The early bird', page S36). Studies focusing on mutations, abnormalities, plasma cell pathways, and interactions with the tumour microenvironment, along with studies of markers to help determine who develops myeloma and who doesn't, will all provide crucial tools to support early intervention.

The research has even wider implications. Because MGUS is easy to diagnose, and is simple to track with regular, non-invasive blood tests, it is easy to follow patients and monitor their possible progression from benign to malignant disease. Information from such studies could help researchers develop a model to provide information not only to halt the disease, but to inform cancer research more broadly — and create a map of the course taken by this deadly disease. ■

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