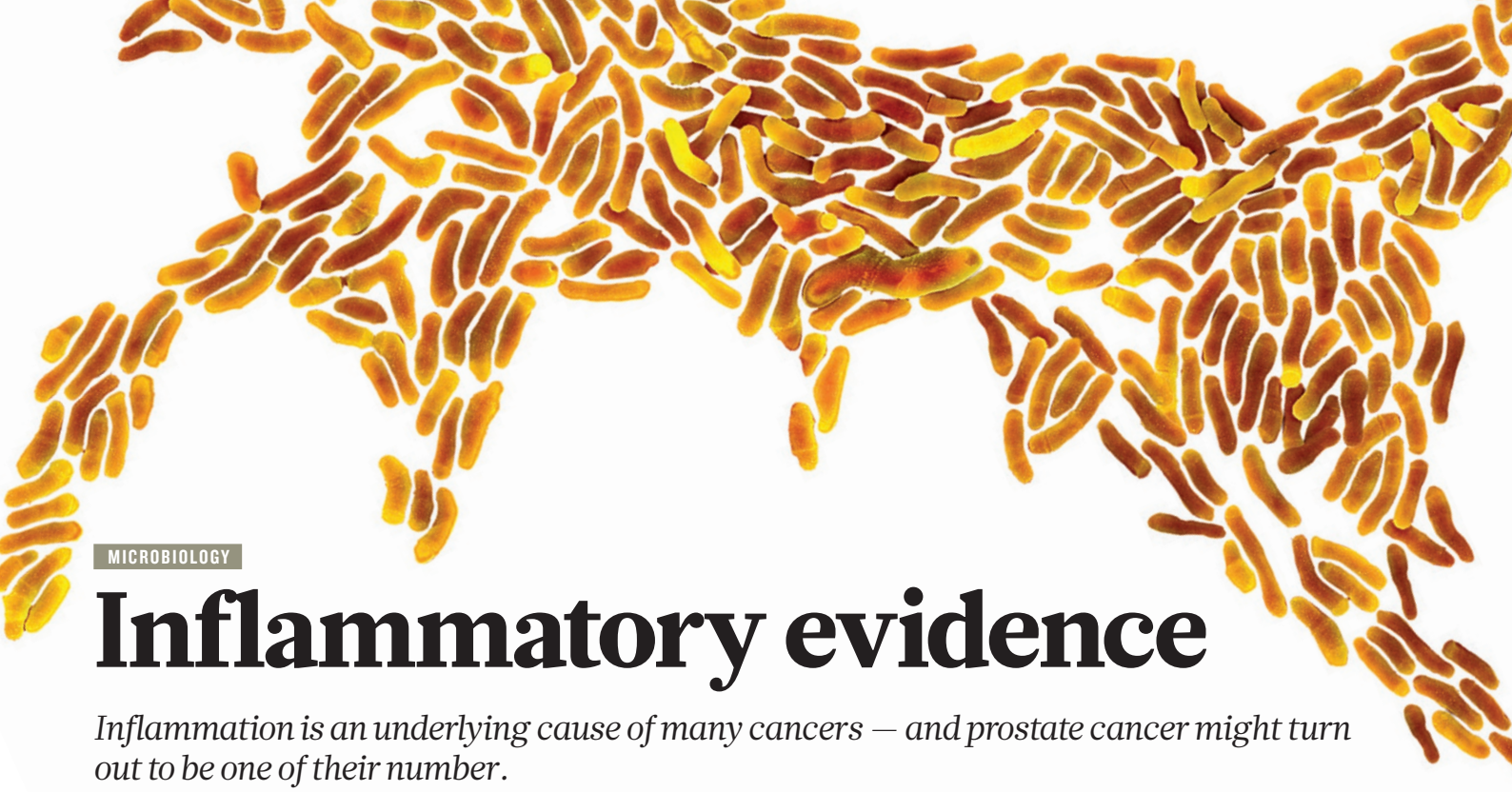

MICROBIOLOGY

Inflammatory evidence

Inflammation is an underlying cause of many cancers — and prostate cancer might turn out to be one of their number.

BY KIRSTEN WEIR

When Angelo De Marzo peers at cancerous prostate tissue through the lens of his microscope, he often sees a total mess.

There are the cancer cells, of course, as well as abnormal cells thought to be precursors to cancer. There are also pockets of a third cell type: shrunken, withered cells that — despite their ailing appearance — are dividing rapidly. And surrounding that sickly stew are areas in which inflammation has set in for the long run.

But that might not be by accident. Inflammation in the prostate gland is common, and it is even more common in men with prostate cancer. De Marzo — a pathologist and oncologist at the Johns Hopkins University School of Medicine in Baltimore, Maryland — is part of a growing group of researchers who suspect that inflammation could be both a symptom and a cause of the disease. If so, physicians might one day be able to treat or even prevent prostate cancer by turning down the volume of the body's immune response.

DOUBLE-EDGED SWORD

The immune system is a fickle friend. It protects us against invading pathogens and attempts to snuff out precancerous cells before they run wild. Inflammation lies at the heart of the immune response. But in the rush to attack potential pathogens, inflammation can cause collateral damage. "It's a two-edged sword," De Marzo says.

In the past two decades, scientists have begun to determine precisely how inflammation over an extended period of time could lead to the development of tumours. The classic example is gastric cancer, which can be caused by persistent inflammation that is triggered by the bacterium *Helicobacter pylori*. Inflammation is also implicated in cancers of the liver, bladder and colon. As many as one-fifth of all cancers might be attributable to inflammation, according to Scott Lucia, a pathologist at the University of Colorado's Anschutz Medical Campus in Aurora.

Results from animals and humans suggest that prostate cancer also belongs on that list. "There's no definitive smoking gun that inflammation causes prostate cancer," says De Marzo, but "there's a lot of evidence building".

One reason for the uncertainty is that most samples of prostate tissue that are available for researchers to study have been removed from patients because of a medical problem — usually, in a biopsy performed after the discovery of an elevated level of prostate-specific antigen (PSA) in the blood. PSA is produced by the prostate gland, and a high concentration of the protein indicates that a person could have prostate cancer. But chronic inflammation alone can also raise PSA levels. As a consequence, men with inflamed prostates might be more likely to undergo biopsies that detect small tumours that would otherwise have gone unnoticed. If so, the association between inflammation and prostate cancer could be just an illusion.

De Marzo, Lucia and colleagues found a way to avoid this 'ascertainment bias' by using data from a fortuitously designed clinical trial. Between 1993 and 2004, the Prostate Cancer Prevention Trial set out to determine whether the drug finasteride could prevent prostate cancer. All participants who did not have cause for biopsy during the course of the trial were required to undergo an end-of-study biopsy, even if their PSA levels were low. By examining samples of benign tissue taken from the prostates of 400 men who were given a placebo in the trial, around half of whom had been diagnosed with prostate cancer, De Marzo and Lucia's team discovered that inflammation was very common[1]. Indeed, 78% of the men who were free from cancer showed signs of inflammation. However, inflammation was still much more likely to be found in men with cancer, appearing in 86% of samples from men with the disease, and 88% of samples from men with the most aggressive, high-grade cancer. "There is a relationship between cancer and inflammation, says Lucia. "As the amount of inflammation goes up, the odds ratio of having cancer — and in particular, high-grade cancer — went up."

Acne-causing bacteria are linked to prostate-cancer mortality.

SPL

Although De Marzo and Lucia's study confirmed an association between inflammation and prostate cancer, it was unable to answer the question of which comes first. "With something as common as inflammation, you see these relationships, but you don't know if they're causative," says Lucia. "If we could remove inflammation, would we lower the risk of prostate cancer? We don't have a means of doing that right now."

INFECTIONS AND DIET

If inflammation does contribute to the development of prostate cancer, it is logical to ask what might be the cause. Infection is the leading suspect, and has been for some time.

In the 1950s, researchers observed that prostate cancer was more common in uncircumcised men[2]. This finding led them to propose that prostate cancer might be triggered by sexually transmitted pathogens, which they reasoned were more likely to be present in uncircumcised men. The hypothesis has since been supported by a number of

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population-based studies. In particular, the bacterial infections gonorrhoea and chlamydia have been linked to an increase in the risk of developing prostate cancer, as has infection with the protozoan *Trichomonas vaginalis*.

Such infections can now be treated quickly with antibiotics. But rodent models hint that a short-term infection can launch what becomes an extended, or chronic, inflammatory response. Karen Sfanos, a pathologist at Johns Hopkins University School of Medicine, found that after a rat or mouse is cleared of a bacterial infection of the prostate, inflammation in the gland can persist for the rest of the animal's life. "Even a single infection seems to set up some kind of chronic inflammatory event," she says.

Sexually transmitted bacteria and protozoa are not the only pathogens that make their way into the prostate, thanks to the gland's location in the body. "The urethra actually passes through the prostate," Sfanos says. "There could be a very rich flora that's poised right there, where the prostate sits, that could continually be a source of exposure to microorganisms."

Sfanos has shown that strains of the bacterium *Escherichia coli* that are associated with urinary tract infections can cause an inflammatory response in the prostate of rodents. And so can *Propionibacterium acnes*, the bacterium associated with the common skin condition acne, according to studies in men. The culturing of *P. acnes* from inflamed prostate tissue led to the finding that men with a history of severe acne had a significantly increased risk of death from prostate cancer[3].

Although infection is likely to cause chronic inflammation of the prostate, another suspect is the food on your plate. Prostate cancer is much more common in the United States and Western Europe than in Asia. "Diet could be one of the factors that explain the differences in rates," says Elizabeth Platz, an epidemiologist at Johns Hopkins Bloomberg School of Public Health.

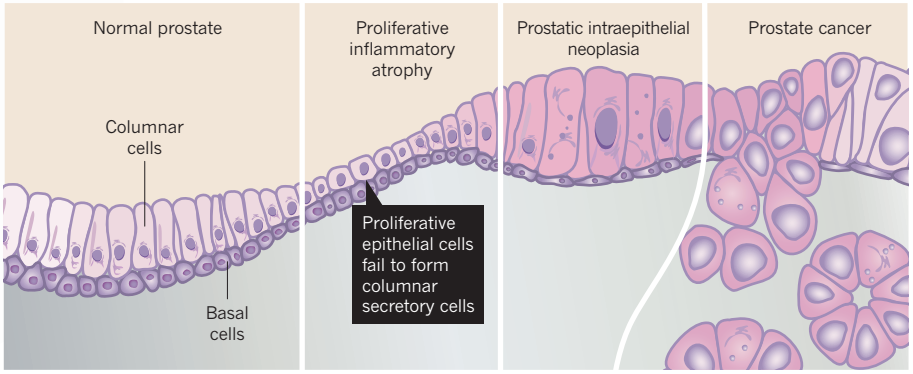
Research has shown that the consumption of certain foods can raise or lower the risk of developing prostate cancer. For example, a diet rich in red meat (and charred meat, in particular) seems to increase the risk. In a study by De Marzo and his team, rats that were fed PhIP — a carcinogenic compound that is abundant in well-cooked meat — developed cancer in the ventral lobe of the prostate[4]. Notably, the team also found that inflammatory cells were more plentiful in the same lobe. Foods with anti-inflammatory properties, such as soya beans and green tea, however, have been shown to decrease the incidence of prostate cancer in animals. Those foods have also been linked to a lower risk of developing prostate cancer in epidemiological studies in humans.

"Diet could be one of the factors that explain the differences in rates."

De Marzo thinks that a number of factors probably come together to create chronic inflammation in the prostate. "Something seems to be targeting the prostate," he says. "We suspect it's a combination of infectious agents and diet."

CANCER CULPRIT

Pockets of shrivelled cells called proliferative inflammatory atrophy may be a precursor to prostatic intraepithelial neoplasia and prostate cancer. These lesions are often associated with chronic inflammation.



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CARCINOGENIC OOZE

De Marzo began to study inflammation in the prostate after noticing the strange pockets of shrivelled cells that he dubbed proliferative inflammatory atrophy (PIA). Despite their appearance, cells in PIA lesions proliferate at almost the same rate as cancer cells. Sometimes, PIA cells seem to merge with abnormal cells from regions of prostatic intraepithelial neoplasia (PIN), which are also thought to be a precursor to prostate cancer (see 'Cancer culprit'). And often, signs of chronic inflammation lurk nearby. "It looks like the inflammation might come first, and these lesions can result," De Marzo says.

Inflammatory cells can elicit the production of DNA-damaging oxidants. They also secrete the signalling proteins cytokines, which have an important role in regulating surrounding cells and can cause them to proliferate, De Marzo says. In other words, there are signs of oxidative stress, genetic instability and runaway cell division in areas where PIA, PIN and inflammatory cells huddle. "You're setting up the primordial ooze for carcinogenesis," says Lucia.

But not all inflammatory cells fight for team cancer. Some prevent precancerous lesions from taking hold. Researchers still have a long way to go to understand which cells, or combinations of cells, are helpful and which cause harm.

Lucia is focusing on a cytokine known as growth differentiation factor 15 (GDF-15), which is involved in regulating inflammatory pathways. GDF-15, he says, has been shown to slow the growth of tumours in the colon in animal studies. With James Lambert, a pathologist also at the University of Colorado's Anschutz Medical Campus, Lucia found that whereas GDF-15 was common in healthy prostate tissue, it was sparse in samples with chronic inflammation[5]. He suspects that the protein acts as a brake on inflammation — a useful tool for a gland that is situated so close to the urethra and the potential pathogens it harbours. "It could be that if GDF-15 is inhibited, chronic inflammation develops," he says. Lucia is now exploring how GDF-15 might inhibit the tumour-promoting factors produced by some inflammatory cells, and possibly help to prevent prostate cancer.

Sfanos, meanwhile, is moving in a different direction by homing in on inflammatory cells that might increase the risk of developing prostate cancer — a daunting task. She is attempting to count and map the locations of different types of inflammatory cell in the prostate, starting with those that are known to be associated with other cancers. Eventually, Sfanos hopes that her work will reveal which combinations of cell types are harmful and which might be protective. "We hope to understand what is a good mix of inflammatory cell types versus what seems to be not so good, as far as the development of advanced disease," Sfanos says.

Physicians might then be able to run a test that determines the mixture of immune cells that are present in the cancerous prostate of a patient. "If there are more inflammatory cells of a certain type, or more immune cells in general, does that give us information about prognosis?" asks Platz. "If it does, perhaps those men need more or less surveillance going forward."

Such work on inflammation could have important implications for the prevention of prostate cancer. "We don't think it's a normal process for the prostate to grow too large or to get cancer," De Marzo says — a point of view that he acknowledges is counterintuitive, given the frequency of these conditions. "If it turns out there is an infectious cause — or two or three or four — and we could treat those, that might ultimately prevent a lot of disease." ■

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