possibilities," Jamieson says. The discovery that TMPRSS2 helps the virus enter cells "felt like the anchor hit ground."

Researchers haven't established that androgens control TMPRSS2 in the lung—ground zero for SARS-CoV-2 infection—as they do in the prostate; studies in lung tissue and cells from mice and humans come to conflicting conclusions. But after the *Cell* paper was published, Andrea Alimonti, head of molecular oncology at Università della Svizzera italiana, strengthened the androgen link by looking at data on more than 42,000 men with prostate cancer in Veneto in Italy. He and colleagues found that patients on androgen-deprivation therapy (ADT)—drugs that slash levels of testosterone—were only one-quarter as likely to contract COVID-19 as men with prostate cancer not on ADT, they reported in the *Annals of Oncology* (see table, p. 1038). Men on ADT were also less likely to be hospitalized and to die, although numbers were small.

Another retrospective study, still unpublished, controlled for age and other medical conditions and got similar results: Of 58 patients with prostate cancer who contracted the coronavirus, the 22 taking ADT were significantly less likely to be hospitalized and to need supplemental oxygen, says William Oh, a prostate cancer physician-scientist at the Icahn School of Medicine at Mount Sinai. "Our conclusion supports the hypotheses that androgen signaling might increase the risk of severe outcomes from COVID-19 and that androgen deprivation may limit those severe outcomes," Oh says.

Science's COVID-19 coverage is supported by the Pulitzer Center.

Two small studies have reported that men with male pattern baldness are overrepresented among hospitalized COVID-19 patients. This type of baldness is associated with high levels of dihydrotestosterone (DHT), a key metabolite of testosterone, in the scalp. An April study of 41 Spanish men hospitalized for COVID-19 found that 71% had male pattern baldness; the background rate in white men is estimated at 31% to 53%. A second study published last month found that 79% of 122 men in three Madrid hospitals with COVID-19 had male pattern baldness.

More circumstantial evidence comes from stem cell biologist Faranak Fattahi, of UC San Francisco. Her team found a strong link between a measure of active androgens in the blood and the severity of COVID-19 disease in data from several hundred male patients in the UK Biobank; they did not find this effect in women.

Such evidence is already inspiring possible therapies. Matthew Rettig, an oncologist who directs prostate cancer research at UC Los Angeles, is leading a double-blind, randomized, placebo-controlled trial of the androgen-suppressing drug degarelix in 200 veterans hospitalized with COVID-19 in Los Angeles, Seattle, and New York City. Patients in the active arm will receive a single injection that virtually zeroes out testosterone levels within 3 days. That reduces expression of the *TMPRSS2* gene, at least in the prostate, to almost nil. Side effects include hot flashes and breast growth and "are equivalent to surgical castration," Rettig says.

But whereas in prostate cancer, the injections are given month after month, "This study only involves a one-time dosage. It's temporary," Rettig says. He hopes to learn in 4 to 5 months whether the treatment helps keep patients off ventilators and reduces mortality.

Several other antiandrogen trials are in the offing in the United States and Europe. Prostate cancer researcher Catherine Marshall of Johns Hopkins University is preparing a trial of bicalutamide, an older, inexpensive androgen receptor blocker, in 20 patients hospitalized within 3 days after they tested positive for COVID-19. Her group will compare outcomes with patients who don't receive the drug. "We think that if this works it's going to work by decreasing the viral load in patients," Marshall says. "That's why we are doing it earlier in people's course of disease."

Women are being included in the trial, she adds, because they have androgens, although at lower levels than men, and because estrogens have been shown to help heal acute lung injury. Bicalutamide raises estrogen levels as well as suppressing androgen activity. Marshall says of the emerging wave of trials: "All these trial ideas have been team science at its best and probably at its fastest."

Adding to the promise of antiandrogens is lab-based evidence from Fattahi's study. Her team screened Food and Drug Administration (FDA)-approved drugs in heart cells in the lab to see which ones reduced levels of the essential SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE2). Key hits included finasteride and dutasteride, drugs that block the conversion of testosterone to DHT, according to a 15 May preprint. Finasteride is FDA-approved to treat male pattern baldness and dutasteride for prostate enlargement. Dutasteride also reduced ACE2 levels in healthy human lung alveolar cells.

Although researchers pursuing the androgen link caution that their hypothesis remains just that until it is borne out in lab and clinical studies, they're optimistic. "When all evidence points to the same thing it's very satisfying," Fattahi says. ■

COVID-19

Blood vessel injury may spur disease's fatal second phase

Damage to vessel lining may drive mysterious clotting disorders, inflammation

By **Catherine Matacic**

Frank Ruschitzka told his pathologist to be ready before the first COVID-19 patient died. In early March, Ruschitzka, who leads the cardiology department at University Hospital Zürich, noticed that patients with the disease had strange symptoms for what was then thought to be chiefly a respiratory infection. Many patients had acute kidney failure, organ damage, and mysterious blood clots. Several weeks later, the first body was autopsied: Tiny clots and dead cells littered the capillaries of the lungs, and inflammation had distended blood vessels supplying every organ in the body.

The pathologist had never seen anything like it. But the results showed Ruschitzka why his patients were suffering so much: The virus had targeted their blood vessels.

Since the Zürich team's findings were published in mid-April, dozens of studies have revealed similar patterns of vascular damage in people who died of COVID-19. For example, a 21 May paper in *The New England Journal of Medicine* showed that the lungs of COVID-19 victims had nine times as many clots as those who died of the H1N1 flu. Other studies have noted inflammatory symptoms in children (*Science*, 29 May, p. 923) and strokes in otherwise healthy young adults. Now, researchers have woven these findings into a new hypothesis explaining why some patients slip into a fatal "second phase" of COVID-19, 1 week or so after hospitalization.

The key is direct and indirect damage to the endothelial cells that line the blood vessels, particularly in the lungs, explains Peter Carmeliet, a vascular biologist at the Belgian research institute VIB and co-author of a 21 May paper in *Nature Reviews Immunology*. By attacking those cells, COVID-19 infection causes vessels to leak and blood to clot. Those changes in turn spark inflam-

mation throughout the body and fuel the acute respiratory distress syndrome (ARDS) responsible for most patient deaths.

"It's a vicious cycle," says Nilam Mangalmurti, a pulmonary intensivist at the Hospital of the University of Pennsylvania, who was not involved in the new research.

This mechanism could explain why the disease pummels some patients who have obesity, diabetes, and cardiovascular conditions: The cells lining their blood vessels are already compromised. If so, drugs used to treat these conditions might help prevent other COVID-19 patients from sliding into serious disease. "[A vaccine] would be terrific," says Richard Becker, a cardiologist at the University of Cincinnati College of Medicine who outlined a similar cardiovascular cascade in a 15 May review in the *Journal of Thrombosis and Thrombolytis*. But until a safe, effective vaccine is available, he says, such therapeutics might be "a good start."

In healthy individuals, endothelial cells help regulate blood pressure, prevent inflammation, and inhibit clotting, in part through the continual production of nitric oxide (NO); they also serve as gatekeepers for molecules passing in and out of the bloodstream. When injured, they send out a complex array of signals to immune cells and clotting factors, which rush to repair the site. And they warn their fellow endothelial cells to be on alert for invaders.

Based on autopsy reports like those from the Zürich hospital, the epidemiology of the disease, and how the new coronavirus behaves in cells in the lab, Carmeliet and colleagues believe the virus can send that system spinning out of control.

When SARS-CoV-2 enters the lungs, it invades cells in the air sacs that transfer oxygen to the blood. Surrounding those sacs are capillaries lined like bricks with endothelial cells. The virus directly invades some of those cells; others become "activated," likely in response to signals from the invading virus and other damaged cells. Some infected cells likely commit suicide. "It's not a quiet death where the cell just dies," Mangalmurti says. "All the contents leak out."

Carmeliet and colleagues suggest damage and other changes in the activated cells trigger vascular leakage, flooding the air sacs with fluid, a hallmark of ARDS. White blood cells swarm to the lungs and NO production likely plummets. Together with the activated endothelial cells, the immune cells release a host of signaling molecules, including interleukins, which raise local blood pressure and weaken cell junctions. Damage to the endothelial cells also exposes the membrane underneath them.

That exposed membrane in turn triggers uncontrolled clotting. The endothelial and immune cells add fuel to the fire, recruiting additional clotting factors and platelets, which help form clots. Those clots degrade into the key biomarker D-dimer, creating the sky-high levels that alert clinicians to patients in trouble (see graphic, below). Eventually, such clotting spreads throughout the body and blocks the blood supply within vital organs.

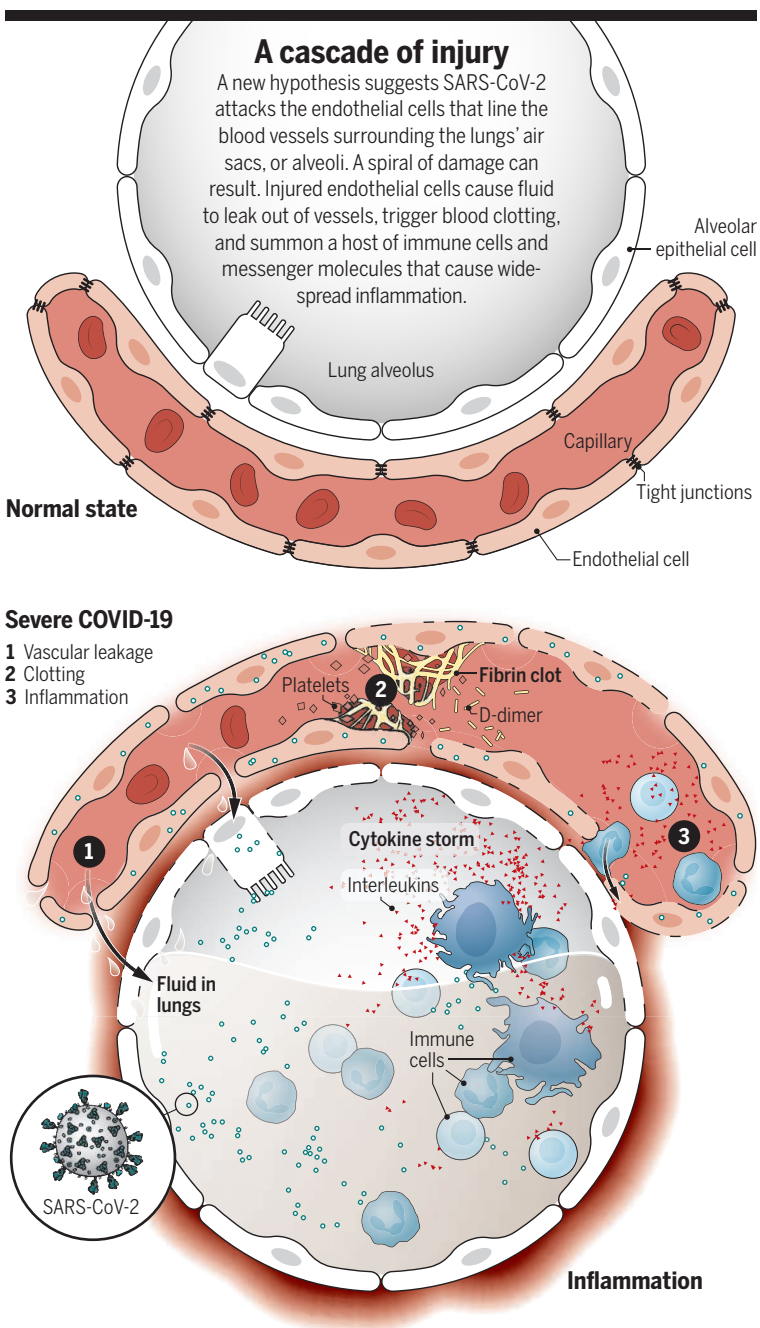
These chain reactions culminate in a final, destructive phase of inflammation. Like clotting, inflammation is an essential defense, sending a diverse army of cells and messenger molecules called cytokines to fight invaders and mop up the debris of battle. But in COVID-19, this reaction spirals out of control in a deadly cytokine storm and plunges patients' bodies into shock.

Ruschitzka says the three-step hypothesis "makes perfect sense" of what he saw in his patients; he's already sending the Carmeliet paper to colleagues. He says the array of pathways may also explain why some young people without known risk factors for COVID-19 become seriously ill: They might have undiagnosed clotting or autoimmune disorders, such as rheumatoid arthritis, that amplify the effects of SARS-CoV-2 infection.

This emerging view of the key role of endothelial cells suggests that a number of existing drugs might dampen or even arrest the fatal second phase of the disease, Becker says. Already, evidence that inflammation and clotting play a role in COVID-19 has inspired dozens of trials in the United States and Europe of anticlotting, anti-inflammatory, and antiplatelet drugs.

Ruschitzka thinks another commonly prescribed drug might help: statins. Typically taken to lower cholesterol, they also reduce inflammation and improve endothelial cell function.

Mangalmurti welcomes such trials, but cautions that patients may respond differently depending on how healthy their endothelial cells are to start. "One size does not fit all." ■



GRAPHIC: TEUWEN *ET AL., NAT. REV. IMMUNOL.* (2020); ADAPTED BY V. ALTOUNIAN/*SCIENCE*

Blood vessel injury may spur disease's fatal second phase

Catherine Matacic

Science **368** (6495), 1039-1040.
DOI: 10.1126/science.368.6495.1039

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.