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MIND body Connections

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Finding Genes that Provide Resilience to Stress

Some individuals are actually biologically resilient to adversity, say researchers at the UCLA Cousins Center for Psychoneuroimmunology, who found that specific genetic variation may disconnect the link between misery and death.

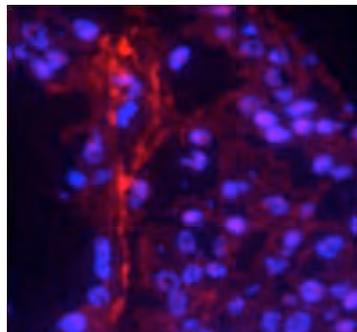
Steven Cole, an associate professor of medicine in the division of hematology–oncology and a research scientist in the Cousins Center and his colleagues have pinpointed a biochemical pathway linking environmental influences—including adverse life events that can lead to depression—to the activation of interleukin-6 (*IL6*), a gene known to cause inflammation and to promote cardiovascular disease and some cancers. Cole and his colleagues also have found that a specific mutation in that gene in humans disconnects the link between life stresses and disease. In such individuals, Cole says, “this variant in the *IL6* gene is programmed to ignore stress.”

The scientists began by using a computer model to look for mutations in the binding sites for so-called transcription factors—proteins that bind to DNA and regulate gene activity. The idea was that naturally occurring variations in these binding sites could affect whether the genes are turned on or off in response to factors like environmental stress, and, ultimately, influence the development of disease.

“We’re trying to track the flow of information from events outside the body to internal changes in gene activity,” Cole says. “We did this for every gene in the human body, but we focused on *IL6* first because we know a lot about its role in health.”

The model identified a naturally occurring genetic variation in one binding site near *IL6* that seemed particularly interesting. It attracted a

transcription factor called GATA-1—which, Cole showed in laboratory studies, could be activated by the stress hormone norepinephrine. The mutated version of the GATA-1 binding site differed in just one nucleotide from the “typical” version, with a cytosine (“C”) nucleotide in place of a guanine nucleotide (“G”). “GATA-1 generally binds to this site if it has a G present, but biochemical studies showed that it won’t bind if there’s a C there instead,” Cole says. “This changes the activation of *IL6* by stress. We then asked whether this matters for human health.”



Nerves (red) and tumor cells (blue) interact to send stress signals to disease sites.

To answer that question, the researchers culled DNA samples and data from a prior epidemiological study. Back in 1988, the study had identified healthy 70- to 80-year-old individuals with depressive symptoms—the kind of depression that could be caused by adverse socio-environmental conditions. In the nearly 12 years after that initial evaluation, Cole and his colleagues found, individuals with the G form of the *IL6* gene—the “typical” version—were more likely to die from inflammation-related diseases, like cardiovascular

disease and some cancers, than were those with the C allele. People with the C allele—approximately 20 percent of the Caucasian population—appear to be “immune to the effects of severe adversity on inflammation-related disease,” Cole says.

“People with the C variant still experience stress, but their *IL6* gene doesn’t notice it,” Cole explains. “*IL6* still turns on from infection—lots of different systems have a vote on how much *IL6* is produced—but in these people, stress doesn’t have a vote.” In the future, he says, understanding such genetic differences “may allow us to selectively target protective interventions to people who are most at risk from stress, but spare others not at risk.”

One enduring puzzle is why the G allele is so common, given that it contributes to stress-related disease, but the C allele is relatively rare, when it confers protection to such disease.

“Most stress responses are believed to have evolved to prepare the body for injury. It’s the classic fight-or-flight response,” Cole says. “In prehistoric times, stress was often associated with tissue damage; if you’re chased by a sabertooth tiger, your body needs to be prepared for injury. *IL6* appears to help activate this anticipatory response to injury. However, people with the C version of the *IL6* gene wouldn’t turn on that response to injury, and may thus have been at a survival disadvantage.”

In modern times, we aren’t often faced with such perils—but our bodies will respond to non-injury stressful events with the same vigor, and that produces inflammation. “Over time, lots of inflammation becomes a bad thing. It serves as fertilizer for cardiovascular disease, certain cancers, and neurodegenerative diseases,” Cole says. ●

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Studies Reveal the Biology of Cancer-related Fatigue

For cancer patients, successful treatment offers a new lease on life—but it doesn't always mean a return to prior good health. Nearly one-third of breast cancer survivors, for example, are saddled with debilitating fatigue that lingers for years after their treatment ends. Julie Bower, a research scientist at the Cousins Center, has spent the last decade investigating the causes of this frustrating fatigue—and its intriguing connection to inflammation.

“Since graduate school, I have been interested in mind/body interactions,” says Bower, an associate professor in the Department of Psychology and Psychiatry and Biobehavioral Science at UCLA, “and in particular the possibility that changes in the body might impact the quality of life and recovery of cancer patients.”

After earning her PhD from UCLA in 1998, Bower began postdoctoral work with Patricia Ganz, a professor of health services at the UCLA School of Public Health and professor of medicine at the David Geffen School of Medicine. Ganz, an oncologist and pioneer in the study of the quality of life of cancer survivors, “was interested in the physical symptoms that were being reported in these survivors, particularly fatigue,” Bower recalls. Oncologists expect to see side-effects from chemotherapy, radiation, and other cancer treatments, “but this fatigue was not going away after treat-

ment, and, at that time, no one knew much about the etiology,” she says.

“The fatigue is extremely distressing,” Bower says. And, researchers realized, it is also surprisingly common; studies have found lingering fatigue in approximately 30 percent of breast cancer survivors—for up to 10 years after treatment has ended.

Around the same time that Bower began working with Ganz, researchers in the field of psychoneuroimmunology had begun looking at how the immune system communicates with the brain. In particular, researchers were studying proinflammatory cytokines—chemicals called into action in response to infection or injury.

“When there is a tissue injury or when we're sick,” Bower explains, “these chemicals send an alarm: ‘Hey, infection here! Come and help!’” Proinflammatory cytokines also communicate with other parts of the body, coordinating the body's response to the assault. For example, the cytokines trigger fever—because the body likes high temperatures, but microbes don't.

In the 1980s and 90s, researchers found that cytokines were having behavioral effects as well. “If you give animals an injection of cytokines, they won't run around in their cages as much, and don't interact as much with other animals,” Bower says. Researchers have coined the term “sickness behavior



Julie Bower

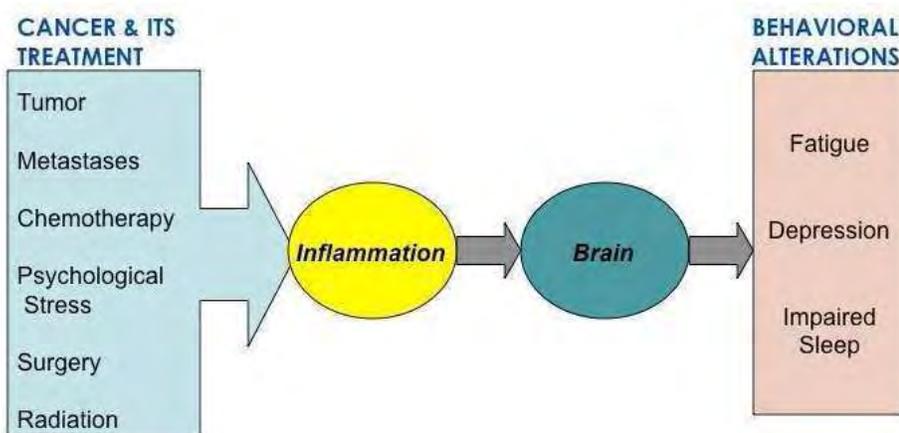
to describe the suite of symptoms, which also includes fatigue, reduced appetite, and irregular sleep.

“Sickness behavior is not a side-effect; it's a critical part of the recovery process,” she says. “It's very adaptive when you're sick to stay in bed—and it's good for other people as well. If you're in bed, you're not spreading the infection.

Bower was intrigued by the two seemingly disparate lines of research: fatigue in cancer survivors and the sickness behavior triggered by proinflammatory cytokines.

“I had been hearing about the fatigue problem from my oncology colleagues, and, on the psychoneuroimmunology side, about studies in animals of proinflammatory cytokines, and I got the idea that maybe these proinflammatory cytokines”—triggered by cancer treatments—“were causing the fatigue in cancer survivors. That's how I got started in this work.”

Her subsequent research proved she was on to something. In one recent report, Bower and her colleagues found that cancer survivors reporting persistent fatigue consistently showed elevated levels of the chemical markers of a number of proinflammatory cytokines—an elevation not seen in patients who



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Studies Reveal the Biology of Cancer-related Fatigue

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bounced back from their treatment without lingering fatigue.

In another study, Bower and her colleagues monitored changes in proinflammatory cytokine markers and in the fatigue of breast and prostate cancer patients before, during, and after radiation treatment. “The cytokine levels were volatile—going up and down. For example, the onset of treatment caused an increase in cytokine levels,” she says, while the end of treatment generally led to reduced levels. Notably, cytokine levels were closely linked with reported fatigue: “In a week when cytokine levels were high, fatigue levels were high;

when downstream marker levels were low, fatigue levels were low.”

In some individuals, the cytokine levels didn’t return to normal levels after treatment ended. “It indicates a chronic inflammatory process,” Bower says, “but we’re still trying to figure out why. What would be causing that in some people and not other people?”

“It makes sense that surgery, chemotherapy, or radiation would trigger a proinflammatory reaction. But why doesn’t it settle down after treatment is over? It may be that some people are genetically predisposed—their system is primed to produce more of these

cytokines,” she says, “or maybe some of the body’s regulatory systems are out of whack. We don’t have any good answers yet, but if we better understand why, and also see who is at risk, we can start to investigate what we can do about it.”

One possibility is a pharmaceutical approach—the use of anticytokine therapies, such as those used for rheumatoid arthritis, psoriasis, and other inflammatory conditions. “In addition,” Bower says, “behavioral approaches, like exercise, yoga, and tai chi, might be effective, and this is our new frontier in identifying novel treatments to alleviate fatigue in cancer survivors.” ●

Inflammation Influences Social Behavior and Depression Risk

Being sick or hurt *feels* bad, but new research by social psychologist Naomi Eisenberger of the Cousins Center is revealing intriguing evidence that inflammation, our body’s response to infection or injury, is more than physical: it affects us socially as well as emotionally—which could increase our risk for depression.

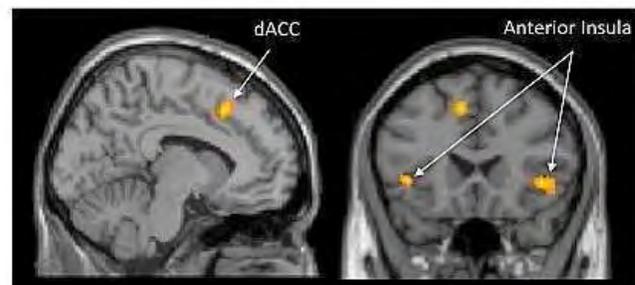
In earlier work described in *Mind-Body Connections*, Eisenberger, an assistant professor of psychology at UCLA, found that social exclusion activates the same center in the brain—the dorsal anterior cingulate cortex (dACC)—that is activated by physical pain. The studies showed that higher levels of self-reported distress were correlated with *more* dACC activity. (One curious implication of the results, Eisenberger has found, “is that taking Tylenol reduces not only physical pain but social pain.”)

More recently, Eisenberger extended these studies to examine how the interplay of inflammation and social behavior plays out in the brain. As in her earlier work, she used a computerized ball-tossing game called “Cyberball” to experimentally induce feelings of social rejection. In the first round of the game, subjects toss a virtual ball back and forth with what they believe are two other volunteers; the other players are, in fact, computer-controlled. In the second round, subjects are excluded from the game when the other two players toss the ball only to each other.

Before beginning the game, subjects were injected with either a placebo or with endotoxin, a portion of the cell wall of *Escherichia coli* bacteria that is used to experimentally induce inflammation in humans. Eisenberger wanted to see whether endotoxin, which is also known to increase depressed mood, also increases neural sensitivity to social rejection, making

depressed mood more likely. During the course of the experiment, blood was drawn hourly from all of the subjects, to look for changes in the level of interleukin-6 (IL6). IL6 is a proinflammatory cytokine—a chemical messenger produced by the immune system that serves to increase inflammatory responses triggered in response to injury or infection by bacteria, viruses, and other foreign agents. “These cytokines may increase our feelings of social disconnection even in the absence of any overt change in behavior,” she says.

The subjects gave hourly reports of their feelings of depression and of social disconnection. As the placebo and endotoxin-receiving volunteers played the Cyberball game, they were scanned using functional magnetic resonance imaging, which measures brain activity. “I was examining was whether our perception of the social world changes when we are experiencing inflammation,” Eisenberger says.



Subjects showing greater inflammatory response to endotoxin showed more activity in brain regions related to physical and social pain.

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Inflammation and Social Behavior—*cont.*

Over the course of the study, endotoxin recipients reported feeling more depressed and more socially disconnected than those receiving placebo. Endotoxin recipients with the biggest increase in IL6 also showed the greatest pain-related activity in the dACC in response to social rejection. Thus, inflammation may increase feelings of social disconnection by making individuals more sensitive to the pain of social rejection.

The studies, says Eisenberger, provide additional evidence that inflammation affects not just how we feel physically, but also emotionally—and can affect our social experience. “It’s counter-intuitive. We normally don’t think that the activity of a system that fights disease should affect how socially sensitive we are—how we feel about others—but there does seem to be a link.”

In fact, infection or injury are known to cause “sickness behaviors,” a coordinated series of responses—including reduced appetite, low energy, fatigue, and altered sleep patterns—thought to encourage recuperation by conserving energy.

It’s not just that a bug or injury makes us feel bad, causing us to withdraw and take to bed; we withdraw *because* of the bug or injury, as a way of healing. The behaviors may be evolutionarily adaptive. “Maybe we need a system so that when people get

sick, they stay away from social groups,” says Eisenberger, preventing, for example, a communicable disease from spreading. (Alternately, she says, it may be that the overlapping brain circuitry that causes the activation of the dACC by both physical and social pain produces an unintended effect: an increase in social pain when we experience physical pain, and vice versa.)

The studies suggest that inflammation can activate areas in the brain that ultimately trigger feelings of social pain, and may help explain why people suffering from an inflammatory disorder such as cardiovascular disease or rheumatoid arthritis are at greater risk for depression.

While sickness behavior may be adaptive, depression is not. Where do things go wrong? As yet, nobody knows.

Eisenberger is now conducting a study to examine how our sensitivity to positive experiences is influenced by inflammation. “One thing that makes depression unique is that it causes a decrease in positive affect and a lack of sensitivity to positive stimuli,” she says. “So can endotoxin can also reduce our sensitivity to positive things—causing less reward-related neurological activity? There are hints in our previous study that this is true.” ●



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The Cousins Center for Psychoneuroimmunology is a research unit of the Jane and Terry Semel Institute for Neuroscience and Human Behavior at UCLA.

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