Explorations and revelations taking place in the medical school



Women with postpartum depression show a decreased connectivity in some neural circuits and unusually low levels of activity in areas of the brain that are associated with emotion.

IT'S NOT JUST THE HORMONES TALKING

THE PATHOPHYSIOLOGY OF POSTPARTUM DEPRESSION

BY REID R. FRAZIER

A new mother's brain is like a house undergoing renovation. The work crew consists of hormones pouring in to promote new cell growth and rewire neural circuits. There's a lot of commotion. This has led to a common perception that when women undergoing dramatic fluctuations in hormone activity—as in premenstrual syndrome, menopause, and pregnancy—get depressed or moody, "it's the hormones talking."

But new evidence from a University of Pittsburgh researcher is showing that postpartum depression is considerably more complicated than that. Eydie Moses-Kolko and her collaborators found that women with the disorder had noticeably different levels of activity in parts of the brain associated with emotion; additionally, these women had a decreased connectivity in certain neural circuits. They published these findings in a recent issue of the *American Journal of Psychiatry*. (Scientists have also reported different patterns of brain activity and connectivity in women with garden-variety depression; however, no studies directly comparing postpartum and nonpostpartum depression have been completed, says Moses-Kolko.)

For the 15 percent of new mothers who experience postpartum depression, the first few months after birth can feel like grief. A mother might grow despondent, lose sleep, have difficulty connecting with her baby, and worry that she isn't being a good mom. She can feel like the infant is deliberately trying to make life hellish. Pangs of aggression toward the baby can creep in.

A little over a decade ago, Moses-Kolko began wondering why this happened in some new mothers. As a resident in psychiatry at Pitt in the 1990s, she saw women who had managed to cope with prior depression or anxiety suddenly wanting to drown their newborns.

"I've been really struck by how ill women can get in the postpartum period, particularly in cases of postpartum psychosis, when there might have been little evidence of prior mood disorder," says Moses-Kolko, an MD assistant professor of psychiatry. The stakes of this question have been heightened by studies suggesting a mother's postpartum depression can have long-term ill effects on her child's mental health.

What sets off the depression in some women remains a mystery. Some think it's simply sleep deprivation causing havoc; insomnia is certainly a risk factor for depression. Women with poor social structures or stressful relationships are at greater risk for postpartum depression, which suggests an environmental role. But so are women with mood disorders, which points to some kind of genetic or epigenetic determinant. Treatment can be as simple as talk therapy, an antidepressant, and a sleeping aid.

To dig deeper into the pathophysiology of postpartum depression, Moses-Kolko used functional MRI to study two groups of new moms—some with postpartum depression and some who were healthy—under functional MRI. She gave them two tests, one that matched shapes (a control task) and another that matched faces.

In the face-matching test, each mother saw a face in an emotional state—perhaps a worried expression—then was asked to find its match between a pair of faces. When attempting to find matching faces, postpartum-depressed women had significantly lower activity in their dorsomedial prefrontal cortex (DMPFC for short), a part of the frontal lobe that is involved in control of emotional responses and empathy. These women also had lower levels of activity in the amygdala—another important region in emotional response—when looking at fearful faces.

Moses-Kolko says these findings suggest a dampening of the emotional response in postpartum-depressed women. "It could be a protective mechanism to just shut things out in order to cope day to day, to be able to take care of a potentially noxious stimulus—the baby," Moses-Kolko says. "Maybe their shutting down is protective, so they don't throw the baby across the room."

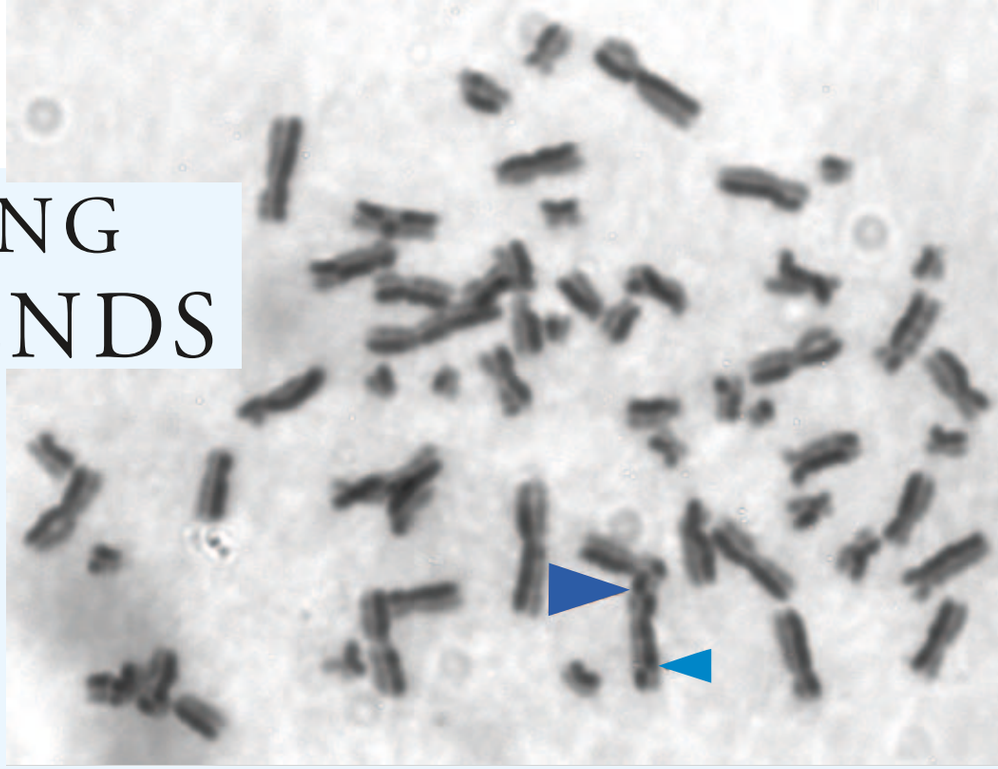
The tests also showed women with postpartum depression had less connectivity between the DMPFC and amygdala than did healthy women. This is significant, says David Rubinow, Assad Meymandi Professor and Chair of Psychiatry at the University of North Carolina and a leader in the field of reproduction-related mood disorders. The prefrontal cortex is believed to regulate brain regions and neural circuits, acting "a bit like a traffic cop," he says. Rubinow adds that Moses-Kolko's work is part of a wave of research that's getting closer to a biological marker for the disorder, which would make early detection—and better treatment—more likely. He says that knowing what to expect before a baby arrives would be a great help for these mothers and their newborns. ■

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CANCER-KILLING DIVIDENDS

A DNA-REPAIR PROTEIN YIELDS SURPRISES

BY MELINDA WENNER MOYER



CHRISTOPHER BAKKENIST

ABOVE: Here, we see a process known as sister chromatid exchange, which is believed to be a manifestation of a DNA-repair pathway. Pitt's Bakkenist believes that disrupting this pathway could be a potent means of killing cancer cells while saving normal cells, especially in cases of lung and pancreatic cancers. (The smaller arrowhead indicates an exchange near the telomere, i.e., the chromosome end. The larger arrowhead indicates an exchange near the centromere.)

Cancer may be a tough adversary, but Christopher Bakkenist, an assistant professor of radiation oncology based at the University of Pittsburgh Hillman Cancer Center, has a surefire tactic: Defeat the disease using wits, not muscle. "It's really only in the last decade that we've tried to be smart with cancer therapies," he says—meaning using approaches that specifically target the cancer without inadvertently harming healthy cells. Now, thanks to insights gleaned from a certain DNA-repair protein, he may have one of the cleverest solutions yet. And in the meantime, he has uncovered some surprising details about cell biology that could change how scientists study drug effects.

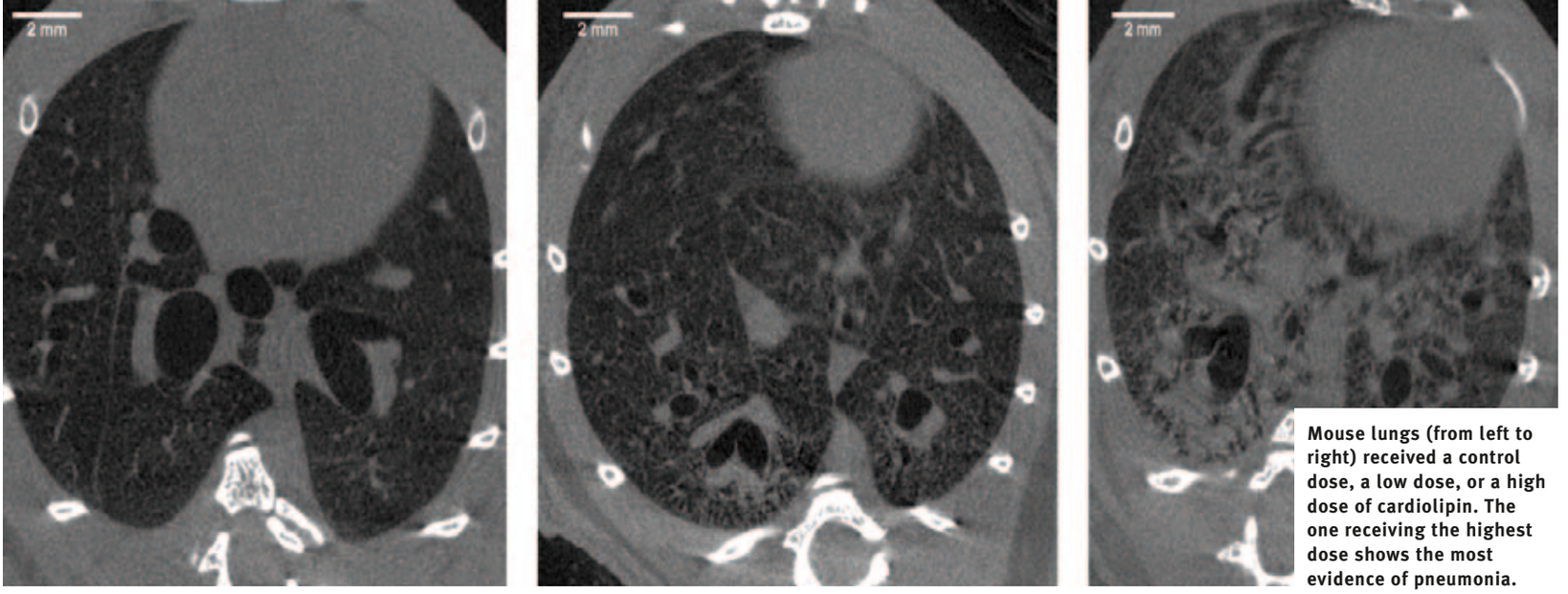
Bakkenist owes his breakthroughs to ATM kinase, a protein the body turns on when exposed to ionizing radiation and other insults to DNA. Although researchers have known that the protein helps repair DNA damage, it has been unclear how, exactly, ATM kinase works its magic. To find out, Bakkenist treated human lung cells with small molecules that inhibit ATM-kinase activity and hunted for the mechanism through which DNA damage accumulated. He had some hints for where to look: People with a rare disease called ataxia telangiectasia (AT)—who suffer from neurodegeneration, sensitivity to ionizing radiation, and predisposition to cancers—are born with mutations in the gene for ATM kinase and are therefore unable to make the protein. Yet they can still repair DNA through a process known as sister chromatid exchange (SCE), a type of genetic recombination in which lesions are mended during DNA replication.

Bakkenist guessed, then, that ATM kinase probably wasn't involved in SCE, so he looked to other repair pathways for his answer. But his guess didn't pan out. "We had eliminated every other possibility we could look at, so we ended up looking at SCEs," Bakkenist explains. Much to his surprise, when he inhibited ATM-kinase activity in normal cells, the cells were unable to conduct SCE—a finding that, to say the least, was "not anticipated," Bakkenist says, because the cells of people who cannot make ATM kinase can conduct SCE just fine. His team published its findings in June 2010 in *Science Signaling*. By shedding light on how ATM kinase functions, Bakkenist's work could help researchers develop better cancer therapies. Cells that are destined to become cancerous often acquire defects in DNA-repair pathways early in development that allow them to accumulate cancer-causing mutations. If cancer cells are later hit with another blow to their DNA-repair mechanisms—through drugs that inhibit ATM-kinase activity, for instance—they will be far less likely to survive radiation therapy than healthy cells, which have redundant repair pathways. "ATM kinase may well be essential for the survival of that cancer. So if we inhibit ATM, it will kill cancer cells," Bakkenist explains. Lung and pancreatic cancer cells, he says, might be particularly vulnerable to ATM-kinase inhibitors because of the specific mutations they accumulate.

Bakkenist's findings could have big implications for pharmacological research overall. Scientists often try to predict the effects of protein-inhibiting drugs by deleting the gene for the protein in animal models. Yet Bakkenist's work shows that cells that cannot make ATM kinase behave differently than cells in which ATM-kinase activity has been inhibited (that is, the protein is still made by cells, but it simply cannot do its job properly). Bakkenist's work suggests that sometimes, cells can maneuver around the loss of a gene in unexpected ways to get a biochemical task done, which means that scientists may want to reconsider using genetic deletions to predict the effects of protein-inhibiting drugs.

Why might these differences exist? Impaired proteins, Bakkenist speculates, may get in the way of important cellular activities such as SCE and essentially "prevent things from happening," he says. In contrast, people who are born without the ability to make the protein at all may adapt to the loss early in development through biological rewiring.

"It's going to be hard to tease these things out," he says. Nevertheless, "it's a bit surprising and a bit exciting." ■



RAMA MALLAMPALLI

Mouse lungs (from left to right) received a control dose, a low dose, or a high dose of cardiolipin. The one receiving the highest dose shows the most evidence of pneumonia.

A VISCOUS CYCLE

STEPPING UP THE "MOTOR OIL" OF THE LUNGS TO TREAT PNEUMONIA

BY JOE MIKSCH

Under the best circumstances, typical bacterial pneumonia can be a rough road. In the course of about two weeks, a person with pneumonia will cough, have trouble breathing, and develop shaking chills and fever. For the lucky ones, antibiotics and rest will restore health over time.

But for some people—particularly those with weakened immune systems, smokers, the very old, and the very young—pneumonia can require hospitalization. And, in more than 10 percent of cases, it can lead to death. The Centers for Disease Control and Prevention reports that in 2007, 1.1 million people in the United States were hospitalized with pneumonia and more than 52,000 died.

But why does pneumonia hospitalize or kill some and spare others, regardless of these risk factors? Rama Mallampalli—Pitt professor of medicine, chief of the pulmonary division of the VA Pittsburgh Health Care System, and director of the Acute Lung Injury Center of Excellence at the University of Pittsburgh—thinks a process involving a structural molecule called cardiolipin might be key.

Mallampalli, an MD, and Pitt colleagues Bill Chen, Bryan McVerry, and Valerian Kagan—along with faculty from the University of Iowa School of Medicine—recently published a paper in *Nature Medicine* that reports that cardiolipin is found in unusually high concentrations in the lung fluid of mice and people infected with bacterial pneumonia.

Under normal circumstances, cardiolipin plays a role in mitochondrial-energy metabolism—a good thing, obviously, because mitochondria provide the power that keeps our cells, and therefore us, alive. So the questions become: Why is there so much cardiolipin in the lung fluid of pneumonia sufferers? And why does it seem to be such a bad actor when let loose in the lungs? "You and I normally have very low concentrations of [cardiolipin] in our lung-fluid secretions," Mallampalli says. "We hypothesized that there may be a protein that basically eliminates or removes [cardiolipin], and there might be a problem related to it."

As the investigation progressed, Mallampalli and his team identified a carrier protein called Atp8b1. They learned it transports cardiolipin, essentially acting as a pump that controls levels of the molecule.

With cardiolipin and Atp8b1 in his sights, Mallampalli traced their interaction: As pneumonia progresses, lung cells die. And as they perish, these cells release their components, including cardiolipin, into the lung fluid. At a point, Atp8b1 is faced with much more cardiolipin than it can process. As cardiolipin levels build, the molecule begins to disrupt the function of surfactant, a lubricant that is essentially the motor oil of respiration. As surfactant fails to work properly, respiration falters, and lung cells acquire even more damage—and a conventional case of pneumonia becomes more severe.

Mallampalli says he intuited that Atp8b1 might play a role here because of earlier work done by others on a rare and very serious liver condition called Byler's disease. Byler's disease patients have a mutation in Atp8b1 and an unusually high incidence of pneumonia in addition to liver failure.

Mallampalli is optimistic that this discovery offers the potential for new anti-pneumonia drugs. "All treatments for pneumonia are antibiotics," Mallampalli says. "This has been a good thing in that we've saved a lot of lives; but on the bad side, this has led to the emergence of drug-resistant bacteria."

Now, Mallampalli says, it may be possible to design drugs that either bind to cardiolipin, rendering it impotent, or that activate Atp8b1, making it a more robust cardiolipin "pump."

"For the first time, we have a new paradigm or model for pneumonia, and it will lead to a nonantibiotic approach to alter the host response to the infection," he says. ■