Rare disease in women pulls together community of researchers and patients

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Madeline Nolan, the New England liaison for the LAM Foundation. Credit: Rick Groleau

It's not cancer, but it grows and spreads to distant organs.

It's not malignant, but women die when it destroys their lungs.

It has no cure, but scientists, physicians and patients are converging to change that.

Lymphangioleiomyomatosis—LAM for short—is a rare disease in which abnormal, smooth muscle-like cells grow out of control, usually in the kidney, lymph nodes and lungs. It develops almost exclusively in women during their childbearing years.

At first, they might feel shortness of breath, which is sometimes confused with asthma and sometimes caused by a collapsed lung. Some women find out they have the disease when CT scans their doctors order for other reasons reveal LAM's telltale cysts, invisible on ordinary chest X rays but sprinkled throughout their lungs.

LAM is in many ways a mystery defined by what it is not. But the story of LAM has evolved rapidly over the past 15 years. That momentum accelerated when a team led by a physician-scientist now at Harvard Medical School identified the genetic mutation at its core and then developed a model that could be used to study it. Their work allowed the molecular machinery to be nailed down by scientists across the world.

A vibrant community of researchers has grown at HMS and the LAM Center at Brigham and Women's Hospital. They in turn are linked to other research labs and hospital clinics around the country united by the LAM Foundation, a driving force in patient support and research funding.

"Our lab was in the right place at the right time to really start to make new contributions to understanding the pathology of LAM and the evolution of the disease," said John Blenis, HMS professor of cell biology. "It turns out that two molecular pathways we've been studying for 20-plus years converge to contribute to LAM."

At a meeting 15 years ago convened by the father of a patient, Blenis learned about the challenge from, among others, Elizabeth Henske, HMS professor of medicine at Brigham and Women's and director of the LAM Center. An oncologist, Henske worked on tuberous sclerosis during her postdoctoral training. Tuberous sclerosis can cause LAM and severe cognitive problems, as well as unusual kidney tumors filled with blood vessels, smooth muscle tissue and fat cells. She had been puzzled because similar tumors occur in women with LAM.

Henske has devoted her career to solving the mystery of LAM. While a rare disease, new ways to treat it may have implications for more common disorders.

"These are tumor-like cells, but they're not malignant-appearing. So it seems like it should be easier to fix than a cancer. And it affects almost only women, so there may be a hormonal element. It just seemed like something we ought to be able to figure out," Henske said. "That's what hooked me in and that's still what I think about all the time."

Shocking diagnosis

Madeline Nolan learned about LAM at the end of a months-long series of referrals to figure out why she was so fatigued and why her bloodwork looked so odd. A hematologist had sent her to a pulmonologist after ruling out a blood disorder. She was 47 years old, she taught phys. ed., and she was shocked.

"I don't smoke, I'm not around toxic chemicals, how do I have a lung disease?" Nolan recalls wondering.

Nolan's pulmonologist couldn't tell her in 1999 why she had a disease that damages her lungs. With tears in his eyes, he told her she might have three or four years before needing a double-lung transplant.

She hasn't gone down that road, although she now uses oxygen and takes a drug that has stalled her disease's progression. Her story mirrors the mystery that LAM still is today.

Now teaching health to high schoolers in Waterbury, Conn., Nolan jokes that the pimples— a side effect from her medication—make her fit in with her students. She talks warmly about other LAM patients, who get together around their appointments at the LAM clinic in Boston as well

at other events throughout New England. Her mission is to promote awareness, support patients and push research as the New England liaison for the LAM Foundation.

"I want to do everything I can to make a cure happen faster," she said. "I want to do this for the next 20-year-old who gets diagnosed."

Scientific serendipity

Tuberous sclerosis and LAM share more than idiosyncratic kidney tumors. Tuberous sclerosis is an inherited disease caused by mutations in genes called TSC1 and TSC2, which patients carry in every cell in their bodies. About 40 percent of girls with tuberous sclerosis also go on to develop LAM in their childbearing years. Women without tuberous sclerosis have a sporadic form of LAM: They carry mutations only in the TSC2 gene and only in their tumor cells.

Henske participated in the cloning of the TSC1 gene in 1999, and she was the one who discovered in 2000 (while working at Fox Chase Cancer Center) that LAM is caused by mutations in TSC2.

At that point, no one knew what TSC2 did. But in what Henske calls a moment almost too good to be true, scientists studying flies to find genes that enlarge cells in the eye discovered that TSC genes control cell size. Other scientists determined that these genes regulate an enzyme called mTOR, a key player in a series of molecular events involved in cancer and one of two major signaling systems studied in the Blenis lab since the early 1990s.

The link between TSC and mTOR led quickly to a clinical trial showing that rapamycin, a natural product that blocks the mTOR pathway (and gives the enzyme its name: mammalian target of rapamycin complex), could shrink kidney tumors in women with LAM. A later clinical trial

found that rapamycin could also stabilize lung function in women with LAM. It's not a cure—the disease continues to destroy the lungs if a woman stops taking the drug—but it stalls further lung damage.

"This is a really beautiful example of pure science," Henske said. "Looking for regulators of cell size in the fly eye led in five years to the completion of a trial in a disease that is just devastating. You can't imagine what it's like for a young woman who's already on oxygen."

Meeting LAM face to face

Henske thinks about those women all the time. To get to her desk, she walks by a quilt hung outside her office honoring women with LAM. Squares depict lives stitched together at LAM Foundation events where scientists, women with LAM and their families all rub shoulders and form bonds. Physicians and researchers give presentations at annual meetings, but patients speak too, telling their stories and touching the hearts of basic scientists who don't always see the people whose lives they hope to help.

Henske's colleague in a nearby office, Jane Yu, proudly wears a new navy blue fleece top embroidered with the LAM Center's name, a gift from Henske on the center's fifth anniversary. HMS assistant professor of medicine at Brigham and Women's, Yu led pioneering research that created the first animal model that closely recapitulates how LAM metastasizes under the influence of estrogen. She later showed that a drug can block LAM cells from spreading to the lung by inhibiting estrogen, confirming the hormone's role in the disease.

Yu finds the LAM meetings unusual—and inspiring.

"Once you are there, you are family: Your sisters are there, your aunts are there. I wouldn't say grandmothers—yet," she said. "You feel that

you are one of them and you want to help. They never give up, and every year I think we should try harder."

Blenis said by going to LAM meetings, he became more interested in researching the disease. "I get very emotional when I go to these meetings, and I think all my postdocs who have ever gone have felt the same way."

Xiaoxiao Gu, a postdoc in the Blenis lab, is also a LAM Foundation fellow. She had two questions she wanted to answer when she started her three-year fellowship in 2011. "Because the hypothesis is that these kidney tumor cells are migrating to the lung in the presence of estrogen, how can I test estrogen responsiveness in those cells? And why is an inhibitor like rapamycin not enough to block disease progression?"

Convergence

In a *PNAS* paper published in September 2013, Gu and Blenis offered an explanation: The two pathways that the Blenis lab has played a major role in defining actually converge in LAM in a way that requires their precise spatial and temporal regulation to generate the disease.

It takes more than the mTOR pathway—the set of molecular activities that rapamycin can inhibit, thereby blocking runaway cell metabolism and growth. It also takes a signaling pathway involved in the development of cancer: a chain of communicating proteins called the estrogen receptor-MAP (ERK-MAP) kinase pathway that transmits signals from the cell surface to DNA in the nucleus of the cell.

The team built on work by Yu and Henske showing that estrogen increases the migration of cells with TSC2 mutations via the MAP kinase pathway. Gu and Blenis found that estrogen signaling in the ERK-MAP kinase pathway is active in LAM cells, establishing that estrogen

collaborates with inappropriate regulation of mTOR, converging to generate disease.

The ERK-MAP kinase pathway, activated by estrogen, starts a process that makes cells more likely to migrate, invade and survive. The mTOR pathway provides the energy and building blocks to support LAM cell growth and to enhance the estrogen-stimulated events.

"It's this amazing integration of different signals at different times that contributes to disease progression," Blenis said. "By discovering how these two pathways converge, it also suggests possible therapeutic options."

The MAP kinase pathway has already been targeted by pharmaceutical companies for other reasons, Blenis said.

"We're defining mechanistically how these pathways converge and verifying the choice of using an estrogen inhibitor in combination with mTOR inhibitors such as rapamycin," Blenis said. "One drug may have some effects, but the combination of the two is going to be significantly greater at treating the disease."

LAM's lessons

Blenis, Henske, Yu and Gu all profess optimism with the field's rapid progress, confident that what they learn about LAM may be applied to other diseases, including cancer.

"The tuberous sclerosis genes are in the center of the universe in terms of how a cell regulates almost everything it does, from metabolism to growth to its decision to divide. Everything depends on mTOR," Henske said. "Many of us who study rare diseases have the very strong belief that the way you figure out a common disease is almost always by

starting with a rare disease."

Knowing the one faulty gene where a rare disease starts is much better than looking at 10 or 100 or 1,000 genes involved in a common disease, Henske said. "That's kind of like looking at a crashed car and trying to figure out if it was the steering wheel or the brakes."

In the Blenis lab, LAM is directly linked to his work on breast cancer metastasis while remaining significant in its own right. LAM patients' pull on the scientists is strong.

"Clinician-scientists have more of a direct impact on patients," Blenis said. "For a basic scientist, this is the whole reason to get into the field: We hope our work will have an impact down the road."

Madeline Nolan and her LAM sisters are waiting.

"We've come such a long way in a short time."

More information: "Integration of mTOR and estrogen–ERK2 signaling in lymphangioleiomyomatosis pathogenesis." Xiaoxiao Gua, Jane J. Yub, Didem Iltera, Nickolas Blenisa, Elizabeth Petri Henskeb, and John Blenis. *PNAS*, 2014. DOI: 10.1073/pnas.1309110110

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