MARCIA

HAIGIS

HARVARD

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Photo by Flynn Larsen

THE MITOCHONDRIAL NETWORKER

She has shown how biochemical discord in the powerhouse of the cell can shape the aberrant metabolism of cancer cells. Disrupting the relevant metabolic circuitry could help treat a variety of malignancies.

Some good deeds, it appears, do go unpunished. Consider Ludwig Harvard's Marcia Haigis. As a freshman at the University of New Hampshire in the early 90s, the young Haigis got certified as an emergency medical technician, working the night shift to rack up the volunteer hours required to retain membership in the ambulance corps. It was after one of those shifts, before 7 a.m., as she took a shortcut to her dormitory through the biology research building, that Haigis discovered her calling. Fascinated by the posters in the hall, she wandered through the only office door open at the time and asked the professor in there, biochemist Rick Cote, if he had a few minutes to talk. A few hours later, she emerged, bleary-eyed but inspired—and with a summer job offer in hand. "That," she recalls, "is how I got hooked on research."

Probing the structural intricacies of an enzyme in Cote's lab that summer awakened in Haigis a fascination with fundamental protein chemistry—not only with its intrinsic beauty but also its potential for answering larger questions about human health and disease. Today, her laboratory at Harvard Medical School explores the biochemical maze of the mitochondrion, the bean-like organelle best known as the cell's power station. Over the past dozen years, she and her colleagues have methodically exposed how the interplay of enzymatic networks within the mitochondrion transmits signals that modulate the cell's metabolism at large, exerting a systemic influence on everything from obesity to immunity to aging and cancer.

In 2017, Haigis and her colleagues published a paper in *Science* revealing that a waste product of metabolism lethally toxic to ordinary tissues—ammonia—looks like good grub to breast tumors. Tracing the fate of the

Photo by Flynn Larsen

toxin in cancer cells, her team revealed how the cells recycle the toxin to fuel unfettered growth. She and her team also showed that targeting that process could open a new approach to treating breast cancer.

Finding a calling

Haigis was born in Las Vegas and then moved with her family to South Korea as an infant, where her father, an officer in the US Air Force, had been stationed when he met her mother. After the family returned to the US, they hopscotched between states from Nebraska to Alabama, and ultimately New Hampshire, where they settled in Portsmouth. Haigis and her two younger siblings spent most of their childhood there.

After majoring in biochemistry in college, Haigis joined the graduate program at the University of Wisconsin–Madison. Her doctoral research under the guidance of the chemical biologist Ronald Raines explored how the molecular geometry of an enzyme that slices up RNA molecules contributes to the enzyme's function. "It was a lab where you learned the fundamentals about protein folding," says Haigis. "With this background, I was eager to work in a field where enzymology and biochemistry had center stage but the driving questions would be directly related to biology."

Haigis found a perfect fit in the study of sirtuins—a family of enzymes that chemically

modify other enzymes in distinct ways to alter their activities. One member of the family, named SIRT1 in mammals, had come about as close as any enzyme gets to pop culture celebrity. Giving yeast, fruit flies and roundworms an extra copy of their respective versions of the SIRT1 gene significantly extended their lives. Other sirtuins, however—mammals have seven in all—languished in obscurity.

Joining Leonard Guarente's lab at the Massachusetts Institute of Technology, Haigis turned her attention to the neglected sirtuins that reside in the mitochondrion (SIRT3, 4 and 5). Her work provided among the first bits of evidence that the mitochondrial sirtuins play a significant role in controlling metabolic processes outside the organelle, a finding that upended prevailing dogma. SIRT4, she showed, represses an enzyme essential to amino acid metabolism called glutamate dehydrogenase. This has the effect of suppressing insulin secretion by pancreatic islet cells in mice.

Touring cancer metabolism

In 2006, Haigis joined Harvard Medical School, focusing her laboratory on how mitochondrial processes, initially involving sirtuins, participate in aging and cellular adaptations to stress. A graduate student in her lab, Lydia Finley, noticed that the loss of SIRT3 activity ultimately boosted the expression of genes essential to glycolysis. This is a metabolic pathway active in the cytoplasm through which the sugar glucose is broken down to generate energy. It also furnishes molecular building blocks essential to cell proliferation.

While healthy cells only resort to glycolysis when there's a shortage of oxygen, cancer cells have long been known to keep it going even when oxygen is abundant—a phenomenon known as the Warburg effect, a hallmark of cancer metabolism. Haigis, Finley and their colleagues found that the loss of the SIRT3 gene induced gene expression patterns and metabolic activity that mirrored the Warburg effect.

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Examining a variety of tumor cells for their SIRT3 status, the researchers discovered that the SIRT3 gene had been deleted in most. Their study, published in *Cancer Cell* in 2011, revealed how the SIRT3 enzyme counters the metabolic reprogramming that drives cancer cell proliferation and survival. Other researchers subsequently reported that mice lacking the SIRT3 gene spontaneously develop breast tumors.

"Our entry into cancer research was the observation that these mitochondrial sirtuins have profound effects on cellular metabolism," says Haigis. "A lot of the metabolic pathways they regulate are central to tumor cell growth."

With that in mind, Haigis and her colleagues began exploring when the mitochondrial sirtuin genes are switched on in cells. They noticed that damage to DNA, which can cause mutations that drive cancer, activated SIRT4. It did so, they reported in a 2013 *Cancer Cell* paper, through its suppression

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of glutamate dehydrogenase and the metabolism of an amino acid named glutamine. That in turn had the effect of arresting cell division.

"SIRT4 seems to dampen mitochondrial metabolism and help cells deal with stress," says Haigis. "It induces a metabolic pause, or what we call a metabolic checkpoint, and gives cells time to repair the damage." Illustrating the importance of that checkpoint, Haigis' team showed that mice engineered to lack the SIRT4 gene developed spontaneous lung tumors within 15 months.

In another study, Haigis' lab took a closer look at what was once a poorly understood enzyme named PHD3, a close relative of a pair of enzymes through which SIRT3 suppresses the Warburg effect. The group's findings, reported in *Molecular Cell* in 2016, revealed that PHD3 silences an enzyme involved in the breakdown of fats inside the mitochondrion for energy, an option normal cells only take when they're stressed out by low nutrient supplies.

Haigis and her colleagues also found that expression of the PHD3 gene is severely suppressed in a subset of cancers that include acute myeloid leukemia. "Certain tumors do not rely on the Warburg effect and are not glycolytic, but they do have an addiction to fat oxidation, or burning fat, and they need it to survive," says Haigis. "We speculated you can target those tumors with inhibitors of fat oxidation."

A toxic treat

Given how often the amino acids glutamate and glutamine pop up in cancer metabolism, Haigis' lab wanted to know what happened to a toxic byproduct of their breakdown: ammonia.

Ordinarily, the body quickly clears ammonia and sends it to the liver, where it is processed and excreted as urine. But

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cancer cells metabolize nutrients furiously as they grow, so ammonia tends to accumulate in tumors. Graduate student Jessica Spinelli observed that breast cancer cells even seem to thrive when it is added to their cultures. This suggested the cells were using it for something. What exactly was less clear.

To find out, Haigis, Spinelli and their colleagues tried first to figure out whether the ammonia was going down certain metabolic pathways that make molecules rich in nitrogen, like the constituents of DNA. After several months of negative results, they decided to scan all the nitrogenous metabolites in the cell at once—more than 200 in all— before finally calling it quits. Adapting an obscure chemical reaction concocted by the 18th century chemist Pierre Berthelot and a procedure for the quantitative analysis of ammonia metabolism—both reported in a 2017 *Scientific Reports* paper—the team stuck an isotopic label on ammonia and fed it to the cancer cells.

As Haigis and her colleagues reported in *Science* in 2017, ammonia was being used by breast cancer cells to generate amino acids, most often glutamate and amino acids generated downstream from glutamate. What's more, the breast cancer cells don't just thrive on the ammonia, they're almost addicted to it: Blocking glutamate dehydrogenase activity retarded breast tumor growth in mice.

The team is now looking at whether ammonia has the same effect in other types of tumors, especially those of the liver, where it is abundant. They are also examining how the high levels of ammonia affect other cells in the environment of the tumor.

"If we identify and understand new metabolic vulnerabilities that are unique to each cell type, we may be able to tailor a metabolic cocktail or precisely target those pathways," says Haigis. The task, she admits, will not be easy, since tumors vary so much. "Identifying the metabolic fingerprint of a tumor before starting a therapy is a major challenge in cancer biology and treatment."

On the plus side, Haigis is on the case.