

The Pay-Off of Persistence

What began as a side project has become a primary focus for this physician researcher.



A college project studying how elephant seals' fat cells change after the seals are weaned triggered Vivien Cheung's long-time interest in how different human traits appear.

Jason Varney

THE CHILDREN CAME TO THE CLINIC USUALLY BEFORE THE AGE OF TWO.

They had difficulty walking or even sitting upright. In some, angry red veins bulged in the corners of their eyes. ¶ Vivian Cheung, then a pediatric neurologist at Children’s Hospital of Philadelphia, recognized the signs of ataxia telangiectasia (AT), an inherited disorder. The good news was that it was rare; the bad news was that there was no cure.

The AT gene defect normally rendered its victims wheelchair bound by the age of 10 and plagued them with respiratory ailments and cancers until they succumbed, often before turning 30.

Cheung had been on track for a medical career. “My dad was a surgeon,” the HHMI investigator says now, with a dutiful daughter’s smile. But while working as a clinical fellow at Children’s, a teaching hospital affiliated with the University of Pennsylvania School of Medicine, she began doing research in her spare time to unravel the mysteries of this heartbreaking disease.

It was a journey that would eventually make her one of the world’s foremost experts on the genetics of DNA repair. In AT patients, a defect in an important repair-related gene leaves them vulnerable to a bewildering variety of bodily dysfunctions: balance and motor-control problems, spider veins in the eyes, diabetes and infertility, immune system defects, and—perhaps strangest of all—an extraordinary sensitivity to ionizing radiation.

“I had long been interested in how different traits appear,” Cheung says. As an undergraduate at the University of California, Los Angeles, majoring in microbiology, she had studied how fat-cell metabolism changes radically in young elephant seals to enable them, after weaning, to hunt fish at half-mile depths. Later, in medical school at Tufts University, she took part in a multiyear epidemiological project in Turkey to study the genetics of lipoprotein levels.

At Penn, Cheung set up a small laboratory to study the genetic havoc of AT, and she quickly focused on the radiosensitivity problem. Patients with the disorder

have inherited two mutant copies of a gene known as *ATM* (*ataxia telangiectasia mutated*). The gene normally codes for an enzyme whose most evident role is to act as the foreman of a special repair crew—called into action after the gravest of cellular events, a double-stranded DNA break. The “ATM crew,” which includes several powerful tumor-suppressing molecules, must either attempt DNA repairs or trigger a cellular self-destruction process known as apoptosis, lest the damaged DNA lead to runaway cancerous growth. Cells that lack this repair capacity are much more susceptible to damage from radiation and are more likely to turn cancerous.

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VIVIAN CHEUNG

“Even ordinary background radiation, from cosmic rays and radon gas, can contribute to cancers in AT patients,” says Cheung.

AT occurs in fewer than 1 in 40,000 children, yet Cheung soon realized, as her lab grew, that radiosensitivity was a trait not confined to these rare patients. Gene-expression studies in her lab suggested that AT carriers, who have one nonworking copy of *ATM* (and represent fully 1 percent of the population), are also more sensitive to radiation. In fact, Cheung noted from the literature that more than 10 percent of all patients receiving radiation therapy for cancer showed signs of excessive damage or secondary cancers.

“That told me that ATM wasn’t the only gene responsible for radiosensitivity,” she remembers.

Cheung still does some clinical consultation at Children’s Hospital. But for the past several years, and with support from HHMI since early 2008, she and her colleagues have been trying to understand the genetic underpinnings of radiosensitivity in AT patients as well as in the wider population. In a study published in *Nature* in April, Cheung and her lab members looked at gene expression responses to irradiation in a large sample of human cells. They were able to link individual differences in these responses to DNA-sequence variations in more than a dozen master regulators of the radiation response, which were found throughout the genome.

“One goal of this is to develop a DNA-based test to determine how radiosensitive a person is likely to be,” she says,

adding that such information is becoming more important, given the rapid increase in the use of radiation for CT scans and cancer therapies over the past two decades. Detailed knowledge about the molecular first responders to radiation damage could help, too, in the development of drugs to make tumors more sensitive to radiotherapy.

Cheung also has a deeper goal in mind, which broadly relates to the popular concept of personalized medicine: “We can apply the same tools developed for this study to see how people differ in their responses to drugs or environmental toxins that they are exposed to in their ordinary lives,” she says. ■

—JIM SCHNABEL