GENETICS AND DISEASE

# Growth Defect Blocks Cancer and Diabetes

Life can be treacherous for Ecuadorians with Laron syndrome, a rare type of dwarfism. As children, they are vulnerable to infectious diseases. As adults, they are prone to fatal accidents, such as falls on stairs that aren't sized for their short legs. But a new study shows that these people, who carry a genetic defect that prevents them from responding to growth hormone (GH), are almost exempt from cancer and diabetes. The paper solidifies a link researchers have long suspected from animal studies and suggests that dialing down the growth-controlling molecular pathways might protect healthy adults from these diseases.

"The strength [of this paper] is that finally someone has made this connection in humans," says physiologist Holly Brown-Borg of the University of North Dakota School of Medicine and Health Sciences in Grand Forks. "The fact that they found such a striking absence of cancer and diabetes in such a large cohort makes it a very valuable study," says mammalian endocrinologist Andrzej Bartke of the Southern Illinois University School of Medicine in Springfield.

Numerous studies show that mice gain from short circuits in the GH pathways. Minimice that can't make GH or lack the receptor that relays its message are less susceptible to cancer than are their huskier counterparts. They also have low quantities of blood insulin, and their cells are sensitive to the hormone—high insulin levels and insulin resistance can be harbingers of diabetes. Although some data support the notion that GH-deficient people derive similar benefits, the evidence has been "anecdotal," says Brown-Borg.

Enter diabetologist Jaime Guevara-Aguirre of the Institute of Endocrinology, Metabolism and Reproduction in Quito, Ecuador. In the late 1980s, he was studying body composition when he chanced on several people with Laron syndrome who lived in small, isolated villages in Ecuador. He has been tracking the group—which now numbers almost 100 people—ever since. They carry mutations that cripple the GH receptor and stunt growth. The tallest men top out at about 140 centimeters (4.5 feet), the tallest women at about 124 centimeters (4 feet).

In 1994, Guevara-Aguirre noticed that none of the subjects had cancer. To investigate, he and his colleagues teamed up with researchers led by molecular geneticist Valter Longo of the University of Southern California in Los Angeles. The scientists analyzed medical information for the 99 subjects Guevara-Aguirre has been tracking, for another 53 Laron patients who died before 1988, and for more than 1600 relatives who didn't have the condition.

Only one of the Laron subjects developed cancer, an ovarian tumor that didn't recur after chemotherapy. By contrast, cancer killed 20% of the normal-sized relatives. The Laron syndrome individuals were also free of type 2 diabetes, the cause of death for 5% of their taller kin, the team reported in the 16 February issue of *Science Translational Medicine*.

**Cancer free.** Jaime Guevara-Aguirre with several of his Laron syndrome subjects in 1988 (*top*) and in 2009 (*bottom*).

The diabetes result was surprising because Laron syndrome often causes obesity, a risk factor for diabetes. But the researchers found that the subjects, like the minimice, had lower blood insulin levels and much higher sensitivity to the hormone than did controls.

Scientists haven't worked out exactly how GH prompts diabetes. But Longo and colleagues did identify a possible mechanism for the Laron subjects' cancer resistance. They immersed human cells in blood serum from either the Laron subjects or the control group and added DNA-breaking hydrogen peroxide. Cells basting in the control serum accumulated more DNA breaks that can spur tumors and were less likely to commit suicide, a mechanism for weeding out potentially cancerous cells. GH rouses another hormone, insulin-like growth factor-1 (IGF-1), and researchers think that both molecules promote cancer. Adding IGF-1 to the serum from the Laron group cut the amount of cell suicide to control levels, possibly increasing cancer susceptibility.

Unlike the dwarf mice with similar genetic defects, the Laron subjects didn't live longer than normal, despite their lack of mortality from cancer and diabetes. Along with higher death rates from accidents, they also fell victim to epilepsy and similar conditions and to other causes.

The study shows that "two major diseases are prevented by a single point mutation in the GH receptor," says Longo. Does that mean that comparable changes in healthy people could prevent cancer and diabetes? It's possible, Longo says. In the future, doctors might prescribe drugs that interfere with the GH pathways for adults who have above-normal levels of IGF-1, much like they currently prescribe statins for people who have high cholesterol, he says.

Other researchers suggest that we should be cautious about intervening in the growth-controlling pathways to forestall disease. "Manipulating this in a healthy person as prevention is a very delicate issue and very complicated," says Bartke. Although it's not necessary for growth in adults, GH might still perform important functions, such as preventing obesity, he says. Reducing insulin levels throughout the body might have a downside, adds geriatrician William Banks of the University of Washington School of Medicine in Seattle. "There could be unexpected consequences on the central nervous system" because insulin in the brain improves mental acuity.

**–MITCH LESLIE**

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