Biomedicine

Inefficient protein tied to lupus

Systemic lupus erythematosus, the autoimmune disease so savage it was named for the wolf, baffles researchers, who do not know why it affects some people more severely than others.

Now, a study by researchers at five major medical centers offers an explanation for one complication of lupus. Jane E. Salmon of Cornell University's Hospital for Special Surgery in New York and her coworkers have found a gene that heightens the risk of lupus-related complications, such as kidney disease.

In lupus, the immune system produces antibodies that attack normal cells as if they were foreign. These antibodies combine with substances from the cells, forming complexes that accumulate and damage tissue. Until now, researchers haven't known why this buildup occurs.

In its study of 257 black patients with lupus and 139 without, Salmon's group found that people with the disease are more likely to have inherited a specific version of a gene that codes for a protein called an Fc receptor. This protein is found on immune system cells. Compared to the more common form, the receptor encoded by this version is less efficient at clearing immune complexes, according to a report in the March 1 JOURNAL OF CLINICAL INVESTIGATION.

"It is a genetic factor that gives you optimal clearance or less optimal clearance—which, if you have lupus, increases your risk of kidney disease," Salmon says.

Repeating DNA surprises once again

In 1991, geneticists discovered a new type of DNA mutation. A small stretch of the genetic material had mysteriously copied itself over and over, disrupting the function of a crucial gene and causing a form of mental retardation called fragile X syndrome. Other diseases, including Huntington's, result from similar mutations in different genes, researchers quickly found.

Since the proliferating genetic bits are trios of nucleotides, the fundamental building blocks of DNA, investigators call these disorders triplet repeat diseases. There are four kinds of DNA nucleotides—A, C, G, and T—and only CAGs and CCGs seemed to repeat inappropriately. Now, investigators have found that GAA can also copy itself unpredictably.

A large number of GAA repeats, anywhere between 200 and 900, in a gene on chromosome 9 causes the progressive disorder Friedreich's ataxia, report Massimo Pandolfo of Baylor College of Medicine in Houston and his colleagues in the March 8 SCIENCE. This disease, which slowly degrades the spinal cord, heart, pancreas, and other organs, occurs only when the gene's two copies—the one inherited from the mother and the one from the father—are both flooded with GAA repeats.

The ability of GAA to repeat offers a challenge to investigators trying to explain the generation of the triplet repeat diseases, observes Stephen T. Warren of Emory University School of Medicine in Atlanta. Based on test-tube experiments with DNA, researchers had proposed that repeated spans of CAG and CGG triplets form unique DNA structures, such as those called hairpins, that are prone to replicate out of control. "The GAA repeat doesn't form these structures," says Warren.

Huntington's and other triplet repeat diseases strike at younger ages and more severely in subsequent generations as the number of CAG or CCG repeats increases. Scientists refer to this tendency as anticipation. Friedreich's ataxia, however, shows that anticipation does not occur in every disease caused by triplet repeats. Though the number of GAA repeats tends to increase with each generation, Friedreich's almost always strikes in adolescence and does not become more destructive. This disorder suggests that triplet repeats may also cause other diseases that don't demonstrate anticipation. "Now one can consider a lot of other disorders as candidates for this type of mutation," says Warren.

New chapters in the leptin tale

The leptin story continues to unfold swiftly. In December 1994, investigators discovered that fat cells secrete this novel hormone and that it appears to travel to the brain and help regulate body weight. Last December, researchers reported that they had found a gene for a leptin receptor, a cell surface protein that recognizes the hormone and signals its presence to the rest of the cell (SN: 1/6/96, p. 6). Yet this receptor appeared to be absent in some brain regions long implicated in the regulation of weight. The leptin receptor was not detected, for example, in the hypothalamus.

Now, in a trio of papers appearing in the Feb. 9 CELL, the Feb. 15 NATURE, and the Feb. 16 SCIENCE, scientists report that the receptor gene actually encodes a variety of leptin receptors, each of which has a different distribution in the brain. One version appears on hypothalamus cells. Furthermore, the investigators found that two obese strains of rodents owe their size to mutations in the leptin receptor gene.

The hormone also appears to play a role in reproduction, report researchers at the University of California, San Francisco (UCSF), in the March NATURE GENETICS. Leptin's discovery in 1994 resulted from the study of an obese strain of mice that fail to make the hormone because their leptin gene is mutated. Curiously, the female mice in this strain are infertile; hormonal abnormalities prevent them from ovulating.

Injections of leptin enable such females to ovulate, become pregnant, and bear healthy progeny, the investigators now report. In the brain, leptin probably controls the release of other reproductive hormones, but it may also act directly upon leptin receptors that researchers have recently found on ovaries. "The central question is what that receptor is doing in the ovary," says UCSF's Farid F. Chehab.

Chehab notes that women with very little body fat, such as marathon runners, sometimes stop menstruating. "They may be depleting their levels of leptin. And if you go below a certain threshold, reproduction shuts off," he says.

Huntington's accomplice captured?

While looking into the crime of Huntington's disease, investigators have nabbed a new suspect—a protein that plays a role in generating energy for cells. In 1993, researchers learned that this fatal neurodegenerative disorder results from unexplained genetic stutters, expansions in the size of a particular gene. The stutters add extra strings of the amino acid glutamine to huntingtin, the protein that the gene normally encodes. Several other genes stutter similarly, leading to neurodegenerative diseases that share characteristics with Huntington's.

In November 1995, researchers found a clue they hoped might reveal the normal function of huntingtin and how mutant versions of it cause Huntington's disease. They discovered a novel brain protein that binds more tightly to mutant huntingtin than to the normal form (SN: 11/18/95, p. 325). No one knows the protein's purpose in brain cells, however.

Now, investigators from Duke University Medical Center in Durham, N.C., and Stanford University School of Medicine have found another brain protein that hugs mutant huntingtins more tightly than normal versions. Equally important, this protein, called GAPDH, has a number of known functions, such as providing energy to cells, report Warren J. Strittmatter of Duke and his colleagues in the March NATURE MEDICINE.

The investigators speculate that brain cell death in Huntington's disease may stem from cells being starved for energy because of inappropriate interactions between mutant huntingtins and GAPDH. Abnormal attachments to GAPDH may also explain other neurodegenerative disorders caused by genetic stutters—the crucial proteins produced in at least two of those diseases also appear to bind to GAPDH.