have led scientists to focus on inflammation, a familiar physiological mechanism whose true import is only now becoming clear.

Many molecules implicated in type 2 diabetes—JNK, IKK, and SOCS3 among them—are components of the inflammatory signaling system, part of the body's immune response. And these signals are activated by food intake.

Whenever we eat a meal, the body responds as if to an infection. In healthy people, this reaction, which accompanies the release of insulin in response to food, dies down after a time. The trouble seems to come when meals are so close together, or so inordinately large, that the body never gets a chance to recover from its inflamed state. "This ancient capacity of fat cells to produce an immune-like response is activated when they're exposed to large amounts of energy," says Hotamisligil. "The body starts perceiving excess amounts of energy as a foreign invader."

While working in Hotamisligil's lab, Kathryn Wellen, Ph.D. '06, identified a new group of molecules called STAMPs that help fat cells cope with the onslaught of energy. Mice without these molecules developed metabolic problems (high blood sugar and lipids, insulin resistance, fatty liver, abdominal fat accumulation) when fed a normal diet; the hope is to harness STAMPs' effects for use against the hazards of overeating in humans. Foods such as fruits and vegetables, herbs and spices, oily fish, and some nuts have natural anti-inflammatory properties, so a diet high in these foods also helps to mitigate this response.

Adipose tissue itself secretes pro-inflammatory molecules that are highly correlated with diabetes risk, independent of other factors. Professor of nutrition and epidemiology Frank B. Hu has found that obese people with high levels of interleukin-6—a potent inflammatory cytokine secreted by fat tissue—are more likely to develop diabetes than those with lower levels. On the other hand, people with high levels of adiponectin, an anti-inflammatory hormone also secreted by fat, enjoy a strong protective effect: people in the highest quintile for circulating adiponectin have a 90 percent reduced risk of getting diabetes. This effect held true in lean and obese subjects, whether active or sedentary, across all age groups. Because circulating levels of these substances are determined in part by genes, such findings help explain why some people are very resistant to developing diabetes, despite having multiple risk factors.

Particularly in obese individuals, adipose tissue contains clusters of macrophages, the immune-system cells that destroy and then digest invading pathogens. There are two types of macrophages: one that attacks viciously and kills alien microbes, and another that swoops in to repair the damage afterward, bringing about healing and tissue repair. The latter type is more plentiful in the fat tissue of lean people; obese people tend to have more

>Genetic Protections

Diabetes does not have a simple, single genetic basis in the Mendelian sense (tall plants or short, blue eyes or brown, diabetic or not). Rather, it is a complex, *polygenic* disease. That is to say, in almost everybody who develops diabetes, several genes act together, with input from environmental factors, to bring it about.

New tools are enabling the systematic study of the genes that underlie the disease, and producing surprising findings. Comparing the genomes of people with and without diabetes, scientists at the Harvard-affiliated Massachusetts General Hospital and the Broad Institute of Harvard and MIT have identified 17 specific genetic variants associated with type 2 diabetes, says professor of genetics and of medicine David M. Altshuler, an endocrinologist and human geneticist who heads the Broad's program in medical and population genetics. Before conducting the analysis, researchers at the Broad and other prominent programs that study the disease made a list of more than 500 "suspect" parts of the genome where they expected to find a correlation with diabetes based on earlier research. Not a single one came back positive. "What this tells me," says Altshuler, "is there's a lot of the biology of the disease that we don't yet understand."

The fact that type 2 diabetes has a far stronger genetic concordance in identical twins than type 1 does is not widely recognized. Someone whose twin has type 1 diabetes has a 30 percent chance of developing it himself; for someone whose twin has type 2 diabetes, the probability is "upwards of 80 percent," says Altshuler.

He hopes genetic analysis will ultimately lead to therapies. It has already yielded intriguing hints about how the disease might work. Of the 17 diabetes "hot spots" identified, 11 were associated with decreases in insulin secretion—and not one was associated with insulin resistance. Type 2 diabetics have both insulin resistance and impaired insulin secretion; this finding implies that the latter plays a stronger role than the former in the progression to disease. In other words, the people who get diabetes are those whose beta cells cannot compensate by pumping out immense doses of insulin to compensate for insulin resistance—and individual genetic makeup strongly influences the body's capacity to generate more insulin. This, too, indicates a closer similarity between type 1 and type 2 diabetes than previously recognized, since type 1 diabetes is characterized by complete breakdown of insulin production when pancreatic beta cells are destroyed.

Another group of researchers is looking beyond the genome to epigenetics: changes in the expression of genes independent of changes in the underlying DNA. Changes in the way DNA is packaged encourage or discourage gene expression, and here the intrauterine environment has powerful influence. Assistant professor of medicine Mary-Elizabeth Patti studies low-birthweight mice as a way to understand the strong correlation between low birthweight and obesity later in life, in both humans and mice. Patti was surprised to find that the *offspring* of the low-birthweight mice—that is, the grandchildren of the mice that were underfed during pregnancy—were also predisposed to diabetes, even though nutrition during their gestation, and their entire lifetime, had been normal.

Although this study brought about low birthweight through gestational caloric restriction, low birthweight can result when the mother's health suffers in other ways—including hypertension and diabetes. So Patti's findings mean that the current epidemic of metabolic disease could result, at least in part, from our grandparents' life experiences. More unsettling is the potential impact on future generations.

But Patti's research has yielded one bit of happy news. Restricting food intake for the low-birthweight mice, so that they eat no more than the baby mice whose weight at birth was normal, keeps the former from gaining weight as rapidly—and from becoming obese and diabetic later in life. "There is a period of plasticity when the organism is still sensitive to manipulation," says Patti. "That's the key point." This research may have revealed a strategy for breaking this metabolic vicious cycle. But, she says, "We clearly need to test this in humans."