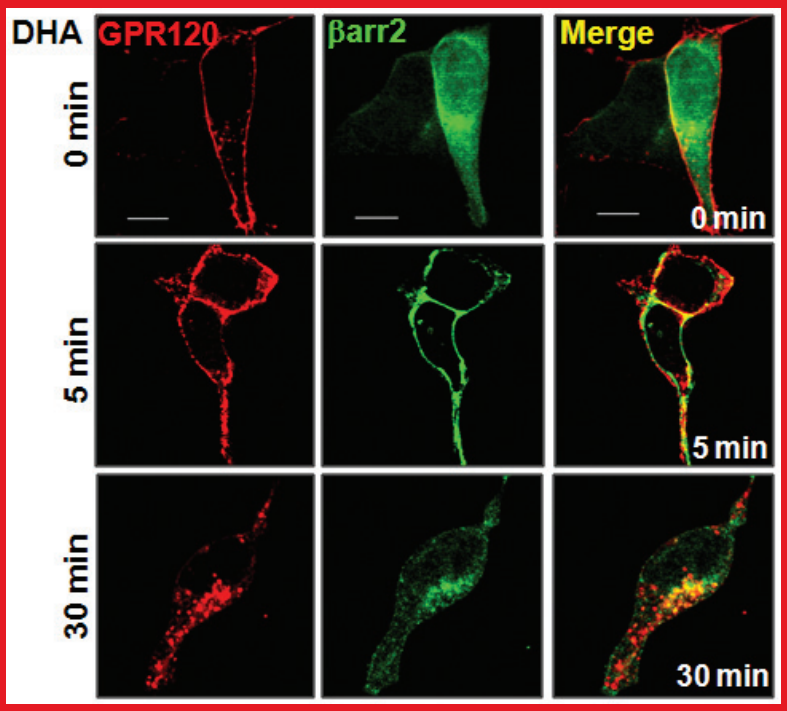

Researchers have visualized the first steps in how fish oil exerts anti-inflammatory effects. This image shows how two cellular proteins, GPR120 (stained red) and beta-arrestin-2 (stained green), interact following exposure to DHA, an omega-3 fatty acid found in fish oil. When the two proteins are in the same place, a yellow signal results ("merge" column). Before DHA treatment, the two proteins are separate—GPR120 is at the cell surface, as shown by the red outline around the cell in the top row, while beta-arrestin-2 is inside the cell, seen as green within this cell. The addition of DHA causes beta-arrestin-2 to move to the cell surface, where GPR120 resides, observed as red, green, and yellow outlines of the cells in the middle row. Later, both proteins move together into the cell's interior, as observed by the red, green, and yellow throughout the cell in the bottom row. As described in an advance in this chapter, this apparent interaction between GPR120 and beta-arrestin-2 following DHA treatment is suspected to block the production of inflammatory molecules that promote insulin resistance in obesity. This research provides important insights into how omega-3 fatty acids may exert their anti-inflammatory effects and could potentially pave the way to new therapeutic options to treat inflammation and insulin resistance.

Images provided by Dr. Jerrold M. Olefsky and reprinted from Cell, 142, Oh DY, Talukdar S, Bae EJ, Imamura T, Morinaga H, Fan W, Li P, Lu WJ, Watkins SM, and Olefsky JM, GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects, 687-698, copyright 2010, with permission from Elsevier.

Obesity

Obesity has risen to epidemic levels in the U.S. Individuals who are obese may suffer devastating health problems, face reduced life expectancy, and experience stigma and discrimination. Obesity is a strong risk factor for type 2 diabetes, fatty liver disease, and many other diseases and disorders within NIDDK's mission.

Approximately one-third of U.S. adults are considered obese based on body mass index (BMI), a measure of weight relative to height.[1,2] Nearly 17 percent of children and teens ages 2 through 19 are also obese, and thus at increased risk for developing serious diseases both during their youth and later in adulthood.[3] Obesity disproportionately affects people from certain racial and ethnic groups and those who are socio-economically disadvantaged.

The high prevalence of obesity in the U.S. is thought to result from the interaction of genetic susceptibility with behaviors and factors in the environment that promote increased caloric intake and sedentary lifestyles. Research is providing the foundation for actions to address this major public health problem by illuminating the causes and consequences of obesity, evaluating potential prevention and treatment strategies, and providing an evidence base to inform policy decisions. The NIDDK supports a multi-dimensional research portfolio on obesity, spanning basic, clinical, and translational research. NIDDK-funded studies of a variety of approaches for preventing and treating obesity include behavioral and environmental approaches in families, schools, and other community settings; medical interventions; and combinations of these strategies. In parallel, Institute-supported investigations into the biologic processes associated with body weight will spark new ideas for intervention approaches. To help bring research results to health care providers and the public, the Institute also sponsors education and information programs.

The NIDDK also continues to play a leading role in the NIH Obesity Research Task Force. The NIDDK Director co-chairs the Task Force along with the Directors of the National Heart, Lung, and Blood Institute, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The Task Force includes representatives from these and numerous other NIH Institutes, Centers, and Offices. Recently, the Task Force developed an updated *Strategic Plan for NIH Obesity Research*, with extensive external input from researchers across the country, professional and other health-focused organizations, and others. The new *Strategic Plan* will reflect the exciting opportunities that have emerged from research progress in the years since NIH developed its first *Strategic Plan* on this major public health challenge. The *Strategic Plan* will be published in early 2011 and will be available on the NIH Web site.

Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter. These represent examples of NIDDK's broad spectrum of research efforts toward reducing the burden of obesity so that people can look forward to healthier lives.

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[1] Statistics Related to Overweight and Obesity. http://win.niddk.nih.gov/statistics/index.htm

[2] Flegal KM, et al: JAMA 303: 235-241, 2010.

[3] Ogden CL, et al: JAMA 303: 242-249, 2010. For children and adolescents, obesity refers to a BMI at or greater than the 95th percentile on growth charts (which are based on previous national surveys).

RISK FACTORS FOR PREMATURE DEATH

Obesity and Related Conditions in Childhood Predict Premature Death: A new study has found that obesity, glucose intolerance, and elevated blood pressure during childhood and adolescence are associated with increased rates of early death. Adult obesity is known to be associated with cardiovascular disease, type 2 diabetes, and premature mortality, but similar relationships with pediatric overweight and obesity have not been clearly shown. By identifying risk factors in adolescence, researchers and clinicians can more effectively prevent and manage chronic diseases before they become more problematic later in life. In this decades-long study, researchers monitored the health of Pima and Tohono O'odham Indians from the Gila River Indian Community in Arizona, a population with the highest known prevalence of type 2 diabetes in the world.

The study participants included almost 5,000 non-diabetic American Indian children and youth. The researchers monitored their health through adulthood, and found several risk factors in children that were associated with risk for early death—before the age of 55—from a variety of causes (not including external causes such as accidents). The 25 percent of participants in the study who had the highest body mass indices (BMI, a measure of weight relative to height) during childhood or adolescence were more than twice as likely to die early than the 25 percent with the lowest BMIs. Similarly, based on results from glucose tolerance testing, the quarter of the group with the highest blood glucose levels early in life, reflecting underlying insulin resistance, were 73 percent more likely to die prematurely than were those with the lowest blood glucose levels. Hypertension was also a pediatric risk factor—the premature death rate among participants with elevated blood pressure was found to be 57 percent higher than those with lower blood pressure. In contrast, cholesterol levels in this group were not linked to extra risk for premature death. Although this study focused on an American Indian population, the rate of obesity in many other ethnic and racial groups has risen dramatically in the past 3 decades. Thus, further study will be important to determine whether youth of other backgrounds are similarly endangered by high BMI, insulin resistance, or high blood pressure. The high prevalence of childhood obesity is of great public health concern, and these findings further underscore the need to prevent and treat obesity early in life.

Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, and Looker HC. Childhood obesity, other cardiovascular risk factors, and premature death. N Engl J Med 362: 485-493, 2010.

REGULATORS OF METABOLISM IN THE BRAIN

Exploring How the Brain Controls Energy-Burning Fat: Scientists have discovered that the activity of brown adipose tissue (BAT), a form of fat that burns calories to generate heat, decreases in adult animals that had been administered monosodium glutamate (MSG) as newborns. Unlike "white fat" which stores fats as an energy reserve, BAT actually uses calories to generate heat that keeps animals warm. Recently, much attention has been given to how the central nervous system is able to control the body's metabolism, and the link between the brain and fat tissue function. In particular, a part of the brain called the arcuate nucleus (Arc) is thought to be important in regulating appetite and influencing calorie burning (energy expenditure) to fuel activity and generate body heat. Previous studies in mice demonstrated that lesions in the Arc produced by neonatal administration of MSG resulted in obesity and decreased BAT activity. However, the precise reasons for why damage to the Arc results in effects on BAT function remain unclear.

Researchers performed a series of experiments in Siberian hamsters to further explore the connection between impaired BAT heat production and Arc damage from MSG exposure, as a way to increase understanding of the regulation of this fat-burning tissue. At 3 months of age, hamsters that were treated with MSG injections as newborns had significantly increased body mass compared to ones that were never given MSG treatment ("control" animals). Additionally, the MSG-exposed hamsters had increased white fat mass compared to the controls. To measure BAT function, both the MSG-treated and control hamsters were exposed to the cold, and the temperature of their BAT was directly measured. Initially, the BAT in both groups of hamsters was able to produce similar temperatures, but the MSG-treated

hamsters were unable to maintain BAT temperature after 2 hours. By 18 hours, the BAT temperature in the MSG-treated animals had decreased significantly compared to the control animals. The inability of the BAT to generate heat in MSG-treated hamsters was not due to an intrinsic defect in the tissue itself since it was able to maintain a constant temperature in a manner similar to the controls when stimulated by a hormone (rather than by cold exposure). The researchers therefore examined the animals' brains to find factors that could possibly account for the disrupted BAT function. Similar to previous studies, neonatal MSG exposure resulted in profound destruction in certain regions of the Arc. Surprisingly, the remaining Arc neurons in the MSG-treated animals appeared intact and similar to the control animals. Additionally, other parts of the brain believed to influence BAT function were also unaffected by MSG treatment. These results indicate that the impaired BAT function is apparently not due to MSG-induced central nervous system damage, but does seem to be caused by a factor that is extrinsic to the BAT. Further research to increase understanding of the factors influencing BAT energy expenditure may help the development of new ways of regulating metabolism, controlling body weight, and combating obesity.

Leitner C and Bartness TJ. Acute brown adipose tissue temperature response to cold in monosodium glutamate-treated Siberian hamsters. Brain Res 1292: 38-51, 2009.

Role for Brain in Cholesterol Regulation: A new study in rodent models suggests that the brain plays a role in regulating cholesterol levels in the blood. Essential for cellular function and activities, cholesterol consumed in the diet or synthesized by the liver circulates throughout the body in special complexes with proteins, referred to as HDL (good) cholesterol and LDL (bad) cholesterol. While it is not fully understood how cholesterol levels are regulated, it is well known that too much LDL cholesterol raises risk for atherosclerosis and cardiovascular disease, whereas increased levels of HDL cholesterol have the opposite effect. Research has shown that many metabolic activities are regulated centrally by a part of the brain, called the hypothalamus, in response to molecular cues received from the gut, pancreas, fat, and other tissues. In this study, researchers asked whether the melanocortin system—a neural circuit in the hypothalamus that is key to regulating body fat, blood pressure, and glucose metabolism—might also regulate cholesterol levels. Two gut hormones, ghrelin and GLP-1, have opposite effects on this neural circuit. Ghrelin inhibits the melanocortin system, increasing appetite and food intake, while GLP-1, a "satiety hormone," stimulates it, reducing food intake and promoting energy expenditure (calorie burning). Through a series of experiments in rodents, the researchers discovered that administering ghrelin or a similarly acting compound into the brain caused total cholesterol levels to rise, while injecting GLP-1 caused them to fall. Further, mice genetically engineered to lack a key component of the melanocortin system also had higher cholesterol levels than their normal counterparts. Intriguingly, the study results indicate that the majority of the increase in total cholesterol caused by blocking the melanocortin system was due to reduced reuptake of HDL cholesterol by liver cells—the body's method for clearing and recycling cholesterol. While the relevance of these results from rodents to regulation of cholesterol in humans has yet to be determined, the study has uncovered yet another possible role for the brain in regulating metabolic activities.

Perez-Tilve D, Hofmann SM, Basford J, et al. Melanocortin signaling in the CNS directly regulates circulating cholesterol. Nat Neurosci 13: 877-882, 2010.

Wiring of Nerve Cell Connections in the Brain Could Affect Obesity: A new research study that was conducted in rodents indicates that resistance to obesity may be conferred by sets of brain cell connections. While a majority of people are susceptible to obesity, a fraction of the population appears resistant to weight gain. The molecular basis for this disparity is not understood. In this report, scientists studied rats and mice to gain greater insight into the role that neuron (nerve cell) wiring in the brain plays in obesity. A series of brain circuits called the central melanocortin system is thought to play a key role in regulating the body's ability to feel hunger or satiety and respond accordingly.

To explore this idea, researchers took advantage of a well-studied laboratory rat population that can be divided into two groups that respond differently to a high-fat diet. The "DIO" rat group fed a high-fat diet is vulnerable to diet-induced obesity, whereas

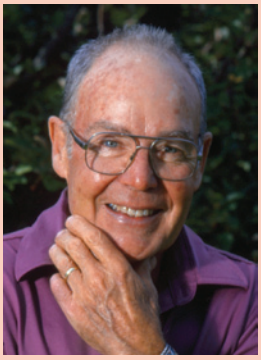
the "DR" rat group is resistant. When the two groups were shifted from a standard diet to a high-fat diet, the DIO rats gained significantly more weight than did the DR rats. The scientists discovered several differences between the brains of obesity-prone and obesity-resistant rats. For example, feeding the rats a high-fat diet affected the number of connections on certain brain cells, called POMC neurons. These neurons are part of the melanocortin system, which is located in the hypothalamus area of the brain, and respond to hormonal signals. In the DIO rats, POMC connections were lost. In contrast, the DR rats' POMC connections increased. The researchers also examined another aspect of neurons in the animals. Typically, neurons are wrapped by cells called astrocytes, which provide protection, support, and a physical environment necessary for proper brain function. These cells are also thought to contribute to the blood-brain barrier, which helps to restrict microorganisms and certain chemicals from entering the brain. The scientists discovered that when the rats were fed a high-fat diet, a greater number of astrocytes were associated with POMC neurons of DIO rats compared with DR rats. The scientists theorized that this increase in the number of astrocytes, a process called gliosis, may limit the ability of satiety hormones to regulate POMC neurons in DIO rats by preventing the development of new neuronal connections, leading to poorly controlled feeding behavior. The scientists also conducted "standard diet" versus "high-fat diet" experiments in mice. Like the rats, two groups of mice that responded differently to a high-fat diet exhibited the same correlation of increased gliosis with weight gain.

Researchers have shown in this study that diet-induced weight gain in rats and mice that are vulnerable to obesity is related to the gliosis of POMC neurons that are located in the hypothalamus. A possible cause of weight gain is that gliosis insulates these neurons from hormonal signals that communicate satiety. If this relationship is also found in people, it would indicate that altered brain wiring connections that are caused by gliosis in response to dietary shifts may play a role in human obesity.

Horvath TL, Sarman B, García-Cáceres C, et al. Synaptic input organization of the melanocortin system predicts diet-induced hypothalamic reactive gliosis and obesity. Proc Natl Acad Sci USA 107: 14875-14880, 2010.

2010 ALBERT LASKER BASIC MEDICAL RESEARCH AWARD

The Discovery of Leptin




Drs. Douglas Coleman (left) and Jeffrey Friedman
Photos courtesy of The Lasker Foundation

Drs. Douglas L. Coleman (Jackson Laboratory) and Jeffrey M. Friedman (Rockefeller University) received the 2010 Albert Lasker Basic Medical Research Award for their discovery of leptin, a hormone that regulates appetite and body weight. This discovery ignited an explosion of research into the molecular circuitry that controls food intake, metabolism, and body weight, and spotlighted the role of adipose (fat) tissue in regulating metabolism. It changed perceptions about the causes of obesity.

In the 1960s and 1970s, Dr. Coleman—a former long-time NIDDK grantee—studied two different types of mice that shared the characteristic of being strikingly obese. These mice had defects in what was referred to as the *diabetes* (*db*) gene or in the *obese* (*ob*) gene, which are separate genes on separate chromosomes. At that time, however, he did not have the genes in hand—the technology for such a feat was still decades away. Based on previous research, Dr. Coleman reasoned that the genetic defects in these mice altered a blood-borne satiety factor that contributed to the severity of obesity and diabetes.

To test this hypothesis, Dr. Coleman conducted experiments with different mice to see whether blood from one mouse might affect the appetite or weight of another. These experiments showed that the blood of mice with the *ob* defect did not have this proposed satiety factor, a result suggesting that the mice were obese because they didn't produce this factor. By contrast, the experiments showed that mice with the *db* defect made too much of the proposed satiety factor, but were nonetheless obese because they could not respond to it. These results, however, faced skepticism from the scientific community because at that time, obesity was considered to be simply a behavioral, not a physiological, problem.

It was not until 2 decades later that Dr. Coleman's proposed satiety factor was identified, and it was determined that obesity can have a physiologic basis. In 1994, with support from NIDDK, Dr. Friedman and his colleagues were the first research team to identify the *ob* gene in mice and in humans. They found that this gene encoded a protein hormone—the factor that Dr. Coleman had earlier inferred must exist. Dr. Friedman called this hormone "leptin," after the Greek word for "thin." Subsequently, researchers also showed that the *db* gene made a protein that interacts with leptin, called the leptin receptor, which is essential for leptin to have its effects. Even more importantly, Dr. Friedman's research showed that leptin was made by adipose tissue and signaled to the brain, where the receptor was located, to regulate appetite and energy expenditure. In rare cases, people suffering from extreme obesity may have a genetic defect that causes them to not make enough leptin to properly regulate their food intake. Researchers have shown that injections of leptin can dramatically reduce appetite and promote weight loss in these individuals.

The discovery of leptin by Drs. Coleman and Friedman dramatically altered the landscape of obesity research. This discovery revealed that adipose tissue more than passively stores fat; it is, in fact, an endocrine organ. Research fueled by this discovery has uncovered a number of other substances that, like leptin, are secreted by fat cells and converge in the brain to control food intake and body weight. In addition, this discovery changed the prevailing view that obesity was a behavioral problem involving solely a lack of willpower. On the contrary, the discovery of leptin highlighted the previously unappreciated molecular component of obesity. As a result, obesity is now addressed as a multi-faceted problem involving a myriad of genetic, molecular, environmental, and behavioral factors that regulate appetite, metabolism, and body weight.

IMMUNE CELL REGULATOR OF WEIGHT LOSS AND INSULIN SENSITIVITY

Signaling Protein Provides New Clues about the Benefits of Omega-3 Fatty Acids: A new study has uncovered a mechanism for the anti-inflammatory effects of omega-3 fatty acids, and shown that they can also enhance insulin sensitivity in mice. Chronic inflammation in fat tissue contributes to the development of insulin resistance seen in obesity. Omega-3 fatty acids, found in fish oil and other foods, reduce inflammation, but the mechanisms by which they exert this effect are not well understood.

Researchers examined the possible role of a signaling protein found in large numbers at the surface of macrophages—cells of the immune system that promote inflammation—and mature fat cells. Through experiments in mouse macrophages, they discovered that cells with the protein, called GPR120, could resist becoming pro-inflammatory if treated with the omega-3 fatty acid, docosahexaenoic acid (DHA). However, when they experimentally reduced the amount of GPR120 produced by the macrophages, the cells no longer responded to the DHA treatment—indicating that GPR120 is important for mediating the anti-inflammatory effects of this omega-3 fatty acid. Other experiments yielded clues as to how GPR120 reduces inflammation, suggesting that DHA treatment mobilizes a third molecule (beta-arrestin-2) to interact with GPR120 and subsequently block the cell's production of inflammatory molecules—including those that can promote insulin resistance. In mouse fat cells, DHA treatment also had the salutary effect of enhancing sensitivity to insulin action in a GPR120-dependent fashion. Having thus far examined isolated mouse cells, the scientists next investigated the impact of GPR120 on inflammation and insulin sensitivity in living animals. To do this, they genetically engineered mice to lack the GPR120 protein and compared these mice to their normal counterparts. Not only were the mice lacking GPR120 innately more insulin resistant, but when both sets of mice were switched to a diet enriched with omega-3 fatty acids after nearly 4 months on a "regular" high-fat diet, mice lacking GPR120 showed no improvement, while the normal mice showed metabolic improvement and decreased inflammation. This experiment confirmed that GPR120 was critical for the anti-inflammatory effect of omega-3 fatty acids in mice, as had been shown in isolated mouse cells. These results provide important insights into how omega-3 fatty acids may exert their anti-inflammatory effects and could potentially pave the way to new therapeutic options to treat inflammation and insulin resistance.

Oh DY, Talukdar S, Bae EJ, et al. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. Cell 142: 687-698, 2010.

GUT MICROBES, ADIPOSITY, AND OBESITY

Intestinal Bacteria May Contribute to Developing Obesity and Diabetes: Scientists recently discovered that intestinal bacteria may have an important role in the development of metabolic syndrome, diabetes, and obesity. Metabolic syndrome is a constellation of disorders that increases the risk of developing diabetes and cardiovascular disease. Hallmarks include elevated blood glucose (sugar), insulin resistance, abnormal blood cholesterol, high blood pressure, fatty liver disease, and obesity—particularly excess abdominal fat. Bacteria that inhabit the digestive tract appear to influence metabolism by affecting the ability to extract energy from food. Furthermore, certain types of intestinal bacteria may play a role in developing obesity, type 2 diabetes, and other aspects of metabolic syndrome. The types of bacteria populating the gut may be determined in part by a protein called Toll-like receptor (TLR) 5. This protein is produced in abundance by cells in the intestinal lining, is important for recognizing microbes, and is part of the innate immune system that can respond to infectious bacteria. Mice lacking TLR5 develop intestinal infections and gain weight, leading scientists to believe that the protein may also influence metabolism, potentially by altering normal gut bacteria.

To further explore the role of intestinal bacteria and TLR5 in developing metabolic syndrome, scientists generated mice that do not produce TLR5 protein. These animals weighed about 20 percent more than normal mice by 20 weeks of age, consumed about 10 percent more food, and produced more body fat compared to their normal counterparts.

The TLR5-deficient mice also developed elevated cholesterol levels, increased blood pressure, and insulin resistance. When fed a high-fat diet for 8 weeks, both normal and TLR5-deficient mice gained weight, but unlike normal mice, TLR5-deficient animals developed type 2 diabetes and fatty livers. One possible explanation was that TLR5-deficient mice ate a greater quantity of high-fat food. When scientists restricted the amount of high-fat food so that TLR5-deficient mice and normal mice ate the same quantity, the TLR5-deficient animals did not become obese, but were insulin resistant. The investigators thought that the metabolic differences observed between the two strains of mice were due to changes in intestinal bacterial populations resulting from the loss of TLR5. Thus, the researchers compared the gut bacteria between the normal and TLR5-deficient mice and uncovered differences in levels of over 100 types of bacteria. To assess whether the changes in bacteria might be causing the metabolic symptoms, the scientists collected intestinal bacteria from TLR5-deficient mice and transplanted these into "germ-free" mice raised in a bacteria-free environment. Similar to TLR5-deficient mice, the mice who received the transplanted bacteria increased their food consumption, developed insulin resistance, and became obese.

This study demonstrates that bacteria in the gut may contribute to changes in appetite and metabolism. Excess calorie consumption along with the resulting obesity and development of type 2 diabetes could possibly be driven, at least in part, by alterations in intestinal bacteria populations due to biological pathways involving TLR5. Understanding how gut bacteria interact with the intestine could provide a means of modulating eating behavior, as well as preventing metabolic syndrome.

Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science 328: 228-231, 2010.

NEW INSIGHTS INTO FAT

Identification of a Key Mediator of Fat Cell Development: Scientists used a novel quantitative method to identify molecular regulators needed to form cells with the potential to become fatty tissues in mice and thereby discovered a critical component of the developmental process that generates fatty (adipose) tissues. Significant progress has been made in uncovering the factors and mechanisms that control the process by which mature fat cells (adipocytes) develop from cells with the potential to become adipocytes (preadipocytes) in response to molecular cues. Little is known, however, about how cells become or are maintained as preadipocytes. To identify preadipocyte regulators, the researchers generated new mouse cell lines and evaluated their capacity to form adipocytes. Creation of cell lines with strong propensity to develop into fat cells, as well as lines with little such capacity, allowed the scientists to use a new quantitative molecular tool they developed to identify regulators present at different levels in these different types of cells. They reasoned that factors important for directing cells to be preadipocytes would likely be present at much greater levels in precursors of fat cells compared to precursors of other types of cells or mature fat cells. One factor in particular, called Zfp423, was chosen for further characterization. As one way to test its role in preadipocytes, the scientists engineered high levels of Zfp423 into cells that would not ordinarily have the capacity to become fat cells and looked to see what happened. They found that increased levels of Zfp423 were able to drive these cells to become adipocytes.

The scientists also tested Zfp423's importance with another approach. Using molecular biology techniques, the scientists decreased levels of Zfp423 in preadipocytes and observed that these cells had reduced ability to become adipocytes and had lower levels of other molecular markers characteristic of adipocytes. They demonstrated that Zfp423 is an important regulator of one of these molecular markers—the *PPAR-gamma* gene, itself another regulator of fat cell development. The researchers also found that Zfp423 plays a key role in production of both major forms of fat in mice (brown fat and white fat). Thus, this important study described a new tool for identifying molecular regulators of cell development and revealed the important role of Zfp423 to the preadiopocyte state. Understanding the formation and properties of fat can help inform strategies to prevent or reduce obesity.

Gupta RK, Arany Z, Seale P, et al. Transcriptional control of preadipocyte determination by Zfp423. Nature 464: 619-623, 2010.

Transitioning from an Early-Stage to Mature Fat Cell: New research has revealed the existence of a critical, transient intermediate state in the formation of fat cells from precursor cells having the potential to become fat cells. Previous research identified molecules involved in the formation of fat, but little was known about how this process is initiated once a precursor cell receives a signal to transition to a mature fat cell. This new study identified a chemical "signature" in the proteins associated with DNA that appears after mouse fat precursors are induced to become mature fat cells. By determining the location of this signature throughout the genome, the scientists were able to identify two proteins—CEBP-beta and the glucocorticoid receptor—that are important in initiating this transition state. These two proteins appear to work together to translate the signal and turn on genes important in the maturation of fat cells, including the master regulator of fat formation, PPAR-gamma protein. The identification of this transition state and the molecular components involved reveals new potential targets and strategies to combat obesity.

Steger DJ, Grant GR, Schupp M, et al. Propagation of adipogenic signals through an epigenomic transition state. Genes Dev 24: 1035-1044, 2010.

RESEARCH ON BARIATRIC SURGERY

Practice Might Not Make Perfect, But It Helps—Surgeons Who Perform More Bariatric Surgical Procedures Have Better Patient Outcomes: The Longitudinal Assessment of Bariatric Surgery (LABS)-1, a prospective observational study examining the 30-day adverse outcomes of bariatric surgery, has revealed that surgeons who perform bariatric surgery more frequently have significantly fewer patients who suffer from complications of this procedure. Obesity is a major public health concern that is associated with increased risk for type 2 diabetes, coronary heart disease, stroke, fatty liver disease, certain types of cancer, and other diseases. Bariatric surgical procedures modify the digestive tract to limit the amount of food that can enter the stomach, decrease absorption of nutrients, or both, and are used to treat extreme obesity. Bariatric surgery has consistently resulted in substantial and sustained weight loss for people with extreme obesity, and has been linked to remission of type 2 diabetes, decreases in cardiovascular risk factors, and reduced mortality over time. However, this operation is technically demanding, and patients undergoing the surgery are frequently at risk for serious complications, including death. One factor that can greatly influence complication rates is the experience of the surgeon performing the operation.

Researchers participating in LABS-1 examined the relationship between the surgeon's experience in performing a type of bariatric surgery called Roux-en-Y gastric bypass (RYGB) and the patients' short-term (30-day) outcomes. Thirty-one surgeons at 10 different centers who are a part of the LABS-1 collaborative participated in the study. From 3,410 initial bariatric surgical procedures performed during the study, the researchers analyzed outcome data with respect to whether the patients had any of several complications, including venous thrombosis, pulmonary embolism, reoperation, non-discharge at 30 days post-operation, repeat hospitalization within 30 days following initial discharge, or death. They also took into account health differences among the patients prior to surgery. After adjusting for individual patients' health characteristics, the investigators found that surgeons who had performed more bariatric surgeries were associated with lower rates of patients with postsurgical complications. The study concluded that for every 10 additional surgical procedures performed per year, the surgeons' rate of patient complications decreased by 10 percent.

These findings support the concept that the more experienced a surgeon is with bariatric surgical procedures, the lower is the risk of adverse post-operative outcomes. Bariatric surgery is an effective weight-loss procedure that is becoming increasingly popular as a treatment for extreme obesity. The safety of such surgery is a critical consideration, with risks examined in the context of long-term benefits. This study emphasizes that the experience of the surgeon performing the procedure can have a significant impact on patient outcome. This and other components of the LABS-1 study are building evidence about the risks and benefits of bariatric surgery, to help patients and health care providers make more informed decisions about undergoing this procedure.

Smith MD, Patterson E, Wahed AS, et al. Relationship between surgeon volume and adverse outcomes after RYGB in Longitudinal Assessment of Bariatric Surgery (LABS) study. Surg Obes Relat Dis 6: 118-125, 2010.