photons from a nonclassical source, as well as using weak laser pulses with an average occupation of much less than one photon.

These ideas can be generalized to two-photon interferometers (*3*, *4*), where there will be interference between sets of four optical paths. This case is illustrated with the two-photon interferometer in the right-hand panel of the figure (*3*), where a pair of entangled photons (ones that are nonclassically correlated) pass through two distant interferometers. The photons are known to be emitted at the same time, but that time is uncertain in the quantum-mechanical sense (a superposition state). If both photons are detected at the same time, they must have traveled the same distance because they were emitted simultaneously. Thus, there is a probability amplitude $\psi_{LA}\,\psi_{LB}$ that both photons took the longer paths and another probability amplitude $\psi_{SA}\,\psi_{SB}$ that both photons took the shorter paths.

The square of the sum of these probability amplitudes now involves interference between four optical paths, such as

$$\psi_{LA}^{*}\,\psi_{LB}^{*}\,\psi_{SA}\,\psi_{SB},$$

as illustrated once again by the red and yellow dots. The probability that photon A will be detected depends not only on the phase shifts in the interferometer that it passed through but also on the phase shifts in the distant interferometer. Any classical explanation of these results would require information to be transmitted faster than the speed of light c (*3*); indeed, a recent experiment showed that the information transfer would need to be four orders of magnitude faster than c (*5*). This situation does not violate special relativity because the photon detection outcomes cannot be controlled by an experimenter to send messages faster than c. Multiparticle interference of this kind only involves interference between pairs of more complicated probability amplitudes and could be tested in future experiments.

The development of a theory that combines quantum mechanics with general relativity is one of the major research goals of modern physics. If gravity can be quantized, it would be possible in principle to perform quantum interference experiments similar to those of the figure with gravitons instead of photons. The unification of these two fundamental theories is complicated by a number of factors, including the fact that summing up all of the possible probability amplitudes gives infinite results that are nonphysical—that is, mathematical singularities in the theory do not appear to be renormalizable to finite values. Small modifications to quantum mechanics may be necessary to achieve a consistent theory of quantum gravity, and experiments of this kind may be useful in setting limits on what modifications are allowed.

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10.1126/science.1192624

MEDICINE

Wnt Fans the Flames in Obesity

The balance between two factors released by mammalian fat cells controls the degree of inflammation and insulin sensitivity in adipose tissue.

Da Young Oh and Jerrold M. Olefsky

Obesity is linked to major adverse health outcomes such as insulin resistance and type 2 diabetes (*1*). The mechanisms underlying insulin resistance in this state are multiple and complex, including the recruitment of immune cells, particularly macrophages, to adipose tissue. This results in chronic, low grade inflammation that is causally associated with insulin resistance. With obesity, adipose tissue mass expands and adipocyte (fat cell) size increases. Collectively, adipocytes constitute the body's largest endocrine organ, producing an array of peptide hormones called adipokines (*2*). On page 454 of this issue, Ouchi *et al*. (*3*) report that a protein secreted by adipocytes acts as an anti-inflammatory adipokine, restraining the chronic inflammatory state and consequently improving insulin sensitivity.

Adipocytes respond to an increase in adipose tissue mass by secreting chemokines that attract monocytes (*4*, *5*). These then become activated proinflammatory adipose tissue macrophages that secrete cytokines which work locally through paracrine mechanisms to cause decreased sensitivity to insulin in nearby adipocytes (*6*). The macrophages also secrete chemokines that recruit further waves of monocytes into the adipose tissue, creating a feed-forward chronic proinflammatory state. The general outline of this scenario is well recognized, but the mechanisms underlying this multistep process are not completely understood.

Ouchi *et al*. now incorporate the function of the cellular Wnt signaling pathway in macrophages and adipocytes into this scenario. The Wnt proteins regulate cell proliferation, differentiation, and developmental processes in many organisms. They are a family of secreted glycoproteins that signal through a cell surface receptor called frizzled (Fz) to stimulate either a noncanonical or canonical signaling pathway (*7*) (see the figure). The canonical pathway stabilizes the cytoplasmic protein β-catenin, leading to increased transcription of target genes. The noncanonical pathway stimulates guanosine triphosphatases (RhoA and Rac1), leading to activation of the serine-threonine kinase c-Jun N-terminal kinase 1 (JNK1).

Ouchi *et al*. show that Wnt5a, which stimulates the noncanonical pathway, is expressed in mammalian adipose tissue. Its expression in mice was induced by a high fat diet and obesity. In mouse immune cells, Wnt5a activated JNK1, which triggered a proinflammatory response. In insulin target cells, such as adipocytes, activated JNK1 impairs the activity of a target protein called insulin receptor substrate–1 (IRS-1), leading to decreased insulin signaling and the development of insulin resistance (*8*). Using gene array analyses, Ouchi *et al*. found that expression of the secreted frizzled-related protein five (Sfrp5) is high in mouse adipocytes, but is decreased in various rodent models of obesity. Sfrp5 acts as a decoy receptor that binds and sequesters Wnt5a in the extracellular environment, thus preventing activation of Fz and attenuating noncanonical Wnt signaling. Therefore, the obesity-induced decrease in Sfrp5 production by adipocytes, along with increased Wnt5a expression, should lead to enhanced inflammatory signaling and insulin resistance,

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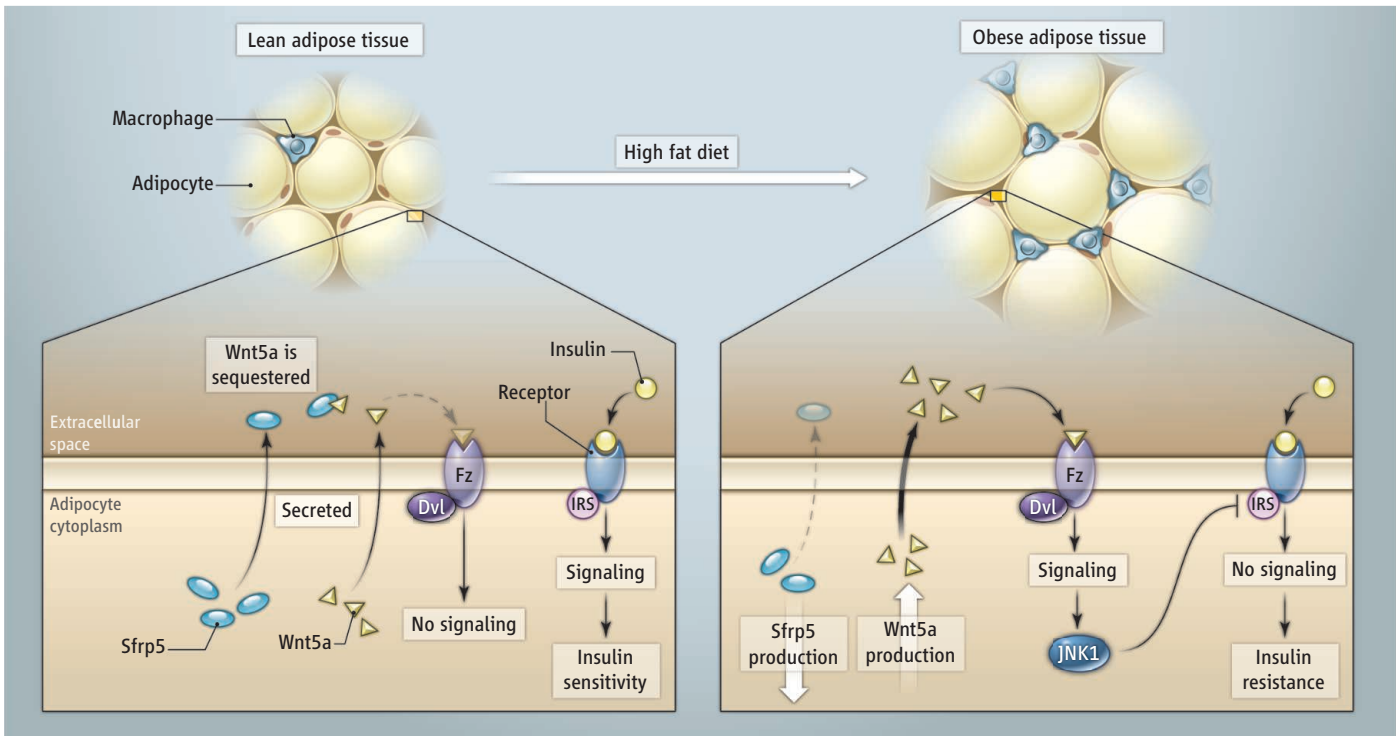

Adipocyte rheostat. Wnt5a stimulates the noncanonical Wnt signaling pathway in adipocytes by binding to frizzled (Fz), which stimulates a pathway that activates dishevelled (Dvl) and JNK1. Sfrp5 is secreted from adipocytes and sequesters Wnt5a, preventing pathway activation of this pathway. This allows adipocytes to respond to insulin. In the obese state, adipocytes enlarge and secrete more Wnt5a, but less Sfrp5. This allows activation of the noncanonical Wnt pathway, which blocks insulin signaling and causes insulin insensitivity. Macrophages present in obese adipose tissue also respond to Wnt5a and produce proinflammatory cytokines.

precisely the situation in obesity.

Ouchi *et al*. also observed that when put on a high fat diet, mice genetically engineered to lack Sfrp5 showed greater adipose tissue inflammation and insulin resistance due to unrestrained Wnt5a activity. By contrast, overexpression of Sfrp5 in adipocytes of these animals blocked Wnt5a activity and prevented the inflammatory, insulin resistant state. Likewise, systemic administration of Sfrp5 into animals lacking Sfrp5 improved the overall state of glucose intolerance and insulin sensitivity and diminished inflammation. Overall, these studies make a strong argument that the balance between Wnt5a and Sfrp5 expression serves as a rheostat to control the degree of noncanonical Wnt signaling in adipose tissue macrophages and adipocytes, which, in turn, modulates inflammation and the state of insulin sensitivity.

Ouchi *et al*. also probed the cellular mechanisms underlying these effects and determined that JNK1 is a control point for Wnt signaling input to inflammatory and metabolic events. When the authors treated mouse macrophages with a small molecule JNK1 inhibitor, the stimulatory effect of Wnt5a on proinflammatory cytokine release was blocked. Furthermore, a lack of JNK1 in the Sfrp5-null mice reversed the effect of Sfrp5 depletion to promote inflammation and insulin resistance.

The concept that noncanonical Wnt signaling promotes a proinflammatory state in adipose tissue adds a new layer to our understanding of obesity and raises several questions. Activation of the noncanonical Wnt pathway in various cell types has pleiotropic effects on many different biological processes, including cell adhesion, migration, actin cytoskeletal organization, lymphopoiesis, and inflammation. In adipose tissue of obese individuals, is the increased signaling by this pathway restricted to inflammation or does it link to these other processes as well? The insulin resistance of obesity and type 2 diabetes is systemic, involving liver and skeletal muscle, in addition to adipose tissue. One question is whether noncanonical Wnt signaling in muscle and/or liver could interact with the insulin signaling pathway in these tissues. Similarly, does systemic administration of Sfrp5 block noncanonical Wnt signaling directly in muscle and liver, or are its effects to improve insulin sensitivity in these tissues indirect?

Stepping back from the more detailed mechanisms, there are general questions that now arise from the observations of Ouchi *et al*. How do proinflammatory events in adipose tissue communicate with the other major insulin target tissues, muscle and liver, to establish a state of systemic insulin resistance? What is the teleologic purpose of immune cell invasion into adipose tissue during the course of obesity? This understanding will guide the development of therapeutics, which could include harnessing the insulin sensitizing effects of Sfrp5 to treat obesity-related insulin resistance. Such approaches are greatly needed as there is now an enormous health burden in the United States (*9*) and other countries brought about by the rising incidence of obesity, type 2 diabetes, and associated metabolic diseases.

References and Notes

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10. Supported by NIH grants DK033651, DK074868, and DK063491.

10.1126/science.1193404