JCI The Journal of Clinical Investigation

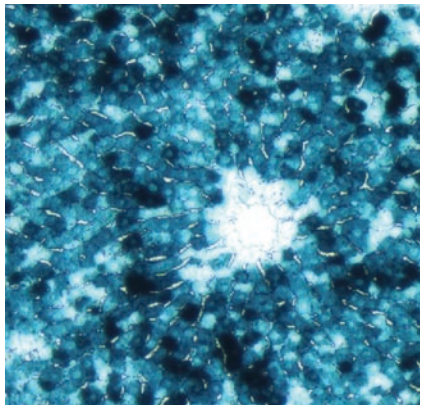
In This Issue

J Clin Invest. 2004;114(2):143-143. https://doi.org/10.1172/JCI120003.

In this issue

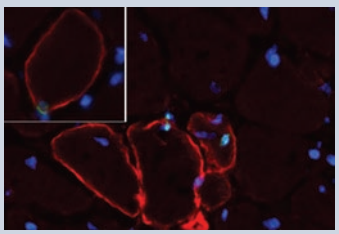
Resistin insulin all over the place Insulin acts on 3 primary target tissues — skeletal muscles, the liver, and fat — to regulate glucose metabolism. Recent evidence suggests that there is cross-talk between these tissues that coordinates overall response to insulin within the organism. The adipocytes release several hormones and cytokines, which appear to be involved in controlling this response. One of these adipose-derived proteins, resistin, is thought to play a role in this, affecting overall insulin response, but current understanding of its molecular mechanisms are limited. In this issue, two different research groups utilize different methodologies — one by increasing, the other by decreasing, resistin levels — to get at these mechanisms. Jerrold M. Olefsky and colleagues developed a hyper-resistemia rat model by injecting rats with an adenoviral vector that overexpressed mouse resistin (pages 224–231). These rats show glucose intolerance, hyperinsulinemia, and hypertriglyceridemia. Phosphorylation of insulin receptor substrates 1 and 2 and Akt activation were reduced in skeletal muscle and fat. Of note, AMP-activated protein kinase in all 3 target tissues was downreglated. Luciano Rossetti and colleagues use antisense oligonucleotide technology to decrease resistin levels in diet-induced insulin-resistant mice (pages 232–239). Mice fed a high-fat diet had an 80% increase in plasma resistin levels and showed severe liver insulin resistance, increased liver G6Pase expression and Akt and GSK3 phosphorylation, […]

Resistin insulin all over the place



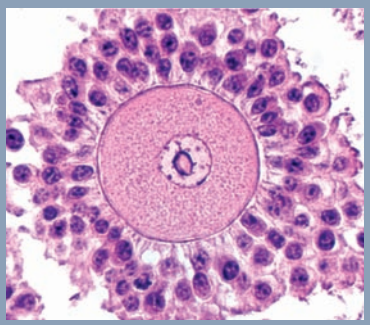
Insulin acts on 3 primary target tissues — skeletal muscles, the liver, and fat — to regulate glucose metabolism. Recent evidence suggests that there is cross-talk between these tissues that coordinates overall response to insulin within the organism. The adipocytes release several hormones and cytokines, which appear to be involved in controlling this response. One of these adipose-derived proteins, resistin, is thought to play a role in this, affecting overall insulin response, but current understanding of its molecular mechanisms are limited. In this issue, two different research groups utilize different methodologies — one by increasing, the other by decreasing, resistin levels — to get at these mechanisms. Jerrold M. Olefsky and colleagues developed a hyper-resistemia rat model by injecting rats with an adenoviral vector that overexpressed mouse resistin (pages 224–231). These rats show glucose intolerance, hyperinsulinemia, and hypertriglyceridemia. Phosphorylation of insulin receptor substrates 1 and 2 and Akt activation were reduced in skeletal muscle and fat. Of note, AMP-activated protein kinase in all 3 target tissues was downreglated. Luciano Rossetti and colleagues use antisense oligonucleotide technology to decrease resistin levels in diet-induced insulin-resistant mice (pages 232–239). Mice fed a high-fat diet had an 80% increase in plasma resistin levels and showed severe liver insulin resistance, increased liver *G6Pase* expression and Akt and GSK3 phosphorylation, and decreased liver AMP kinase phosphorylation. After treatment with a resistin-specific antisense oligonucleotide, plasma resistin levels normalized and liver insulin resistance was completely reversed, as were the effects on *G6Pase*, Akt, GSK3, and AMP kinase phosphorylation. Acute treatment with recombinant mouse resistin to previous high-fat diet plasma levels was sufficient to redevelop insulin resistance. The work by these two groups substantiates the important physiological role resistin plays in the development of insulin resistance and its potential involvement in diseases such as type 2 diabetes mellitus and syndrome X.

Stem cells get a workout



Muscular dystrophies are characterized by severe muscle damage, ultimately through the loss of the ability to regenerate muscle. Generating alternative sources for precursor cells to replenish muscle fibers offers a potential therapeutic strategy to treat myopathies. Having shown that a cellular marker called AC133 is required for myogenic cell differentiation, Yvan Torrente and colleagues now demonstrate that AC133-positive stem cells are a promising new source for muscle-replenishing satellite cells (pages 182–195). The authors isolated human circulating AC133-positive stem cells from normal blood, then cocultured them with mouse myoblasts or Wnt-expressing cells. The cells were subsequently injected into skeletal muscle tissue of dystrophic mice. The human stem cells colonized damaged muscle fibers, expressed muscle fiber markers, and formed functional myofibers that restored muscle function. The injected mice also experienced amelioration of the clinical symptoms of muscular dystrophy and a restoration of the satellite cell pool. This study provides new leads in the treatment of these debilitating muscle diseases.

Female infertility cAMP



In mammals, oocyte development is arrested until just before ovulation, at which point meiosis is completed. Meiotic maturation can be blocked by cAMP in vitro, but it is uncertain whether the molecular mechanisms involved here likewise occur in vivo. To investigate this process, Vincent Manganiello and colleagues created a cyclic nucleotide phosphodiesterase 3A (*Pde3a*) knockout mouse, because the breakdown of cAMP in oocytes is primarily carried out by PDE3A (pages 196–205). The female *Pde3a*$^{-/-}$ mice were both viable and carried out ovulation but were completely infertile. Male *Pde3a*$^{-/-}$ mice, on the other hand, were fertile. The authors showed that in the oocytes, there was virtually no cAMP-specific PDE activity; cAMP levels were higher; the oocytes were arrested in germinal vesicle stage; and meiotic maturation could be restored by inhibiting protein kinase A. The data here indicate that the meiotic blockade is in response to increased cAMP-PKA signaling pathways. Furthermore, the reversible nature of the *Pde3a*$^{-/-}$ phenotype suggests that PDE3A may be a viable contraceptive target. The *Pde3a*$^{-/-}$ mouse will be an excellent model of female infertility for exploring this further.