Leishmania susceptibility. "There's a major apparent discrepancy that needs to be resolved. I wouldn't care to decide on the basis of the published data," says Coffman.

Complicating matters even more, other teams, including Kopf's and that of Steven Reiner of the University of Chicago, have been studying resistance to *L. major* in IL-4 knockouts and, in as yet unpublished work, have come up with opposite results: The mice did become resistant. For most of these animals, there may be a good explanation. The knockouts were created in the 129 strain, which is naturally resistant to the parasite, then backcrossed with BALB/c mice up to 10 times to introduce the knocked-out gene into the BALB/c genome. The problem is that a lot of the genes flanking the IL-4 gene in the resistant mice may also end up in the BALB/c mice, and some of these might be responsible for their resistance, rather than the IL-4 knockout itself. Murphy's team, for example, has come up with an intriguing candidate: a gene acting in the pathway by which interferon γ signals are transmitted into the cell interior.

Still, one contradictory result is harder to explain away. Kopf has also conducted *L. major* infection experiments with the same knockouts made by Noben-Trauth and Ledermann and found that they are resistant. (These results have not yet been published since Köhler gave Noben-Trauth first rights to the *Leishmania* experiments.) The results of the two groups, he says, are "not easy to reconcile." He does suggest, however, that the explanation might lie in the different *L. major* strains the two groups used, and he is currently repeating the experiment with the same parasite strain used by Müller.

Until these issues are resolved, immunologists looking for the prime controller of *Leishmania* susceptibility won't know whether IL-4 is down for the count—or ready to spring to its feet again.

–Jean Marx

OBESITY RESEARCH

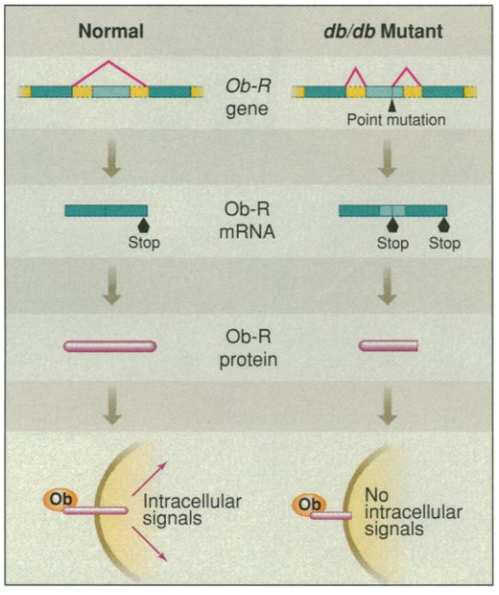
Researchers Nail Down Leptin Receptor

Nowhere has research been moving faster in the past year than in the study of obesity. Just over a year ago, Jeffrey Friedman's team at Rockefeller University cloned the *obese* gene (*ob*), which when mutated causes mice to become grossly fat, and showed that its protein product, leptin, is a key weight-control hormone. Last December, researchers at Millennium Pharmaceuticals, in Cambridge, Massachusetts, took another big step, cloning DNA that appeared to encode the receptor through which leptin exerts its effects. At the time, there was concern that they might not have the right receptor. But now, three groups have confirmed the identification by showing that the leptin receptor is the product of a gene called *db*, which has long been thought to encode the receptor for a weight-controlling hormone.

The findings—published by Louis Tartaglia's team at Millennium in the 9 February issue of *Cell*, by Friedman's group in the 15 February *Nature*, and by a team led by Rudolph Liebel, also of Rockefeller, on page 994 of this issue—prove this is the physiologically important receptor gene, says Bruce Spiegelman, an obesity researcher at Harvard Medical School. "With this new information in hand," he adds, researchers can move forward with confidence to "study how [leptin] signals through [this] receptor." And, as most pathologically obese humans seem to have defects not in *ob*, but in either leptin receptors or the signaling pathways triggered by the receptors, any new understanding of the receptors may aid in the design of new drugs for treating obesity.

When Tartaglia's team first cloned the DNAs encoding the leptin receptor in mice and humans, they had noted an anomaly that raised questions about whether they had the right receptor. Their clone from mice encoded a shorter form of the receptor than the human clone did. The receptor it coded for lacked the part that transmits leptin signals within the cell. They proposed that the short receptor might transport leptin across the blood-brain barrier, and speculated that mice must also make a long form that executes leptin's weight-controlling effects. But it was also possible that their gene simply did not code for the key receptor.

But the Tartaglia team had reason to doubt that was the case—evidence suggesting their receptor gene might be the *db* gene. Researchers had suspected that *db* might code for the leptin receptor, because Jackson Laboratory biochemist Douglas Coleman had shown 20 years ago that *db* mutant mice are fat because they can't respond to the weight-regulating product of the *ob* gene. So when Tartaglia's group mapped its receptor gene to the same genetic region as *db*, they were encouraged. That didn't prove their gene was *db*, however, because the large region they had mapped it to contains dozens of genes.



Cutting it short. The *db* mutation apparently produces a shortened, and probably nonfunctional, leptin receptor.

Now further evidence comes from Liebel's team, which reports additional mapping that seems to place the mouse receptor gene right on top of *db*. They also found that in rats the leptin receptor gene maps to that species' counterpart of *db*, known as *fatty*.

Meanwhile, studies carried out by Friedman's and Tartaglia's groups provided more proof. They've discovered abnormal mRNAs made from the receptor gene in *db* mutant mice that apparently code for a nonfunctional receptor. That is very good evidence that *db* is indeed the receptor gene.

The abnormal RNAs seem to be caused by a mutation that alters the way the noncoding introns are spliced out of the RNA produced by the receptor gene, so that the mRNA which should produce the long form of the receptor is interrupted by an abnormal insert. That extra piece of RNA contains a signal that prematurely stops production of the receptor protein, so that instead of the long form of the receptor, it makes a protein that looks more like the short form and probably lacks signaling ability.

As a result, the *db* mice apparently make none of the functional long form of the receptor, and that would explain why they get so fat. "It is nature's knockout," Tartaglia says. "If this had not turned out to be the case, we would have had to demonstrate the importance of our receptor ... by knocking it out and hoping we got a fat mouse."

But it is only one of several mutations that inactivate *db*. Liebel's team studied another mutant form of the gene, called db^{Pas}, and found that it apparently has a partial duplication, while the *fatty* mutation looks like a deletion. "We are hoping that by identifying the nature of these mutations we will get a better understanding of how the receptor actually works," says Liebel. And that will keep the obesity field moving at a fast pace for the months and years to come.

–Marcia Barinaga