hope has often been more hype than realization. The story of Marfan syndrome and mutations in the FBN1 gene illustrates that identifying a mutation is only the first step in understanding the molecular pathophysiology of the disorder and that the pathway to treatment may be both complex and full of insights into unexpected areas of biology (24, 25). Perhaps in a short time we may see the use of TGF-β blockade in preference to β-adrenergic blockade as a more effective treatment of many aspects of Marfan syndrome—and treatment is the ultimate goal of understanding this complex phenotype.

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Unbuckling lipodystrophy from insulin resistance and hypertension

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Lipodystrophy and insulin resistance are the core features of human PPARγ deficiency states. Metabolic complications in PPARγ deficiency, such as hypertension, have been considered to be secondary to insulin resistance. However, a new mouse model that expresses the analog of a human PPARγ mutation displays minimal lipodystrophy and insulin resistance but rather severe hypertension (see the related article beginning on page 240). Furthermore, the mutant protein appears to directly modulate the renin-angiotensin system in adipose tissue, providing evidence of the pleiotropic effects of PPARγ.

Nonstandard abbreviations used: angiotensin II (ATII); familial partial lipodystrophy type 3 (FPLD3); metabolic syndrome (MetS); renin-angiotensin system (RAS); type 2 diabetes mellitus (T2DM).

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The commonly occurring metabolic syndrome (MetS) is considered to result from complex gene-environment interactions and has been associated with future onset of type 2 diabetes mellitus (T2DM) (1) and both all-cause and cardiovascular mortality (2). MetS is defined clinically according to deviation from threshold values for three or more of five quantitative traits; namely, waist circumference, blood pressure, and plasma concentrations of glucose, high-density lipoprotein cholesterol, and triglyceride (3). Insulin resistance has long been considered the core biochemical defect linking these metabolic disturbances, which are strongly correlated among and within patients, suggesting the existence of common underlying molecular mechanisms. No molecule is more central to the metabolic and vascular pathways of MetS than PPARγ (4). The effect of altered activity of the PPARγ receptor on whole-body insulin sensitivity has been appreciated for years. For instance, in both mice and humans, activating PPARγ ligands has ben-
official effects on insulin sensitivity (5). But recent studies of rare patients with loss-of-function mutations in PPARγ and of mice in which Pparg has been manipulated have shown similarities and discrepancies, which underscore PPARγ’s physiological complexity and its pleiotropic effects.

Mutations in PPARγ cause human lipodystrophy
In humans, the relationship between PPARγ activity and insulin sensitivity appears to be relatively straightforward: increased PPARγ activity via activating ligands leads to increased insulin sensitivity (5), while reduced receptor activity via germline loss-of-function mutations, such as P467L, leads to insulin resistance (6). Human PPARγ mutations are associated with the recently identified syndrome familial partial lipodystrophy type 3 (FPLD3, OMIM 604367), which is characterized by relative depletion of subcutaneous fat on extremities along with preservation of central and visceral fat stores. The experiments by Tsai, Maeda, et al. reported in this issue of the JCI (7) show that Ppargγ465L/+ mice − whose genotype is homologous to that of heterozygous PPARγP467L/+ patients − also have repartitioning of adipose stores, albeit in a somewhat different pattern compared with that associated with human FPLD3. These findings, together with previous reports (8–11), firmly establish PPARγ deficiency as a cause of lipodystrophy and confirm the key adipogenic role of PPARγ.

Disproportionate hypertension in Ppargγ465L/+ mice
The next question is whether lipodystrophy associated with PPARγ deficiency is mechanistically linked with insulin resistance and its complications, particularly hypertension. Among FPLD3 patients with mutant PPARγ, adipose tissue repartitioning had been proposed to explain, at least partially, insulin resistance and hypertension, largely through analogy with other lipodystrophies of different molecular etiologies, since insulin resistance is a prominent component of each of these (6). In lipodystrophies, reduced fat storage capacity has been thought to result in increased circulating fatty acids and ectopic triglyceride storage in such sites as skeletal muscle, leading to insulin resistance with consequent development of complications, including hypertension. However, Tsai et al. show that Ppargγ465L/+ mice did not develop significant insulin resistance (7), in contrast to the severe insulin resistance seen in human PPARγP467L heterozygotes (8). This disparity might be due to a species difference in which human PPARγ retains a more direct link with insulin resistance. Also, the greater relative loss of adipose tissue in human PPARγP467L heterozygotes compared with Ppargγ465L/+ mice suggests that adipose tissue loss might still contribute to insulin resistance in human PPARγ deficiency.

On closer inspection, however, the extent of lipodystrophy among patients with mutant PPARγ similarly seems insufficient to account fully for the severity of insulin resistance. In this regard, it is instructive to compare FPLD3 with another autosomal dominant form of partial lipodystrophy, namely FPLD2 (OMIM 151660), which results from mutations in LMNA encoding nuclear lamina A/C (6). Like patients with FPLD3, FPLD2 patients have site-specific adipose tissue loss, followed by insulin resistance with hypertension and dyslipidemia, which become even worse as patients age and develop T2DM (12). However, analysis of metabolic subphenotypes indicated that fat loss was more extensive among patients with mutant LMNA (FPLD2) than those with mutant PPARγ (FPLD3) (13). In contrast, insulin resistance and hypertension were more severe among patients with FPLD3 than those with FPLD2 (13). Thus, insulin resistance and hypertension in FPLD3 seemed to be disproportionate to the extent of lipodystrophy compared with FPLD2, which would be consistent with additional independent effects of mutant PPARγ (6, 13). The findings in the Ppargγ465L/+ mice further weaken the case for direct links among adipose redistribution, insulin resistance, and hypertension (Table 1). Could the mutation itself directly mediate hypertension?

PPARγ modulates the renin-angiotensin system
Tsai et al. (7) show that the PPARγ mutation independently affects other pathways, in particular the renin-angiotensin system (RAS). Both human PPARγP467L heterozygotes and Ppargγ465L/+ mice are hypertensive, despite the fact that the mice are minimally insulin resistant. The hypertension in the Ppargγ465L/+ mice is associated with increased expression of RAS components in various adipose depots, specifically angiotensinogen and the angiotensin II (ATII) receptor subtype 1 in inguinal and gonadal fat, respectively (7). This suggests that impaired adipogenesis might locally activate the RAS, with a potential paracrine role for ATII. Alternatively, mutant PPARγ might have other effects on vascular tone. In any event, the findings suggest a more direct role for PPARγ in blood pressure regulation, possibly through linkage with the RAS. Such a link could be one reason why blood pressure decreases with thiazolidinedione treatment (14) and also why hypertensive heterozygotes for the PPARγ loss-of-function mutation F388L respond well to angiotensin-converting enzyme inhibitors (10).

Thus, Tsai et al. have provided novel insights that advance our understanding of PPARγ physiology (7). In both humans and mice, heterozygous PPARγ mutations are associated with lipodystrophy, but in the mouse there is apparently an uncoupling between the adipose repartitioning and hypertension. Furthermore, the hypertension in the Ppargγ465L/+ mice might be functionally linked with RAS

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**Table 1**

<table>
<thead>
<tr>
<th>Species</th>
<th>Mutation</th>
<th>Extent of partial lipodystrophy</th>
<th>Insulin resistance</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human FPLD2 (LMNA)</td>
<td>Ppargγ465L/+</td>
<td>Pronounced fat loss on extremities and gluteal region</td>
<td>Moderate to severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Mouse FPLD3 (PPARG)</td>
<td>Ppargγ465L/+</td>
<td>Moderate fat loss on extremities</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Mouse Ppargγ465L/+</td>
<td>Mild fat redistribution</td>
<td>Minimal or absent</td>
<td>Severe</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Table 1: Comparison of selected phenotypes of human lipodystrophies FPLD2 and FPLD3 and the mouse Ppargγ465L/+.
activity in adipose tissue. The studies cannot resolve whether human PPARG mutations in FPLD3 might act in a dominant negative manner to interfere with function of the normal allele product or whether haploinsufficiency of PPARY activity is more important. Interestingly, simple haploinsufficiency of PPARY activity in mice by removal of one Pparg allele actually protects against insulin resistance (15), supporting the idea that missense mutations have distinct effects compared with simple reduction in PPARY. In any event, the findings of Tsai et al. reinforce the importance of PPARY in adipogenesis (4), highlight the role of adipose tissue as an endocrine organ (16), and also support the idea that PPARG mutations affect metabolic and vascular phenotypes through multiple mechanisms, some of which are distinct from effects on adipose tissue mass or distribution.

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Innate immunity dictates cytokine polarization relevant to the development of pulmonary fibrosis

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New data support the importance of the innate immune response in the resolution or progression of pulmonary fibrosis. The presence of CXCR chemokine receptor 3–expressing cells, specifically pulmonary NK cells, is necessary to produce IFN-γ. This is critical in the polarization of the immune response to injury toward a favorable Th1 response and resolution. In contrast, a Th2 response is associated with progressive fibrosis (see the related article beginning on page 291).

Pulmonary fibrosis is a host response to a variety of known and idiopathic processes and is clinically characterized by insidious onset of dyspnea and abnormal lung func-