Unbuckling lipodystrophy from insulin resistance and hypertension

Robert A. Hegele, Todd Leff


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 PPARG mutation displays minimal lipodystrophy and insulin resistance but rather severe hypertension. Furthermore, the mutant protein appears to directly modulate the renin-angiotensin system in adipose tissue, providing evidence of the pleiotropic effects of PPARγ.

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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.

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-

Nonstandard abbreviations used: angiotensin II (ATII); familial partial lipodystrophy type 3 (FPLD3); metabolic syndrome (MetS); renin-angiotensin system (RAS); type 2 diabetes mellitus (T2DM). Conflict of interest: The authors have declared that no conflict of interest exists. Citation for this article: J. Clin. Invest. 114:163-165 (2004). doi:10.1172/JCI20042382.

Unbuckling lipodystrophy from insulin resistance and hypertension

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eficial effects on insulin sensitivity (5). But recent studies of rare patients with loss-of-function mutations in PPAR γ 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, results in decreased receptor activity and reduces sensitivity (6). Human PPAR 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 Pparg P465L/+ mice did not develop a phenotype similar to the severe insulin resistance seen in human PPARγ P467L 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 PPARγ P467L heterozygotes compared with Pparg P465L/+ 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 lamin 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 the mouse 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 Pparg P465L/+ 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 PPARγ P467L heterozygotes and Pparg P465L/+ mice are hypertensive, despite the fact that the mice are minimally insulin resistant. The hypertension in the Pparg P465L/+ 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 PPAR 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 reparationing and hypertension. Furthermore, the hypertension in the Pparg P465L/+ mice might be functionally linked with RAS.

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<td>Comparison of selected phenotypes of human lipodystrophies FPLD2 and FPLD3 and the mouse Pparg P465L/+</td>
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activity in adipose tissue. The studies cannot resolve whether human PPARG mutations in PFLD3 might act in a dominant negative manner to interfere with function of the normal allele product or whether haploinsufficiency of PPARY activity is more interesting. 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 PPARY 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 CXC 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 function. The pathology of pulmonary fibrosis demonstrates features of dysregulated and abnormal repair with exaggerated vascular remodeling, fibroproliferation, and deposition of extracellular matrix, all leading to progressive fibrosis and loss of lung function. However, the most devastating form is idiopathic pulmonary fibrosis (IPF). IPF is a chronic and often fatal pulmonary disorder with a mortality rate as high as 70% five years after diagnosis (1, 2). The prevalence of IPF increases with age (2, 3). There has been an increase in the incidence of this disorder over the last 10–15 years in many Western countries, including the United Kingdom, New Zealand, and Germany (3). The inability of current immunosuppressive therapies to alter the prognosis of this disorder has renewed scientific interest in multiple areas and has raised additional questions as follows: (a) why are certain individuals susceptible to this disease? do genetic, environmental, or a combination of these factors contribute to the pathogenesis of this disorder? (b) why is the host response to injury to the alveolar capillary wall in susceptible individuals predominated by fibrosis and loss of alveolar architecture instead of resolution? and (c) what are the initial events within the host in response to injury that ultimately set the stage for polarization of the response toward either resolution or perpetuation of fibrosis?

Nonstandard abbreviations used: bronchoalveolar lavage (BAL); CXC chemokine receptor 3 (CXCR3); idiopathic pulmonary fibrosis (IPF); usual interstitial pneumonia (UIP).

Conflict of interest: The authors have declared that no conflict of interest exists.