PERSPECTIVE

Becoming fat

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Most people do not wish to become fat, for cosmetic as well as medical reasons. Despite this, there is an international epidemic of obesity fueled by sedentary lifestyles and high caloric consumption among people living in industrialized societies. Obesity is characterized by excess adipose tissue, and rational intervention requires an understanding of adipocyte genes, development, and function. The peroxisome proliferator activated receptor γ (PPAR γ), a member of the large family of nuclear hormone receptors, has received enormous attention as its role has emerged in the formation of adipose tissue, as well in the pathogenesis and treatment of diabetes, cardiovascular disease, and cancer (Kersten et al. 2000). In this issue of *Genes & Development*, Rosen et al. (2002) and Ren et al. (2002) provide answers to two fundamental questions regarding the role of PPAR γ in the making of a fat cell.

Shortly after its initial description as an orphan receptor related to PPAR α (Chen et al. 1993; Kliewer et al. 1994), PPAR γ was found to be particularly abundant in adipose tissue and induced during adipocyte differentiation (Chawla et al. 1994; Tontonoz et al. 1994a). PPAR γ has since been shown to be sufficient (Tontonoz et al. 1994b) as well as necessary (Barak et al. 1999; Rosen et al. 1999) for adipocyte differentiation. A variety of adipocyte genes are transcriptional targets of PPAR γ (Auwerx 1999). PPAR γ ligands, most notably the thiazolidinedione (TZD) class, ameliorate insulin resistance and represent exciting new therapies for type 2 diabetes. This effect of TZDs is likely to be multifactorial, including numerous effects on adipocyte gene expression that lead to altered secretion of adipocyte proteins and fatty acids (Olefsky and Saltiel 2000).

In addition to PPAR γ , the bZip-containing C/EBP transcription factors have established roles in adipogenesis (Loftus and Lane 1997). C/EBP β and C/EBP δ are transiently increased early in adipogenesis (Cao et al. 1991). When constitutively expressed, these factors are sufficient to induce adipocyte differentiation (Yeh et al. 1995), in part owing to induction of PPAR γ (Wu et al. 1995; Schwarz et al. 1997). C/EBP α is induced later. Like PPAR γ , expression of C/EBP α is sustained in the mature adipocytes (Fig. 1A; Birkenmeier et al. 1989; Christy et

al. 1989). C/EBP α has been shown to be critical for adipogenesis (Freytag et al. 1994; Lin and Lane 1994), and C/EBP α and PPAR γ positively regulate each other's expression (Shao and Lazar 1997; Hamm et al. 1999). However, previous studies have shown that PPAR γ can induce adipogenesis in the absence of C/EBP α (Fig. 1B; Hamm et al. 1999; Wu et al. 1999).

Until now it was unknown whether C/EBP α could induce adipogenesis in the absence of PPAR γ . This is the fundamental question addressed by Rosen et al. (2002), who mutated the PPAR γ gene in mouse embryonic stem cells, which were used to generate embryonic fibroblasts (MEFs) incapable of expressing PPAR γ . Normal MEFs can be induced to differentiate into adipocytes, and the PPAR γ null cells allowed Rosen and colleagues to spotlight the role of PPAR γ in the hierarchy of adipogenic transcription factors. Their study shows that ectopic expression of C/EBP α could not rescue the failure of PPAR γ null MEFs to differentiate into adipocytes (Fig. 1C). Therefore, rather than being an equal codirector of the adipocyte differentiation program, PPAR γ has a leading role in the adipogenic hierarchy. C/EBP α undoubtedly plays a supporting role in maintaining specific aspects of the adipocyte phenotype, including insulin sensitivity (Hamm et al. 1999; Wu et al. 1999) and lipid accumulation (Wang et al. 1995). The dominance of PPAR γ also sheds light on the mechanism of lipoatrophy in mice expressing a dominant-negative bZip polypeptide from an adipocyte-specific promoter (Moitra et al. 1998). In this setting, loss of function of all C/EBP proteins most likely interferes with adipocyte differentiation by blocking the induction of PPAR γ .

There are two main isoforms of PPAR γ : PPAR γ 1 and PPAR γ 2 (Fig. 2A). These are generated from a single gene by differential promoter usage. PPAR γ 1 protein is the translation product of *PPAR γ 1* and *PPAR γ 3* mRNAs, which differ only in their 5' untranslated regions (Fajas et al. 1998). A distinct mRNA encodes PPAR γ 2 (Tontonoz et al. 1994a). PPAR γ 2 contains an additional 31 amino acids at its amino terminus, after which it is completely identical to PPAR γ 1. The amino terminus of PPAR γ functions as a ligand-independent transcriptional activation domain (Adams et al. 1997). The activation function of the extended amino terminus of PPAR γ 2 is somewhat more potent than that of PPAR γ 1, and its activity is affected by insulin (Werman et al. 1997). An amino-terminal serine that is phosphorylated by MAP

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Figure 1. Role of $PPAR\gamma$ and $C/EBP\alpha$ in adipogenesis. (A) $PPAR\gamma$ and $C/EBP\alpha$ are both induced during normal adipogenesis. (B) Expression of $PPAR\gamma$ overcomes the absence of $C/EBP\alpha$. (C) Expression of $C/EBP\alpha$ fails to overcome the absence of $PPAR\gamma$. (TG) Fat stored as triglycerides.

kinase and negatively regulates $PPAR\gamma$ activity (residue 112 in mouse $PPAR\gamma 2$) is present in both $PPAR\gamma 1$ and $PPAR\gamma 2$ (Hu et al. 1996; Adams et al. 1997; Shao et al. 1998). Other properties of $PPAR\gamma 1$ and $PPAR\gamma 2$, including DNA binding, ligand binding, and interaction with coactivators, are mediated by identical domains and are also quite similar (Fig. 2A).

In addition to adipocytes, $PPAR\gamma$ is expressed in other cell types, most abundantly in macrophages and colonocytes. $PPAR\gamma 1$ is the isoform expressed in extra-adipose tissues, whereas $PPAR\gamma 2$ expression is adipocyte-specific. In macrophages, $PPAR\gamma$ ligands inhibit cytokine gene expression (Jiang et al. 1998; Ricote et al. 1998) and induce the expression of another nuclear receptor, LXR, that enhances the expression of ABC reverse cholesterol transporters (Repa et al. 2000; Chawla et al. 2001b; Chinetti et al. 2001). Together these effects are antiatherosclerotic, as empirically shown in rodents (Li et al. 2000)

and humans (Minamikawa et al. 1998). In colonocytes, activation of $PPAR\gamma$ has been suggested to increase proliferation in the *min* mouse model of intestinal neoplasia (Lefebvre et al. 1998; Saez et al. 1998) yet to be antiproliferative in other colon cancer models (Brockman et al. 1998; Sarraf et al. 1998). Ligands for $PPAR\gamma$ also have beneficial effects in inflammatory bowel disease (Su et al. 1999; Desreumaux et al. 2001). Although some of the anti-inflammatory effects of TZD ligands may be $PPAR\gamma$ -independent (Chawla et al. 2001a), $PPAR\gamma$ -dependent effects on nonadipose tissues are almost certainly mediated by $PPAR\gamma 1$ because that is the predominant isoform. In contrast, the relative importance of the two $PPAR\gamma$ isoforms for adipogenesis has remained an open question because $PPAR\gamma 1$ and $PPAR\gamma 2$ are expressed at comparable levels in adipocytes.

Ren and coworkers (2002) have elegantly addressed this question. First, $PPAR\gamma$ expression was eliminated in

Figure 2. Role of PPAR γ 2 in adipogenesis. (A) PPAR γ isoforms. Mouse PPAR γ 1 and PPAR γ 2 are shown. (DNA) DNA-binding domain. (B) Adipogenesis is induced by ectopic PPAR γ 2 but not PPAR γ 1 in cells whose endogenous PPAR γ gene expression is repressed.

mouse 3T3-L1 preadipocytes, a classic model for studying adipogenesis, using a novel strategy. Transcriptional repressors were engineered to bind specifically to the PPAR γ gene via novel zinc fingers, and inhibit PPAR γ gene expression via a potent KRAB repression domain. Lack of PPAR γ was established and found to prevent adipocyte differentiation, confirming previous work in PPAR γ null models (Barak et al. 1999; Rosen et al. 1999). Ren and coworkers then used retroviruses to restore expression of either PPAR γ 1 or PPAR γ 2. Although both proteins could be expressed at comparable levels, only PPAR γ 2 was able to rescue the adipogenic phenotype (Fig. 2B). This experiment conclusively shows that PPAR γ 2 is uniquely suited for adipogenesis.

This result at first seems inconsistent with previous studies suggesting that the amino terminus of PPAR γ is unnecessary for adipogenesis (Tontonoz et al. 1994b; Shao et al. 1998). However, those studies involved ectopic expression of wild-type and mutant PPAR γ in cells that, unlike those used by Ren et al., could express PPAR γ 2 from the endogenous gene. Because PPAR γ positively regulates its own expression, it is very possible that induction of endogenous PPAR γ 2 by ectopic PPAR γ 1 might reconcile the earlier studies with the present result. It would actually be quite interesting and important to confirm the divergent adipogenic functions of PPAR γ 1 and PPAR γ 2 in the PPAR γ null MEFs used by Rosen et al. (2002), because endogenous PPAR γ 2 could

not be generated after PPAR γ 1 expression in this model system.

A positive feedback role for PPAR γ 1 on PPAR γ 2 might be an important function of endogenous PPAR γ 1, whose protein levels are actually higher than those of PPAR γ 2 in adipocytes (Xue et al. 1996). This would be analogous to the role of C/EBP α in up-regulating PPAR γ expression during normal adipogenesis. The model of PPAR γ gene expression knockout developed by Rosen et al. (2002) could also be used to confirm the dominance of C/EBP α over PPAR γ in adipose conversion of 3T3-L1 cells, the system in which the importance of C/EBP α in adipocyte differentiation has been most rigorously evaluated.

The dramatic difference in adipogenic potential of PPAR γ 1 and PPAR γ 2 is surprising, given their highly similar properties when studied in vitro. However, there are other examples of transcription factors whose biologically relevant functional domains were not predictable from molecular studies. For example, the transactivation domain of the GATA-1 transcription is dispensable for erythropoiesis, whereas another domain is critical (Weiss et al. 1997). C/EBP α itself has cellular functions that are independent of DNA binding (McKnight 2001). The unique role of PPAR γ in adipogenesis is particularly interesting in light of the observation that a common human genetic variation in PPAR γ affecting only PPAR γ 2 (the Pro12Ala mutation) provides protection from insulin resistance (Deeb et al. 1998; Altshuler et al. 2000). This variation has very modest effects on the measurable in vitro functions of the PPAR γ 2 protein (Deeb et al. 1998).

Together, these new findings move the field forward by illuminating the role of the γ 2 isoform of PPAR γ as a critical regulator of adipogenesis. PPAR γ 1 and C/EBP α proteins are induced during adipogenesis and are highly expressed in mature adipocytes, where C/EBP α and probably PPAR γ 1 play important functional roles. However, PPAR γ 2 would seem to be the preferred target for treatments aimed at stopping a cell, and ultimately a person, from becoming fat.

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