PERSPECTIVE

‘No, really, how do they work?’

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“How do the antidiabetic thiazolidinediones work?” If your 3-yr-old asked this question it would be easy to answer: “They function as agonists to activate PPARγ.” Inquisitive minds being what they are, this answer would suffice only for a moment and a more incisive query would soon follow: “But how does PPARγ activation affect diabetes?” You could keep the cycle going for another round by responding: “When it is activated, PPARγ turns on the expression of appropriate target genes that function to increase insulin sensitivity.” And you might manage to delay the inevitable by handing her a printout of PPARγ targets identified by gene arrays. But 3-yr-olds are not easily sidetracked by such obvious ploys and you would soon face the inevitable “No, really, how do they work?”

In this issue, Lazar and colleagues (Guan et al. 2005) add an intriguing new answer that moves beyond some stereotypic assumptions about PPARγ and nuclear receptors. But appreciating it requires some examination of these assumptions.

Pioglitazone (Actos) and rosiglitazone (Avandia) are related thiazolidinedione (TZD) compounds that are widely prescribed insulin sensitizers, with yearly sales of each exceeding a billion dollars. Although they are indeed quite specific PPARγ agonists, they were not initially discovered by modern high-throughput screening approaches, as one might assume, but in decidedly low-throughput animal-based screens for effects on insulin resistance (Fujita et al. 1983). Their identification as PPARγ activators was based on the guesses of several groups (Forman et al. 1995; Lehmann et al. 1995) who managed to link a side effect of these compounds, their ability to promote adipogenesis, with the then recently identified role of PPARγ in that process.

In addition to their obvious therapeutic benefits, the TZDs have provided a remarkable pharmacologic tool to explore the pathology of type II diabetes, certainly one of the most important medical problems facing western populations today. This has sparked intense interest in the function of the PPARs, with >3000 papers in this area since 1990. Particularly considering the massive amount of new information on the mechanisms of transcriptional activation by nuclear hormone receptor agonists, one might also assume that the molecular basis for the antidiabetic effects of TZDs, particularly the identity and the functions of the therapeutically relevant target genes induced by PPARγ, would be well known. But that is only partly right.

The main problem is that PPARγ acts in adipose tissue, while insulin acts primarily in other tissues, notably skeletal muscle and liver. A number of solutions have been proposed, and many have good experimental support. While it is not possible to adequately address this issue here (for reviews, see Picard and Auwerx 2002, Rangwala and Lazar 2004), PPARγ activation in adipocytes is thought to improve metabolic parameters at the whole-body level, for example by increasing fat deposition and decreasing serum levels of free fatty acids, which inhibit insulin signaling. Importantly, PPARγ activation in adipocytes also modulates production of an emerging and in some cases still controversial series of adipocytokines, increasing expression of factors thought to promote insulin action, such as adiponectin, and decreasing expression of inhibitory signals, such as TNFα and resistin.

So how do TZDs really work? At one level, the continuing studies on the functions of both induced and repressed PPARγ target genes in fat and other tissues will provide a basic framework for understanding their effects. At a different level, the question is how TZDs actually alter expression of the functionally relevant targets, and this is where the studies from the Lazar lab raise and answer some unexpected questions.

The specific question they addressed was relatively simple: Why are some PPARγ target genes induced as its levels increase during adipogenesis, while others are expressed at low levels in adipocytes and dramatically up-regulated by TZDs? In their studies, the first group was exemplified by the classic target aP2, and glycerol kinase (GyK) represented the second. In adipocytes, PPARγ binds to its response element in the aP2 promoter and recruits a variety of coactivators, resulting in histone modification and eventually RNA polymerase binding and transcription. Neither PPARγ binding nor coactivator recruitment is affected by TZD treatment. To characterize the GyK response, Guan et al. (2005) first identified a conventional DR-1 PPAR/RXR-binding site upstream of its basal promoter and ruled out one obvious answer to their question by showing that this element is bound by PPARγ in the absence of TZD treatment. As expected, all of the coactivator recruitment and histone modifications observed for aP2 are also seen with the
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GyK element in TZD-treated cells where the gene is ac-
tive, but they are absent in the untreated cells. Guan
et al. (2005) solve the mystery of why the PPARβ bound
to the GyK element does not activate transcription in
these untreated cells with the quite unexpected demon-
stration that it recruits the corepressors SMRT and NCoR
and the histone deacetylase HDAC3 to GyK [Fig. 1]. Sev-
ereachs confirms that GyK expression is nega-
tively regulated by these factors in the untreated adipi-
cytes, and show that they are displaced by TZD treat-
ment.

In another surprise, overexpression of the coactivator
PGC-1α also results in decreased corepressor binding to
GyK and increased basal expression, but in agreement
with previous studies, does not affect aP2 expression.
TZD treatment induces PGC-1α expression in adipi-
cytes. Thus, TZDs presumably regulate GyK expression
directly by displacing corepressors from and recruiting
other coactivators to PPARγ, and indirectly by increasing
PGC-1α levels.

As always, answering one question raises others. In
particular, how can the same receptor in the same cells
bring corepressors to one gene and coactivators to an-
other? Obviously there must be something different
about the genes, and it could be either the sequence of
the PPARγ response elements themselves or the activity
of other nearby proteins. The former appears to be ruled
out by the fact that replacement of the GyK-binding site
with the aP2 site did not alter the TZD responsiveness of
the promoter. Thus, the unfortunately murky concept of
"promoter context" is presumably the answer.

What does this tell us about how TZDs work? At the
most basic level, we now know that they can directly
regulate gene expression not only by promoting coac-
tivator binding, but also by dismissing corepressors. As
pointed out by Guan et al. (2005), this suggests that se-
nective PPARγ ligands that block corepressor binding but
do not recruit coactivators might increase expression of
genes leading to insulin sensitivity while avoiding unde-
sirable side effects such as adipogenesis.

Over the last several years the potential effects of par-
tial agonists and antagonists have gotten increased at-
tention, and it is well known that individual nuclear
receptor ligands can both induce and repress target gene
expression. The current results take these concepts one
step further by suggesting that distinct activation ligands
for a single receptor may have opposite effects on expres-
sion of a single target gene in a single cell. For GyK,
TZDs and the intriguing but elusive endogenous PPARγ
ligand in adipocytes [Tzameli et al. 2004] provide one
example. Based on differential repressive effects of LXRα
in macrophages and intestine [Wagner et al. 2003], en-
dogenous and synthetic LXR ligands may also have simi-
dar disparate effects. Perhaps this is a trick that Mother
Nature knows well.

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