PPAR—the good news and the bad

A number of pharmaceutical companies are following the fortunes of the new diabetes drug troglitazone with trepidation. Although many had hoped it would be the first in a new class of diabetic medicines (*Nature Med.* **3**, 135; 1997), recent announcements that it is associated with liver failure have more than tempered the excitement. Since its launch for the treatment of type II (adult onset) diabetes in March 1997, the drug—sold as Rezulin by Warner-Lambert—has been associated with at least 26 deaths from liver failure. In June 1997, the National Institutes of Health stopped a nationwide troglitazone study after a patient died, and the drug was banned by Britain's Committee on Safety of Medicines in December last year.

The bad news about troglitazone is far from over. Three papers in this issue report on studies of the drug in mouse and human colon cancer cells and two of these raise concerns that, in susceptible individuals, troglitazone may promote the development of colon cancer.

Troglitazone is a synthetic ligand for a nuclear hormone receptor known as PPARγ—which is a member of the large family of peroxisome proliferator-activated receptors. PPARγ is of particular interest because of its expression pattern in cell types as diverse as adipocytes, hepatocytes, fibroblasts and epithelial cells, and because it is known to mediate the effects of a broad range of natural ligands. Such an impressive portfolio has generated interest in PPARγ ligands as possible treatments for a variety of diseases.

Like other PPARγ ligands, troglitazone induces cell differentiation and in the case of diabetes is thought to trigger adipocyte differentiation and maturation, leading to improved glucose uptake and a concomitant reduction in serum glucose levels. Although clinical trials have shown only a modest effect on glucose levels, the novelty of this approach—manipulating PPARγ signaling—and the huge potential for tackling many other equally common diseases, has meant that the drug has attracted considerable research attention. A number of natural and synthetic ligands for PPARγ have now been identified.

The conceptual approach to investigating the role of PPARγ ligands in disease is straightforward: pick a disorder; identify the target cell population and associated PPARγ expression; introduce the ligand to both wild-type and diseased cell populations and observe the results. The three papers in this issue follow this pattern and examine the effects of troglitazone on colon epithelia. Lefebvre *et al.* and Saez *et al.* both use Min+/- mice as the experimental setting. Min+/- mice, recognized as a good model for human familial adenomatous polyposis coli, lack one functional copy of the *APC* tumor suppresser gene, thus predisposing them to colon cancer. The third study, by Sarraf *et al*, uses human colon cancer cells that develop into tumors when transplanted into nude mice.

PPARγ is expressed in most human colon cancers studied and may also be found in other human cancers. So the hope must have been that activating PPARγ would bring about differentiation of cancer cells and thereby reduce tumor development in favor of a differentiated and stable cell phenotype. And the good news is that Sarraf *et al.* found that treatment with troglitazone resulted in a reversal of events associated with colon cancer, and yielded smaller human colon tumors in the nude mice. But in contrast, both Lefebvre *et al.* and Saez *et al.* report that treatment with troglitazone—and a second PPARγ ligand, rosiglitazone—resulted in an increased number of tumors in Min+/- mice.

Why the discrepancy? The simplest explanation is that the *APC*-disrupted Min mouse model is not a faithful mirror of the human colon cancer model used by Sarraf *et al.* Although many patients with colon cancer have APC mutations, others do not and PPARγ may have quite a distinct role in these two groups.

In an accompanying *News & Views* article, Brian Seed points out that although the 11 human cancer samples studied by Sarraf *et al.* came from patients with and without *APC* mutations (and therefore a simple APC positive-, APC negative-based discrepancy is unlikely as all samples showed at least some tumor growth inhibition), for now it would be wise to avoid treating patients with *APC*-mutated colon cancer with troglitazone-like compounds.

As is so often the case for the biomedical research community, this research is exciting and stimulating, but raises far more questions than it answers.