Chapter 8
Animal Models in PPAR Research

Seeking a better understanding of physiological and pharmacological roles of PPARs, genetically engineered animal models were developed. A PPARα knockout mouse model allowed the study of the in vivo role of the receptor and demonstrated that fibrates decrease plasma lipid levels and induce hepatomegaly and hepatic peroxisome proliferation in a PPARα-dependent manner (Lee et al. 1995). Development of mice humanized for PPARα provided insights toward understanding mechanisms of carcinogenic response to peroxisome proliferators. Treatment of these animals with PPARα ligands induced genes encoding peroxisomal and mitochondrial fatty acid metabolizing enzymes and produced a hypolipidemic effect without hepatocellular proliferation. This finding suggested that structural differences between human and mouse PPARα could possibly account for the susceptibility of mouse, but not human, to hepatocarcinogenicity upon treatment with PPARα agonists (Cheung et al. 2004).

Although the elimination of PPARγ expression is embryo-lethal, due in part to disrupted placental function, tetraploid rescue experiments that bypass the placental defects allowed knockout embryos to develop to term. Resulting fetuses survived to birth but died of cerebral and intestinal hemorrhage and exhibited a lack of adipose tissue (Barak et al. 1999).

When PPARβ/δ-null mouse was generated, the embryos had placental defects and a substantial proportion died in mid-gestation. Although surviving embryos developed into smaller pups compared to wild-type animals, they lived to become fertile adults (Peters et al. 2000a).

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