Recognition that peroxisome proliferator chemicals are potent hepatic mitogens and carcinogens in rats and mice has generated concern about possible human health risks associated with exposure to several of these chemicals, many of which have medical or commercial utility. Our broad objective was to improve the estimation of human health risk following peroxisome proliferator exposure by defining a subset of the molecular events associated with the rodent tumors. Our working hypothesis was that peroxisome proliferator-induced tumors in rodents result from specific, peroxisome proliferator-activated receptor-α (Pparα)-modulated changes in gene expression. The research was directed toward three specific aims. First, we sought to identify genes associated with hepatocarcinogenesis induced by the peroxisome proliferator, Wy-14, 643, in the rat. The principle conclusion of these studies — that peroxisome proliferators dysregulate expression of hepatic acute-phase protein genes — suggested possible perturbations in cytokine signaling networks that also regulate cell growth. Second, although Pparα is necessary for the rodent hepatocarcinogenesis induced by peroxisome proliferators, we were interested in identifying more proximate mediators of the increased cell proliferation. Thus, we examined cytokine signaling in mice treated with peroxisome proliferators. We found that peroxisome proliferator-induced increases in cell proliferation is not mediated via Tnfα signaling, but instead may be mediated through interleukin-1β or interleukin-6. Third, because Pparα is necessary for the cell proliferation that follows peroxisome proliferator exposure, we hypothesized that the receptor may play a role in hepatocellular proliferation induced by other stimuli. Following partial hepatectomy, liver regeneration in Pparα-null mice is transiently
impaired, and may result from altered expression of genes regulating the G₁/S cell cycle checkpoint in hepatocytes from these mice. Overall, our studies suggest that hepatic Pparα activation (1) alters inflammatory mediators, (2) modulates several potentially mitogenic cytokines, and (3) is necessary for normal liver regeneration after partial heptectomy. Our data, compared with data from similar experiments on human hepatocytes, may provide further clues about the differences and similarities between peroxisome proliferator exposure in humans and laboratory animals.