# Multifaceted function of the transcription regulator PPAR

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Among nuclear receptors, the peroxisome proliferator-activated receptors (PPARs) have emerged as sensors of fatty acids and fatty acid derivatives, translating modifications in the intracellular levels of these molecules into changes in metabolic activities. In mammals, many aspects of metabolism are under circadian control. This regulation is achieved by clock-controlled transcription factors whose abundance and/or activity oscillate during the day. In the liver, the clock-controlled proline and acidic amino acid-rich domain basic leucine zipper (PAR bZip) proteins play a key role in a cyclic release of fatty acids, which act as ligands for PPARα. Activated PPARα then stimulates the transcription of genes encoding proteins involved in the metabolism of lipids and glucose. Inborn errors of lipid metabolism illustrate the importance of proper milk fat oxidation in newborn mammals. Remarkably, the liver exhibits functional lipid catabolic competence at birth; however, it is unclear how this critical trait is regulated. Our present examination of mouse fetal liver reveals that the genes required for milk lipid catabolism are already stimulated during labor, rather than only after birth. Furthermore, this regulation is controlled by a fetal

glucocorticoid receptor–PPARα axis. Fetal PPARα selectively regulates fatty acid oxidation genes without impacting adaptive effectors—like FGF21, which is apparently repressed by histone deacetylation. PPARα-null pups develop congenital steatosis, as well as increased anaplerosis that compensates for reduced energy gain from milk lipids. This study identifies a developmental axis regulating lipid catabolism gene expression and suggests that, apart from the known adaptive functions, PPARα also plays a proactive role in orchestrating lipid catabolism at birth.