Roles of PPARα in Liver Health and Diseases

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Nuclear receptors (NRs) are ligand-dependent transcription factors. Their activation modulates the expression of genes controlling vital processes including development, metabolism and reproduction. Among them, the peroxisome proliferator-activated receptors (PPARs) are activated by fatty acids and their derivatives. Multiples roles of the PPARα isotype in liver will be discussed. In the mouse, PPARα controls genes required for lipid catabolism already before birth. We identified an endocrine developmental axis in which fetal glucocorticoid receptor primes the activity of PPARα in anticipation of the sudden shift to milk as postnatal nutrient source from which energy can be efficiently extracted. PPARα plays a pivotal role in the management of energy stores during fasting by orchestrating the genomic and metabolic responses required for homeostasis under this energy stress condition. Among the many regulated pathways, a major one is the biosynthesis of ketone bodies. PPARα is also required together with the carbohydrate-sensitive transcription factor carbohydrate-responsive element-binding protein (ChREBP) to balance the fibroblast growth factor 21 (FGF21) glucose response. Recently, we reported that hepatocyte PPARα activity is involved in the cross-talk between adipose tissues and the liver during fat mobilization. Ketone body and FGF21 production, two PPARα-dependent responses, is impaired upon fasting in a genetically-induced absence of adipose triglyceride lipase (ATGL) in adipocytes. Interestingly, liver gene expression analyses unveiled a set of fasting-induced genes sensitive to both ATGL deletion in adipocytes and PPARα deletion in hepatocytes. The PPARα-dependent responses in the liver also affect brown adipose tissue (BAT) activity. Liver PPARα is protective against NAFLD as shown by hepatocyte-specific PPARα deficiency in different models of steatosis and during ageing. In diet-induced mouse models of NAFLD, PPARα emerged as a sexually dimorphic transcription factor. Further in vivo experiments demonstrated that hepatocyte PPARα also determines a sex-specific response to fasting thereby identifying PPARα as a potential sexually dimorphic drug target. Similarly, liver molecular signatures in humans also showed sexually dimorphic gene expression profiles with a sex-specific co-expression network for PPARα. In conclusion, the multifaceted roles of PPARα offer an attractive field for the future development of ligands with numerous potential clinical applications.