Investigation the mechanisms of E2/ERβ inhibited the PPARα tumor promotion functions in Hep3B cells

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Peroxisome proliferator-activated receptor-α (PPARα) is a member of the nuclear receptor superfamily. Administration of its ligands, fenofibrate and fatty acid, can cause hepatocarcinogenesis in rats and mice. Our previous studies demonstrated that PPARα mRNA expressed significantly higher in liver tumor part, and overexpressed ERα induced apoptosis but also inhibited PPARα expression and cell proliferation in Hep3B cell. However, ERα and ERβ may play similar or opposite functions in different cancers. Therefore, we aim to further determine the role of PPARα in hepatocarcinogenesis, and define how ERβ regulates the PPARα in Hep3B cells. Our data show the overexpressed ERβ not only overcome fenofibrate effect to induce the protein levels of Cyt.c, Caspase 9 and Caspase 3 but also inhibit the protein levels of Bcl-xL, Bcl-2, p-Bad, cyclin A, E and PCNA. All these effects cause the enhancement of mitochondrial dependent apoptotic pathway and the attenuation of cell proliferation. Moreover,the overexpressed ERβ not only reduced the level of mRNA, protein expression of PPARα, but also even its downstream Acyl-CoA oxidase (ACO). The EMSA was applied to identify the ERβ, actually mediates through the binding of PPARα promoter to repress PPARα promoter activity and gene expression. In addition, the direct interaction between ERβ and PPARα proteins was observed by co-immunoprecipitation assay. The E2/ERβ might even inhibit fenofibrate-induced the nuclear translocation effect of PPARα. Taken together, ERβ might directly downregulate PPARα gene expression and inhibit the nuclear translocation to suppress the proliferation and induce the apoptosis of Hep3B cells.