Description of the MoA/AOP linked with PPARgamma receptor dysregulation leading to liver fibrosis

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Background

- Liver fibrosis is a wound healing response to a variety of chronic injuries including toxic injury from chemicals.
- Hepatic stellate cells (HSCs) activation represents a key cellular event in the development of liver fibrosis that requires reprogramming of HSCs gene expression, orchestrated by the changes in the expression and/or the activity of key transcription regulators.
- Peroxisome proliferator-activated receptor γ (PPAR γ) is a member of the nuclear hormone receptor family that has been shown to function as a key transcription regulator in the liver.
- PPAR γ protein level is high in the quiescent HSCs and its expression and activity are reduced during HSCs activation.
- While increased PPARγ expression in HSCs is essential for protection against liver fibrosis, its increased activity in hepatocytes is one of the key MIEs leading to steatosis (Fig. 1)

Objectives

- To describe possible MIEs on the level of the HSCs, triggering PPARγ reduced expression that result in fibrosis
- To identify key pro-fibrotic events downstream from PPARγ dysregulation that lead to fibrosis

Methods

1. Literature search – main steps to identify key studies are shown in Fig. 2
2. The studies are analyzed and ranked according to an array of carefully defined criteria
3. On the basis of the selected studies the events related to PPARγ dysregulation in HSCs are identified

Results

Conclusions

- There are several key events identified in HSCs leading to PPARγ down-regulation:
  - Increased TGF β1 expression
  - Decreased RA concentration
  - Decreased RXR expression
  - Increased leptin expression
- Two of the most characteristic key pro-fibrotic events downstream from PPARγ dysregulation are:
  - Activation of PDGF
  - Activation of EGF
- Decreased PPARγ expression/activity is an intermediate key event responsible for HSCs activation resulted in fibrosis

Figure 1.

Figure 2.

Figure 3.