A mechanism for the anti-fibrogenic effects of the pregnane X receptor (PXR) in the liver: Inhibition of NF-κB?

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Abstract

The liver is susceptible to chronic damage through exposure to a variety of toxins (e.g. alcohol) and viruses (e.g. hepatitis C). Obesity, autoimmune diseases (e.g. autoimmune hepatitis) and a variety of genetic diseases (e.g. Wilson’s disease) also lead to chronic liver damage. This damage results in scarring fibrogenesis, structural disruption and functional impairment of the organ. Recent work suggests that there is cross-talk between the PXR and NF-κB pathways. This cross talk may explain the observation that PXR activators inhibit liver fibrosis in in vitro and in vivo animal models of the disease.
this reviw will focus on the two transcription factors and their potential interaction.

1. The PXR

The pregnane x receptor (NR1I2) – or PXR - is a nuclear receptor transcription factor that regulates the expression of a range of genes associated with endobiotic and xenobiotic clearance (Kliewer et al., 2002; Chang and Waxman, 2006). PXR function is normally activated through contact with a range of ligands, including existing licensed drugs (e.g rifampicin) and endogenous compounds (steroids, bile acids) (Kliewer et al., 2002; Chang and Waxman, 2006) (see Figure 1 and Table 1).

2. Liver fibrosis and NF-κB
Liver fibrosis occurs in response to chronic liver damage. It is associated with an inflammatory reaction to tissue damage which stimulates hepatic stellate cell trans-differentiation to myofibroblasts and/or existing liver myofibroblast proliferation (Iredale, 2007). In a chronic liver damage setting, liver myofibroblasts secrete and promote the accumulation of scarring extracellular matrix (e.g. collagen type I) that ultimately distorts tissue structure, disrupts blood flow, leading to cirrhosis (Iredale, 2007). A number of reports have indicated that NF-κB plays a pivotal role in liver myofibroblast viability and fibrogenesis (Elsharkawy et al., 1999; Wright et al., 2001; Kweon et al., 2003; Oakley et al., 2005; Anan et al., 2006).

The term NF-κB describes a transcription factor heterodimeric complex of Rel factors that mediate the expression of genes associated with inflammation in response to a range of stimuli (Ali and Mann, 2004) (see Figure 1 and Table 1). Critically, NF-κB is constitutively active in pro-fibrogenic liver myofibroblasts due to an excess of Rel factors via an epigenetic down-regulation of the inhibitory I-κB protein (Mann et al., 2007). A major function of NF-κB in liver myofibroblasts is the inhibition of apoptosis (Elsharkawy et al., 1999; Wright et al., 2001; Oakley et al., 2005). Accordingly, inhibition of NF-κB in vitro (Elsharkawy et al., 1999; Wright et al., 2001) and in vivo (Wright et al., 2001; Oakley et al., 2005) stimulates liver myofibroblast apoptosis and promotes fibrosis reversal.

With respect to treatments for liver fibrosis, a potential concern with the use of inhibitors of NF-κB without their specific targeting to liver myofibroblasts could be the death of hepatocytes (and therefore an exacerbation of liver damage). In vitro, hepatocytes readily undergo apoptosis when NF-κB is inhibited under pro-inflammatory
and oxidising (NF-κB activating) conditions (Bradham et al., 1998; Hatano et al., 2001a), the likely environment in a chronic liver damage setting. This response may also occur in vivo (Chang et al., 2006; Beraza et al., 2007; Geisler et al., 2007) although some data suggests it may be an in vitro phenomenon (Luedde et al., 2005).

3. The PXR and liver fibrosis

Recent work from this laboratory has shown that PXR ligand activators are anti-fibrogenic in human liver myofibroblasts in vitro (Haughton et al., 2006) and in in vivo animal models of liver fibrosis (Marek et al., 2005). Using mice with a disrupted PXR gene, the role of the PXR was unequivocally established (Marek et al., 2005). The mechanism of action of the PXR was independent of any effects on liver damage (using carbon tetrachloride) and is likely associated with a novel function for the PXR in cells other than hepatocytes and its recognised function as a regulator of genes associated with endobiotic and xenobiotic clearance (Wright, 2006). This is supported by recent work in other labs that has proposed that PXR activation inhibits the expression of genes regulated by inflammation in the gut such as IL-1β and iNOS (Zhou et al., 2006; Shah et al., 2007).

4. The PXR inhibits NF-κB transcriptional function

It is known that the nuclear receptor peroxisome proliferator activated receptor-γ (PPARγ) inhibits NF-κB (Su et al., 1999; Wang et al., 2007). The effect of PXR activators on NF-κB transcriptional regulation was therefore investigated using a human
monocytic U937 cell line stably transfected with a luciferase gene under control of NF-κB response elements (Axon et al., in press). Treating this cell line with the cytokine tumour necrosis factor α (TNFα) or bacterial lipopolysaccharide (LPS) induced expression of luciferase. Co-treatment with PXR activators inhibited the expression of LPS-induced luciferase but not TNFα-induced luciferase activity. These data suggest that the PXR may inhibit NF-κB function with respect to some NF-κB activation signals. Lack of effect on TNFα-activated NF-κB may have been associated with a stimulation of apoptosis by this cytokine in the U937 cell line.

5. Conclusions

There is now evidence within the literature to suggest that the PXR nuclear receptor inhibits NF-κB and inhibits inflammation. With regard to liver fibrosis however, there remain a number of questions. These include whether NF-κB and the PXR interact within hepatocytes and/or liver myofibroblasts? With respect to the latter, NF-κB inhibition is known to stimulate apoptosis, yet PXR activation in myofibroblasts inhibits proliferation and fibrogenicity but does not promote apoptosis (Haughton et al., 2006). It is tempting to hypothesise that the PXR may interact selectively with specific Rel combinations or act on selected NF-κB response elements to bring about a selected inhibition of NF-κB function. The precise mechanism(s) of interaction are yet to be determined.

*Rel proteins were so named because of their sequence homology with the retroviral oncoprotein v-Rel (reticuloendotheliosis viral oncogene).
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Figure Legends

**Figure 1. Schematic diagram of PXR and NF-κB signalling.** TLR4, toll like receptor 4 is the receptor for LPS (for review see Doyle and O’Neill, 2006). TNFR, TNFα receptor (for review see Wullaert et al., 2007). There are sub-types for this receptor. TNFR1 is associated with interactions with soluble TNFα and hepatocyte apoptosis (Doi et al., 1999). RXR, retinoid X receptor; ER6, response element for the human PXR (Lehmann et al., 1998); NF-κB RE, response element for transcriptionally functional Rel dimers; IKK, IκB kinase; I-κB, the functional inhibitor protein of NF-κB