Human Histidine-rich Glycoprotein (HRG)

HRG (50kD) is expressed in the liver and an abundant plasma protein (100-300 µg/ml).

- has been called the "solar army knife of blood" with many presumed functions:
  - Coagulation and fibrinolysis (e.g. binds Plasminogen, Fibrinogen, Heme, Heparin; inhibits clot-mediated coagulation, normalization of vessel architecture in tumors, anti-angiogenic activity)
  - Virulence modulation (binds complement factors, Fcg receptor - immune complex removal, Immunoglobulin)
  - Tumor growth and metastasis reduction (Reduced in HCC and direct modulation of M1-M2 phenotype of TAM/macrophages)
  - Direct bacterial and fungicidal activity
  - Reduced in sepsis and liver insufficiency
  - Reduced in Prostatecancer

FXR controls HRG expression

Luciferase reporter assay in HuH7 cells identifies relevant ER-2 element in the human HRG promoter

FXR-related plasma markers:

HRG mRNA normal versus HCC

HRG - marker for liver specific FXR activation - novel clinical applications (?)

- HRG is expressed almost exclusively in human and mouse liver
- HRG mRNA is controlled by FXR agonist PX20606 in human hepatoma cells and in mouse wt but not FXR-"livers"
- HRG is a direct FXR target gene
- HRG is specifically increased in plasma from all volunteers receiving PX20606 but not in those receiving placebo
- HRG was found to be decreased in patients during sepsis, liver failure, pre-eclampsia and HCC leading to possible new applications for FXR agonists
- HRG influences macrophage polarization (M2→M1) to exert anti-tumor activity (local and periphery) perhaps in other tumor types

FXR controls the tumor suppressor Histidine Rich Glycoprotein (HRG)

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Abstract

The farnesoid X receptor (FXR) is strongly expressed in liver and intestine, controls bile acid and lipid homeostasis and exerts tumor-protective functions in liver and intestine. Histidine-rich Glycoprotein (HRG) is an abundant plasma protein produced by the liver with the proposed function as a pattern recognition molecule involved in the clearance of immune complexes, necrotic cells and pathogens, the modulation of angiogenesis, the normalization of deranged endothelial vessel structure in tumors and tumor suppression.

FXR recognition sequences were identified within a human HRG promoter fragment that mediate FXR-FXR agonist dependent reporter gene activity in vitro. We show that HRG is a novel transcriptional target gene of FXR in human hepatoma cells, human upcyte® primary hepatocytes and 3D human liver microtissues in vitro and in mouse liver in vivo. Prolonged administration of the potent non-steroidal FXR agonist PX20606 increased HRG levels in mouse plasma. Finally, daily oral administration of this FXR agonist for seven days resulted in a significant increase of HRG levels in the plasma of healthy human male volunteers during a clinical Phase I safety study. HRG might serve as a surrogate marker indicative of liver-specific FXR activation in future human clinical studies. Furthermore, potent FXR agonists might be beneficial in serious health conditions where HRG is reduced, e.g. in hepatocellular carcinoma but also other solid cancers, liver failure, sepsis and pre-eclampsia.

References

6. Deuschle et al., The nuclear bile acid receptor FXR controls the liver derived tumor suppressor HRG submitted to J Cancer

In vivo in C57BL/6 and FXR-KO mice

Liver mRNA

HRG
Shp
Plasma HRG
Plasma Cholesterol

HRG mRNA expression in human hepatocytes

HepAR
Huh7

3D human liver microtissue
Upcyte® hepatocytes

FXR and the type 3 cysteines

FXR
hFXR
b
Synovo

Agonist activity (potency nM, HEK293)

<table>
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<th>Agonist</th>
<th>FXR</th>
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Phase 1 study - repeated dose

Repeated dosing over 7 days with FXR agonist PX20606 leads to significant plasma HRG increase in a (double blinded) phase I study in healthy human male subjects.

FXR - function - indications - ligands

- Inhibition of Bile acid synthesis (CYP7A1)
- Induction of Cholesterol (BSEP)
- Inhibition of Glucuronogenes (UGT1)
- Inhibition of Lipogenesis (SREBP-1c)
- Induction of Transhepatic Cholesterol Efflux (SR-B1, ABCB4)
- Supporting Liver Regeneration after Injury (FOXH1)
- Reduction of Inflammation (NRF2)
- Protection against Infection (Cathelicidin, Defensins)

Potential Clinical Applications for FXR agonists

- Cholestasis (PBC)
- Gallstones
- Type 2 Diabetes
- Inflammatory Bowel Disease
- NAFLD
- NAISH
- Hepatocellular Carcinoma

Potential FXR agonists

GW4064 (1000 nM HEK293)