Bile acid receptor FXR: metabolic regulator in the gut

Sungsoon Fang
Nuclear hormone receptor

1905: Ernest Starling coined “hormone”
1929: Estrogen structure
1958: “Estrogen receptor” by Elwood Jensen
1985: GR and ER genes were cloned by Evans and Chambon,

Evolutionary conserved from c.elegans to human (48 NRs in human). 13% of FDA-approved drugs target nuclear receptors
# Nuclear receptor family

<table>
<thead>
<tr>
<th>Endocrine Receptors</th>
<th>Adopted Orphan Receptors</th>
<th>Orphan Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-affinity hormonal ligands</td>
<td>Low-affinity dietary ligands</td>
<td>Unknown ligands</td>
</tr>
<tr>
<td>GR glucocorticoid</td>
<td>LXR $\alpha,\beta$ oxysterols</td>
<td>SF-1</td>
</tr>
<tr>
<td>GR glucocorticoid</td>
<td>LXR $\alpha,\beta$ oxysterols</td>
<td>SHP</td>
</tr>
<tr>
<td>MR mineralocorticoid</td>
<td>FXR bile acids</td>
<td>SHP</td>
</tr>
<tr>
<td>ER $\alpha,\beta$ estrogen</td>
<td>PPAR $\alpha,\delta,\gamma$ fatty acids</td>
<td>TLX</td>
</tr>
<tr>
<td>AR testosterone</td>
<td>PXR xenobiotics</td>
<td>TLX</td>
</tr>
<tr>
<td>PR progesterone</td>
<td>CAR xenobiotics</td>
<td>PNR</td>
</tr>
<tr>
<td>TR $\alpha,\beta$ thyroid hormone</td>
<td>RXR $\alpha,\beta,\gamma$ 9-cis-RA</td>
<td>LHR-1</td>
</tr>
<tr>
<td>VDR vitamin D</td>
<td>SF-1</td>
<td>DAX-1</td>
</tr>
<tr>
<td>RAR $\alpha,\beta,\gamma$ retinoic acid</td>
<td>SHP</td>
<td>GCFN</td>
</tr>
<tr>
<td>HNF-4 $\alpha,\gamma$</td>
<td>TR2,4</td>
<td>HNF-4 $\alpha,\gamma$</td>
</tr>
<tr>
<td>ERR $\alpha,\beta,\gamma$</td>
<td>Rev-erb $\alpha,\beta$</td>
<td>ERR $\alpha,\beta,\gamma$</td>
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<td>NCUP-TF $\alpha,\beta,\gamma$</td>
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</table>
Precise regulation of NR transcriptional activity

Active repression
Co-repressors recruit chromatin modifying enzymes (HDACs)

Ligand-mediated activation
Exchange repressive (HDACs) for activating enzymes (HATs)
Diet is the factor to determine our physiology
Chronic Inflammation and Diabetes: Walking the Line

Obesity → Chronic Inflammation → Diabetes
Targeting Metabolic syndromes

Metabolic Diseases: Obesity* and Diabetes (Type II)*
(Burns Fat improves Insulin resistance)

Insulin therapy: feeding signal
FXR responds to feeding signals via BAs

- LIVER
- GALL BLADDER
- INTESTINE
- BLOOD
- Chylomicrons

FXR

Bile circulation pathway from liver to intestine.
Question: Does intestinal FXR regulate whole body metabolism?
FXR paradox:

FXR KO mice: dyslipidemia, hyperglycemia
FXR agonist: GW4064
acute treatment in normal chow
→ improved glucose/lipid metabolism

Ob/FXRKO: improved metabolic phenotypes
FXRKO with HFD: improved metabolic phenotypes
FXR agonist in DIO: more obese than control
Developing new ligands for FXR is promising to treat metabolic diseases

FXR is a molecular target for the effects of vertical sleeve gastrectomy

Karen K. Ryan¹, Valentina Tremaroli², Christoffer Clemmensen¹,³, Petia Kovatcheva-Datchary², Andriy Myronovych⁴, Rebekah Karns⁵, Hilary E. Wilson-Pérez¹, Darleen A. Sandoval¹, Rohit Kohli⁴, Fredrik Bäckhed²,⁶ & Randy J. Seeley¹
Development of novel FXR agonists is required to avoid the adverse effects of FXR activation.
Fexaramine

- Structurally distinct from natural bile acids
- Distinct gene expression profiles compared to GW4064 or bile acids

Mol Cell, 2003
Fex: intestinal specific-FXR agonist

Treatment (PO or IP)

5 days

Serum collection

LC/MS quantitation

IP injection

PO Injection

Serum Fexaramine (nM)

200

150

100

50

0

**

FEX EC50 = 25nM

Oral gavage

Relative Expression

4

3

2

1

0

Liver

kidney

ileum

Vehicle

Fexaramine

FXR

SHP

BSEP

OSTβ

FXR

SHP

OSTβ

FXR

SHP

FGF-15

IBABP

OSTα

OSTβ
Anti-obesity effects by FEX

Graphs showing the effect of Fexaramine on body weight and serum glucose levels compared to Vehicle and Vehicle-HFD groups.
Enhanced energy expenditure in BAT by FEX

FEX-treated mice consume more glucose and lipid as energy sources
Enhanced energy expenditure in BAT by FEX

**Enhanced core temperature in Fex compared to Vehicle.**

**Gene expression changes in OXPHOS in BAT.**
Browning in white adipose tissues by FEX

UCP1 staining

Vehicle

Fex

Oxygen consumption rate (pMoles/min)

**
Reduced hepatic gluconeogenesis and lipogenesis

Vehicle

Fex
Fex improves glucose homeostasis

Clamp study:
→ heavier mice for fexaramine to prepare body weight-matched cohort (Olefsky lab)

[Graph showing body weight over time for Vehicle and Fexaramine groups]

[Bar graphs comparing Basal HGP, GDR, FFA suppression, and HGP suppression for Vehicle and Fexaramine groups]
Fexaramine effects

**TYPICAL DIET PILL**
- affects multiple targets throughout the body

**FEXARAMINE**
- targets only the gut

**Side effects:**
- pulmonary hypertension, heart disease, elevated blood pressure, restlessness, dizziness, insomnia, headache, anorexia, constipation, diarrhea, decrease in absorption of fat-soluble vitamins

*Studied in animal models*

- Gluconeogenesis ↓
- Lipogenesis ↓
- Inflammation ↓
- Browning ↑
- Energy expenditure ↑
Fexaramine: Therapeutic strategy for treatment of T2D?
Is Fexaramine bariatric surgery mimetic?

Weight loss
Elevated FGF19
Decrease of TCA level
Increase of CA level
Is gut-specific FXR agonism bariatric surgery mimetic?

- **FGF15 orthologue:** FGF19 (human)

- **Serum FGF-15 (pg/ml)**
  - **Vehicle:** N.D.
  - **Fexaramine:**

- **Ileal FXR target genes**

- **Weight loss**
- Elevated FGF19
- Decrease of TCA level
- Increase of CA level

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- FGF15
- Tsku
- Enpp7
- Ttc36
- Pck1
- Per1
- Slc5a12
- Ace
- Homer2
- Gadd45b
- Aqp1
- Pcsk9
- Ephx2
- Ms4a10
- Akr1c19
- Tsc22d3
- Cyp2d26
- Treh
- Endod1
- Tfrc
- Slc30a10
- Gpnmb
- Lpl
- Fa2h

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**Normalized expression**

- Disorder: 0
- Moderate: -2 (green)
- Marked: -2 (dark green)
- Marked: +2 (red)
- Marked: +2 (dark red)
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Browning↑
Energy expenditure↑

Gut-specific FXR agonism: potent therapeutic strategy to treat metabolic syndromes
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