INTERACTIONS BETWEEN DRUG PROPERTIES AND HOST FACTORS: ADAPTIVE MECHANISMS

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INTRODUCTION

• Drug-induced liver injury (DILI) is a multifactorial disorder
• Certain drug properties are associated with severe clinical hepatotoxicity
• Drug-induced ALT elevations in <0.001% to 20% prescriptions
  • Most resolve
  • Non-progressive chronic liver enzyme elevation
  • Rare serious liver injury, acute liver failure
• Drug and host: two key players in determining DILI risks

• What determines DILI risk, phenotypes and outcomes?
DRUG-HOST INTERPLAY IN HUMAN HEPATOTOXICITY

- CONCEPT -

• Interplay of specific drug and host attributes
  • Cellular, molecular levels
  • Injury process
  • Inflammation
  • Immunological responses
  • Tissue regeneration

• Determine individual susceptibility to specific drug (or drug class), phenotype, and outcome
DRUG’S MULTIFACETED PROPERTIES

- **Physiochemical**: molecular weight, lipophilicity, solubility
- **Pharmacological**: dose, metabolism, elimination, protein binding
- **Toxicological**: reactive metabolite formation, mitochondrial toxicity, oxidative stress
- **Targeted biophysical**: therapeutic class
- **Off-target biophysical**: cellular biology, injury/repair, immune response, visceral blood flow
- **Immunological**: some drugs induce specific immunoreactions
HOST FACTORS

- Genetic variants
- Race/ethnicity
- Age
- Gender
- Sex hormones
- Co-morbidity
- Co-medications
- Environmental: alcohol, smoking, nutrients,..
- Gut flora: gut-liver interaction, impact immune/inflammatory response

- Drug delivery to the liver
- Drug metabolism/transport
- Cellular stress response
- Inflammation
- Immune response
- Tissue injury & repair
PRELIMINARY CONCEPTUAL FRAMEWORK FOR DRUG-HOST INTERACTION

Drug properties

Drug

Cellular injury initiation
- Pharmacological responses
- Toxicological responses
- Cell death

Host response to injury insult
- Immune/inflammation
- Repair
- Tissue injury

Clinical phenotype and outcome

Host factors
DEFINITION OF ‘ADAPTATION’

- Adaptation: diverse host responses to minimize toxic cellular insults, inflammation, and tissue injury, leading to the resolution of cellular stress, cellular dysfunction, inflammation and tissue damage.
  - Cellular stress responses
  - Inflammation/immune response
  - Tissue injury/repair
- Compromised adaptation results in clinically significant DILI and may lead to serious clinical outcomes
OUTLINE

• Drug-host interaction in:
  • Cellular stress responses
  • Inflammation/Immune response
  • Injury/Repair

• Future investigations of DILI drug-host interactions
  • Experimental
  • Clinical

• Bi-directional translation in research network
DRUG-HOST INTERACTION IN CELLULAR STRESS RESPONSE
DRUG-HOST INTERACTION IN CELLULAR STRESS RESPONSE
COVALENT BINDING-PROTEIN DAMAGE & REPAIR/DEGRADATION

**Drug**

- Extensive liver metabolism
  - Atorvastatin
  - Disulfiram
  - Terbinafine

**Host**

- Alterations in drug metabolizing enzymes
  - Female sex ↑
  - Inducers/inhibitors ↑↓

**Protein repair & degradation**

- Thioredoxin
- Thioredoxin reductase
- Glutathione reductase
- Methionine sulfoxide reductase
- Lysosomal functions
- Aging

**Reactive metabolite formation**

- APAP
- Isoniazid
- Phenytoin
- Carbamazepine
INTERPLAY OF GENDER, AGE AND DRUG PROPERTIES IN DRUG-INDUCED LIVER INJURY: ANALYSIS OF ADVERSE EVENT REPORTING AT WHO VIGIBASE™

**Significant Hepatic metabolism**

- No gender difference: 75%
- Gender specific (F > M) *: 87%
- Gender specific (F > M) #: 85%
- Gender specific (M > F): 57%

*: overall
#: young (age <50) only

(DDW 2015)
118 DILI cases
- Causal drugs: 57.6% anti-TB drugs, 18.6% antibiotics, 5.9% anti-epileptic drugs
- 7 SNPS of thioredoxin reductase 1 gene
- No associations with any of 7 SNPs
- Significant association with a TTA haplotype (below)
Dysregulation of protein degradation pathways may mediate the liver injury and phospholipidosis associated with a cationic amphiphilic antibiotic drug

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Drug (PF-04287881) 7-day exposure

Mouse diversity panel (34 strains)

mRNA expression

Resistant strains
Susceptible strains

Elevated serum ALT (88%)
Hepatocellular hypertrophy
Hepatocellular single cell necrosis
Kupffer cell vacuolation (phospholipidosis)

Differentially expressed pathways

Protein ubiquitination pathway
Drug transport, phospholipid metabolism, lysosomal function
DRUG-HOST INTERACTION IN CELLULAR STRESS RESPONSE

CELLULAR STRESS/ALTERED STRESS RESPONSE

**Drug**

- Mitochondrial toxicity/oxidative stress
  - Valproic acid
  - APAP
  - Troglitazone
  - Flutamine
  - Stavudine

**Host**

- Altered stress responses
  - Increased cellular oxidants
  - Depleted antioxidants
  - Fatty liver
  - Impaired cellular protein repair/degradation
  - Mitochondrial dysfunctions
  - Impaired mt DNA repair

- Altered ER stress response
  - Pre-existing ER stress
  - Medications to induce/ameliorate ER stress

**ER stress**

- Indomethacin
- Diclofenac
- Benzodiazepines
- Valproic acid
- APAP
RELATIONSHIP AMONG LYOSOSOMAL DYSFUNCTION, OXIDATIVE STRESS, AND MITOCHONDRIAL DYSFUNCTION - A MODEL OF PARKINSON DISEASE

Impaired degradation of macromolecules and damaged organelle

(Molecular Neurodegradation 2009 4:24)
### PHARMACOLOGICAL MODULATORS OF ER STRESS

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Mediator</th>
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<tbody>
<tr>
<td>mTOR inhibitors</td>
<td>Rapamycin</td>
<td>Autophagy ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IRE1/JNK ↓</td>
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<tr>
<td>Chemical chaperones</td>
<td>4-PBA</td>
<td>GRP78 ↓, CHOP ↓</td>
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<tr>
<td></td>
<td>TUDCA</td>
<td>Calcium efflux ↓, eIF2α ↓, CHOP ↓</td>
</tr>
<tr>
<td>AMPK activators</td>
<td>Metformin</td>
<td>AMPK ↑, PPARδ ↑, eIF2α ↓, JNK ↓, IRS-1 ↓</td>
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<tr>
<td></td>
<td>Salicylate/Salsalate</td>
<td>AMPK ↑</td>
</tr>
<tr>
<td></td>
<td>AICAR</td>
<td>AMPK ↑</td>
</tr>
<tr>
<td>GLP-1 receptor agonists and DPP-4 inhibitors</td>
<td>Exenatide</td>
<td>PKA ↑, ATF4 ↑, BIP ↑, Bcl2 ↑, JunB ↑, SERCA ↑, Autophagy ↑, C/EBPβ ↓, Akt/PERK/CHOP ↓, IRE1α/JNK-p38 ↓</td>
</tr>
<tr>
<td></td>
<td>Vildagliptin</td>
<td></td>
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<td>Gemigliptin</td>
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<tr>
<td>PPARs agonists</td>
<td>Fenofibrate</td>
<td>IRE1α/XBP1/JNK ↓, AMPK ↑, eNOS ↑, SERCA ↑, Autophagy ↑, SC1 ↑</td>
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<tr>
<td></td>
<td>Pioglitazone</td>
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<td></td>
<td>GW1516</td>
<td>AMPK ↑, ERK1/2 ↓, Autophagy ↑</td>
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<td>ARBs</td>
<td>Valsartan</td>
<td>PUMA ↓, GRP78 ↓</td>
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<tr>
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<td>Losartan</td>
<td>PLC-IP3-calcium ↓</td>
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<td>Olmesartan</td>
<td>GRP78 ↓, CHOP ↓</td>
</tr>
<tr>
<td></td>
<td>Telmisartan</td>
<td>GRP78 ↓, CHOP ↓</td>
</tr>
</tbody>
</table>

Reporting frequency of liver events ↓ in VigiBase™

APAP, INH, VA
DRUG-HOST INTERACTION IN INFLAMMATION & IMMUNE RESPONSE
DRUG-HOST INTERACTION IN INFLAMMATION/IMMUNE RESPONSE

Hepatitis
- Ibuprofen
- Isoniazid
- ketoconazole

Pro/anti-inflammatory
- Genetic variants (IL-4, IL-10, IL-6, ..)
- Sex hormones (E2, P4, ..)
- Co-medications
- Altered microbiome
- Intestinal disease (hepatic LPS influx↑)
- Obesity

Immune-mediated
- Trimethoprim/sulfamethoxazole
- Ciprofloxacin
- Halothane
- Amodiaquine

Immune response
- HLA variants
- Gender
- Sex hormones
- Immunomodulators
- Immunosuppressants
DRUG-HOST INTERACTION IN TISSUE INJURY & REPAIR
DRUG-HOST INTERACTION IN INJURY/REPAIR

**Drug**
- Hepatocyte necrosis
  - APAP
  - Diclofenac
  - Flutamine

**Host**
- Apoptosis vs. necrosis
  - Female sex $\rightarrow$ apoptosis?
  - Impaired cellular energy supply $\rightarrow$ necrosis?

**Altered tissue repair**
- Aging $\downarrow$
- Histone acetylase / de-acetylase (Valproate, hydralazine deriv.) $\downarrow$
- $\downarrow$ FXR (reduced bile acid pool) $\downarrow$
- Co-medications $\downarrow\uparrow$

**Cholestatic injury**
- Methyltestosterone
- Amoxicillin/Clavulanate
- Clarithromycin
- Azithromycin

**Cholangiocyte injury/repair**
- Male gender?
- Estrogens?
FUTURE INVESTIGATIONS OF DRUG-HOST INTERACTIONS IN DILI
EXPERIMENTAL INVESTIGATIONS

Introduce biological variances to experimental designs (e.g., sex, sex hormones, age) to assess specific drug-host interactions

• Established DILI mouse models
• Human primary hepatocytes
• Engineered human liver models
• Organs-on-a-chip
• Induced pluripotent stem cells
NIH to balance sex in cell and animal studies

Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

(Nature 509, 282-283, 2014)
CLINICAL INVESTIGATIONS

- Integration of **drug properties** in clinical/genetic analysis
- Further develop **knowledge base** of:
  - Drug properties (**Liver Toxicity Knowledge Base**, NCTR/FDA)
  - Degree of hepatotoxicity (**DILIRank**, Drug Discovery Today, 2016)
  - Clinical phenotypes – unified resource?
- Implement new **data-mining** tools (e.g., topic modeling) - combine genetic and clinical data?
- Theoretical approach vs. unsupervised approach
DEVELOPMENT OF RESEARCH NETWORK SYNTHESIZING MULTIDISCIPLINARY RESEARCH FINDINGS IN DILI

VA DILI DB

VA Data Warehouse

LKTB

NCTR

Knowledge base of drug properties

Bi-directional translation of research findings and hypotheses

Established multi-disciplinary DILI research collaborations

DILI registries
Animal experiments
In-vitro assays
Other EMRs

Facilitate discovery and enhance drug safety in future

Supply additional data as needed

Link specific drug properties to study drugs via ATC codes

Data extraction

Customized Analytic tables
SUMMARY

• Heterogeneity in risks, phenotypes, and outcomes of DILI may be explained by multilayered interplay of drug properties and host attributes in adaptive mechanisms.

• Future investigations incorporating drug properties, biological variances, and their potential interactions in study designs will aid in better understanding of DILI pathobiology and facilitate future personalized drug safety.
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