Tapping untapped: Exploring Role of ALDH in Pharmacogenetic and Toxicogenetic Studies

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Xenobiotic Metabolism

Food, Pollutants, Drugs

Phases I, II, III

Metabolism

Living Organism

Metabolites
Xenobiotic Metabolism

• Non-specific defence against xenobiotics – maximize polarity with minimal intervention.

• Phase-I, non-synthetic
  • Includes: Oxidation, reduction, hydrolysis
  • Important Enzyme Systems:
    • Monooxygenase Systems:
      • Cytochrome P450 (CYP) or mixed function oxidases
      • Flavin-containing monooxygenases
    • Monoamine oxidases
    • Alcohol/ Aldehyde Dehydrogenases
Xenobiotic Metabolism

• Phase-II, synthetic
  • Glucuronidation, sulfation, glutathionation, acetylation etc.

• Phase-III (according to some resources)
  • Efflux transporters, such as ATP Binding Cassette (ABC) Transporters. ABCB1, ABCC2 etc.
Xenobiotic Metabolism

Electrophiles

\[ \text{R} - \text{R} \quad \text{R} = \text{O} \]

Lipophilic

Phase I

Nucleophiles

\[ \text{R-OH} \quad \text{R-SH} \quad \text{R-NH}_2 \]

Oxidation

Hydrolysis

Reduction

Phase III
We know the Sensory and Motor Homunculi.

How should the “Metabolic Homunculus” appear?
Relative Quantities of P450s in Liver

Relative Contribution of P450s in Drug Metabolism

Relative importance of CYP450 isoforms in drug metabolism

**Phase I**
- Oxidation, Reduction, Hydroxylation, Hydrolysis
  - CYP3A4/5/7
  - CYP2D6
  - CYP2C9
  - CYP2C19
  - CYP1A1/2
  - CYP1B1
  - CYP2A6
  - CYP2B6
  - CYP2C8
  - Esters
  - DPD
  - NQO1
  - ADH
  - ALDH
  - Epoxide hydrolase

**Phase II**
- Acetylation, Glutathionation, Sulfation, Methylation, Glucuronidation etc.
  - NAT1
  - NAT2
  - GST-M
  - GST-T
  - GST-P
  - GST-A
  - STs
  - UGTs
  - COMT
  - HMT
  - TPMT
  - Others
Aldehyde Dehydrogenases

• Many isoenzymes – our focus is ALDH3A1

• Broad spectrum of biological activities
  • Biosynthesis of retinoic acid
  • Metabolic and Detoxification functions:
    • Aldehyde metabolism, e.g. Benzaldehyde
    • Alcohol (acetaldehyde) metabolism
    • Ester hydrolysis
    • Metabolism of lipid peroxidation and reduction of oxidative stress
    • Prevention of UV light induced damage to cornea
    • Metabolism of GABA and some amino acids
    • Clearance of certain anticancer drugs
Our previous reports...

- Certain genotypes increase cyclophosphamide clearance (CYP2C19/ALDH3A1) and predispose to neutropenia (GSTA1) in breast cancer patients


- Prevalence frequencies of some alleles (CYP2C19, ALDH3A1, ABCB1, ABCC2) among breast cancer patients showed differences when compared with HapMap database

  ([Afsar NA et al. Basic Clin Pharmacol Toxicol, 2010]).
Current study

• To estimate genotype profile among healthy adults (Karachiites; n=155; both genders).
  • Phase-I metabolism (CYP1A1 *2A/*3, CYP1A1*2C, CYP2B6*4, CYP2B6*6, CYP2C9*2, CYP2C19*2, CYP2C19*17, CYP2D6*4, CYP2D6*10, CYP3A4*22, CYP3A5*3),
  • Phase-II metabolism (ALDH3A1, GSTA1 -69, GSTM1)
  • Efflux transporters (ABCB1 1236, ABCB1 2677, ABCB1 3435, ABCC2 -24, ABCC2 3972, ABCC2 1249)

• Techniques: Saliva samples; PCR followed by RFLP or PSQ
Data (variant allele frequency) compared with major ethnic groups in HapMap.

The genotype data of KHI samples is given below:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>% Frequency</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/C</td>
<td>8.1</td>
<td>3.7 - 12.5</td>
</tr>
<tr>
<td>C/G</td>
<td>50.0</td>
<td>41.9 - 58.1</td>
</tr>
<tr>
<td>G/G</td>
<td>41.9</td>
<td>33.9 - 49.8</td>
</tr>
</tbody>
</table>
Important functions

• ALDH3A1
  • determines plasma clearance of cyclophosphamide and ifosfamide by shunting to inactive metabolite pathway (Afsar et al. 2012 EJCP)
  • helps generate NO from organic nitrates (Lin et al. 2013 Nitric Oxide)
Important functions

• **ALDH3A1**
  - has shown association with prostate and breast cancers (Yan et al. 2014, Br J Ca)
  - protects against UV-induced corneal damage (Chen et al. 2013, P Ret Eye Res)
  - maintains visual clarity along with ALDH1 (Lassen et al. 2007, J Biol Chem)
Important functions

• **ALDH3A1**

  • helps synthesize CoQ and protects against mitochondrial dysfunction (Stefely et al. 2016 Nat Biotech)

  • protects cells against 4-HNE, a toxic product of lipid peroxidation (Black et al. 2012 Free Rad Bio Med)

  • protects oral and respiratory tract mucosa from food, air pollutant and smoking-induced damage (Giebułtowicz et al., 2010 Acta Biochim Pol. ; Jang et al. 2014, Free Rad Bio Med)
Increased likelihood of

• Oxidative stress especially due to lipid peroxidation – and its consequences – aging, cancers, CVS disorders etc.

• Development of atherosclerosis – CVS disorders

• Damage from aldehydes and electrophiles in food and polluted environment – aging, degeneration, cancers

• Damage to oral, pharyngeal, laryngeal and respiratory tract mucosa by tobacco smoking – numerous consequences
Potential adverse consequences of loss of ALDH3A1 function – future research potential

Increased likelihood of

• Development of cancers and their metastasis

• Mitochondrial dysfunction leading to a number of degenerative and chronic effects

• Infertility – sperm motility problems

• Visual impairment due to UV radiation

• Suboptimal efficacy of organic nitrates
Summary

- Loss of ALDH3A1 function
- Reduced efficacy of Oxazophorines/ Nitrates
- Lipid Peroxidation, Accumulation of 4-HNE
- CoQ deficiency/ Mitochondrial Dysfunction
- Cardiac dysfunction/ Dementia/ Infertility
- Smoking injury
- Atherosclerosis
- Cardiovascular Disease/ Stroke
- UV damage to Cornea
- Toxicity of environmental / industrial pollutants
- Cancers
- Pulmonary Disease
Thank You

Our Team:

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