Drug-induced transcriptional modules in mammalian biology: Implications for drug repositioning and resistance

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Outline

• Introduction

• Drug-induced regulation of target expression

• Drug-induced transcriptional modules
  ▸ Identification and characterization of modules
  ▸ Functional discovery of hypothetical genes
  ▸ Towards drug repositioning via modules
Computational approaches integrating drug-related information to gain a systems level understanding of drug action

- Drug-target interactions
- Drug-target information (sequence, structure)
- Drug target pathway neighborhood
- Drug metabolism
- Toxicology
- Side effects
- Chemical similarity
- Drug-induced cellular phenotypes
- Disease-related gene expression profiles
- Drug-induced gene expression profiles

Iskar et al. (2011) Drug discovery in the age of systems biology: the rise of computational approaches for data integration. Current opinion in biotechnology 23 (4), 609-616
Recent studies integrating side effect information with drug-target relations


Integration of drug-information resources: a special focus on gene-expression compendium of drug treatments

Drug-target interactions
Mode of action
Structural features

Drug-induced gene expression profiles

The Connectivity Map
(www.broadinstitute.org/cmap/)

SIDER resource
(http://sideeffects.embl.de)

STITCH resource
(http://stitch.embl.de)

The DrugMatrix database
(GEO: GSE8858)

1 Kuhn et al. NAR (2012)  3 Natsoulis et al. MSB (2008)
Drug-induced gene expression profiles were used to generate a drug-drug similarity network

• Iorio et al. (2009) Identifying network of drug mode of action by gene expression profiling. Journal of Computational Biology 16 (2), 241-251

Inferring novel drug-disease associations based on anti-correlated expression profiles


- Sirota et al. (2011) Discovery and preclinical validation of drug indications using compendia of public gene expression data. Science Translational Medicine 3 (96), 96ra77-96ra77

- Dudley et al. (2011) Computational repositioning of the anticonvulsant topiramate for inflammatory bowel disease. Science Translational Medicine 3 (96), 96ra76-96ra76
Comparison of the Connectivity Map and the DrugMatrix database

<table>
<thead>
<tr>
<th>Source</th>
<th>Human cell lines</th>
<th>Rat liver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Connectivity Map dataset (build 02)</td>
<td>Liver pharmacology and xenobiotic response repertoire from Iconix Biosciences (GEO: GSE8858)</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>6 hours</td>
<td>mainly 6 hours, 1, 3 and 5 days</td>
</tr>
<tr>
<td>Genes</td>
<td>22277 probe sets</td>
<td>10455 probe sets</td>
</tr>
<tr>
<td></td>
<td>Detection call filtering</td>
<td>Unique genes</td>
</tr>
<tr>
<td></td>
<td>Unique genes</td>
<td>7122 genes (6134 orthologous pairs)</td>
</tr>
<tr>
<td></td>
<td>8964 genes</td>
<td>Matched orthologous pairs</td>
</tr>
<tr>
<td></td>
<td>5346</td>
<td>3618</td>
</tr>
<tr>
<td></td>
<td>2516</td>
<td>3618 genes</td>
</tr>
<tr>
<td>Drugs</td>
<td>1309 compounds</td>
<td>344 compounds (&gt;250 drugs)</td>
</tr>
<tr>
<td></td>
<td>Filtering for normalization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common in all cell lines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>990 compounds (&gt;650 drugs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>849</td>
<td>141</td>
</tr>
<tr>
<td></td>
<td>203</td>
<td></td>
</tr>
</tbody>
</table>

ATC classification

- Cardiovascular system
- Antiinfectives for systemic use
- Respiratory system
- Dermatologicals
- Genito-urinary sys. & sex hormones
- Various
- Blood and blood forming organs
- Nervous system
- Sensory organs
- Musculo-skeletal system
- Antiparasitic products
- Antineoplastic & immunomodulating
- Systemic hormonal prepar.

October 25, 2011
Mean centering among treatments eliminates batch effect in the Connectivity Map resource

Assessment of drug-induced gene expression profile similarity (DIPS) with structural similarity and ATC classification

2D Chemical Structural Similarity
(Tanimoto score > 0.8)

Anatomical Therapeutic Chemical Classification
(Sharing 4th level)
Drug-induced regulation of target expression

Aim: Systematic analysis of feedback regulation of drug targets induced by its inhibitors/activators

STITCH 2.0 target relations and actions
Small molecules
Drug target (Present call)
mRNA transcription
Agonists/antagonists vs all treatments

Expression change
8% of drug targets are differentially regulated at the expression level upon drug perturbation

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Drug Action</th>
<th>Direction of Regulation</th>
<th>Scatter plots of drug-induced drug-targets against all other treatments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Histone deacetylase 3</td>
<td>T</td>
<td>↑</td>
<td>-</td>
<td>Hemmatazad et al.</td>
</tr>
<tr>
<td>2. Endoplasmin</td>
<td>T</td>
<td>↑</td>
<td>-</td>
<td>Hadcock et al.</td>
</tr>
<tr>
<td>4. Prostanoid EP2 receptor</td>
<td>↑</td>
<td>↓</td>
<td>-</td>
<td>Desai et al.</td>
</tr>
<tr>
<td>5. Histone deacetylase 7</td>
<td>T</td>
<td>↓</td>
<td>-</td>
<td>Hemmatazad et al.</td>
</tr>
<tr>
<td>6. Interleukin-8</td>
<td>T</td>
<td>↓</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>7. Lanosterol 14-α demethylase</td>
<td>T</td>
<td>↑</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>8. DNA Topoisomerase 2-α</td>
<td>T</td>
<td>↓</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>9. Calmodulin 1</td>
<td>T</td>
<td>↓</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>10. cAMP-specific 3',5'-cyclic phosphodiesterase 4D</td>
<td>T</td>
<td>↑</td>
<td>-</td>
<td>Libra et al.</td>
</tr>
<tr>
<td>11. Thymidylate synthase</td>
<td>T</td>
<td>↑</td>
<td>-</td>
<td>Desai et al.</td>
</tr>
<tr>
<td>13. Tubulin, Beta 2c</td>
<td>T</td>
<td>↓</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

- Activation
- Inhibition
- Up-regulation
- Down-regulation

Average difference gene expression

- Activation
- Inhibition
Conclusions I

• Batch effect in the Connectivity Map resource can be eliminated by using treatments rather than untreated controls to estimate background.

• Benchmarking highlighted that drug-induced gene expression profiles reflect the mechanism of action and chemical structure of drugs.

• 8% of drug targets were found to be feedback-regulated at the expression level upon drug treatment. In addition to known cases reported in literature, we also identified novel feedback loops that may have a role in the development of drug tolerance.
Identification and characterization of drug-induced transcriptional modules in three human cell lines and rat liver

\section*{Drug-induced gene expression profiles}

\textit{In vitro} Connectivity Map\textsuperscript{1}

- MCF7
- PC3
- HL60

\textit{In vivo} DrugMatrix\textsuperscript{2}

- 990
- 344

\section*{Identification of modules\textsuperscript{3}}

- Drugs
- Genes

\section*{Conservation of modules}

- MCF7
- PC3
- HL60
- Rat liver

\section*{Characterization of modules}

- Drugs:
  - ATC code
  - Target proteins
  - Side effects

- Genes:
  - GO terms
  - KEGG / BioCarta pathways
  - Protein-protein networks

- Novel Drug MoA
- Novel functions for hypothetical genes

References:


72% of human drug-induced modules are present in multiple cell lines
Conservation estimates across cell lines and organisms are robust to variations in chemical space.
Characterization of gene and drug members of drug-induced transcriptional modules
Inferring novel regulators of cellular cholesterol levels using drug-induced transcriptional modules
Prediction and confirmation of novel cell-cycle inhibitors via drug-induced transcriptional modules

CODIM1

Cell cycle blockers, e.g. base analogs

Expression fold change

MCF7
PC3
HL60

Cell viability [% of control]

HL60
IC50 = 6.1 μM

HL60
IC50 = 1.7 μM

Cell cycle Analysis:

EMBL
Identification of novel drug-target relations using cell line-specific drug-induced transcriptional modules
Conclusions II

- Our analysis framework has delineated the modular architecture of regulatory networks in mammalian cells perturbed with various drugs, resulting in a compendia of drug-induced transcriptional modules.

- Drug-induced transcriptional modules are conserved across cell lines (72%) and organisms (15%).

- Drug-induced modules can be used to infer gene function (e.g. novel regulators of cholesterol levels) and drug action (e.g. new cell cycle blockers and new modulators of PPARγ, ADRA2C and ERα).

- Drug-induced transcriptional modules can be regarded as transcriptional markers for specific (off-) targets or side effects to systematically evaluate the efficacy and safety of new chemicals during early drug development.
Acknowledgements

Peer Bork
Vera van Noort
Georg Zeller
Kasia Kaminska
Bork Group

Helmholtz Zentrum München
Monica Campillos

Technical University of Dresden
Michael Kuhn

Collaborators

EMBL
Structural & Computational Biology
Anne-Claude Gavin

Cell biology and Biophysics
Peter Blattmann
Rainer Pepperkok

University of Copenhagen
Lars Juhl Jensen