

Toxicogenomics: New Molecular Fingerprints

Essay

***Submitted for fulfillment of the M.Sc. Degree in
FORENSIC MEDICINE AND CLINICAL TOXICOLOGY***

By

DOAA TAWFIK MOHAMED ALI EL-SHEIKH

(M.B., B. Ch.)

***Demonstrator of FORENSIC MEDICINE AND CLINICAL TOXICOLOGY
Faculty of Medicine, Cairo University***

Supervised by

Prof. Dr. ALY GAMAL ELDIN ABDEL AAL

***Professor of FORENSIC MEDICINE AND CLINICAL TOXICOLOGY
Faculty of Medicine – Cairo University***

Prof. Dr. DINA ALI SHOUKRY

***Professor of FORENSIC MEDICINE AND CLINICAL TOXICOLOGY
Faculty of Medicine – Cairo University***

Prof. Dr. MANAL MOHY EL-DIN ISMAIL

***Professor of FORENSIC MEDICINE AND CLINICAL TOXICOLOGY
Faculty of Medicine – Cairo University***

***Faculty of Medicine,
Cairo University***

2008

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Table of Contents

Contents	Page
Abstract	1
Introduction & Aim of Work	2
History	7- 18
Toxicogenomics	19-50
☒ A shift in paradigm	21
☒ Why Toxicogenomics?	24
☒ Toxicogenomic studies.	37
☒ Toxicogenomics technologies.	41
☒ Toxicogenomics related technologies	47
Transcriptomics	51-65
☒ Systems beyond transcriptomics.	51
1. Open systems	52
2. Closed systems	56
Proteomics	66-78
☒ If we can measure gene expression, why bother with proteomics?	68
☒ Proteomics versus protein chemistry	69
☒ Applications of proteomics	70
☒ Tools of proteomics.	72

Metabolomics and Metabonomics	79-88
☒ Metabonomics: the new science of metabolic integration.	80
☒ Principles of metabolomics and metabonomics.	81
☒ Metabolomics offers several advantages over genomics and proteomics.	85
☒ Metabolomic analysis	85
Bioinformatics	89-103
☒ Principles	93
☒ Bioinformatics isn't just about database.	100
Applications of Toxicogenomics	104-152
1. Hepatotoxicity	104
2. Cardiotoxicity	120
3. Nephrotoxicity	130
4. Carcinogenesis	136
5. Teratogenesis	149
Toxicogenetics	153-160
☒ Variability in human genome.	154
☒ Applications of Toxicogenetics.	158
☒ Toxicogenetics & Toxicogenomics provide complementary information.	160
Limitations, Validation and Toxicogenethics	161-181
1. Limitations.	161
2. Validation.	168

3. Toxicogenethics.	171
Future perspectives and Recommendations	182-188
Summary	189-192
References	193-261
Arabic Summary	1-3

List of Figures

Figures	Heading	Page
Fig. 1	Relative predictive value of predictive safety assessment methods from the discovery to the preclinical stage.	29
Fig. 2	Protein identification with peptide mass fingerprinting.	31
Fig. 3	The role of genetic susceptibility and computational models on the continuum from exposure to disease outcome.	42
Fig. 4	Comparison of toxicogenomics and conventional toxicology.	49
Fig. 5	Overview of transcription profiling technologies.	55
Fig. 6	Biological context of genomics and proteomics	66
Fig. 7	Key steps in proteomic analysis	73
Fig. 8	The “Omics” sciences are characterized by complex datasets of related phenomena each of which taken as a whole constitute a picture of an organism	80
Fig. 9	Summary of the different metabolomics-based strategies for sample preparation and sample analysis	87

Fig. 10	A schematic overview of bioinformatics.	92
Fig. 11	How technology intersect with biology.	100
Fig. 12	Mechanism of acetaminophen toxicity providing a summary of pathways leading to toxicity.	112
Fig. 13	Toxic cascade of events in APAP-overdosed mouse liver.	114
Fig. 14	Metabolism of Isoniazid in the liver	116
Fig. 15	The pathway of fatty acid synthesis and the relative induction or repression of genes with statistically significant differences.	119
Fig. 16	Potential mechanisms of cardiovascular injury and dysfunction mediated by PM and/or O ₃ exposure.	122
Fig. 17	A chronic exposure of the pulmonary system and skin to ozone and UV radiation	129
Fig. 18	Overview of genotoxic and non-genotoxic effects of carcinogens	137
Fig. 19	Pathway Studio diagram of common regulators of differentially expressed genes	144
Fig. 20	Tumor promotion and tumor initiation.	148

Fig. 21	Interaction of genes and drugs	154
Fig. 22	The effects of genome polymorphism on gene function.	157
Fig. 23	ICCVAM test method validation process	169
Fig. 24	Three steps in the development of a diagnostic classifier	170

List of Tables

Tables	Heading	Page
Table 1	Transcriptome analysis: Differences between open and closed systems	54
Table 2	Differences between protein chemistry and proteomics	69
Table 3	Analytical tools used in proteomics	75
Table 4	Contemporary metabolomic platforms and their applications.	84
Table 5	Strategies for metabolomics analysis	86
Table 6	Summary of publicly available databases and tools for in silico toxicology	97
Table 7	Gene expression profiles of some hepatotoxicants causing induction of CYP-P450 family	106
Table 8	Gene expression profiles of some hepatotoxicants causing Necrosis.	110
Table 9	Genes associated with renal injury by cisplatin.	133
Table 10	Known transcription factors involved in teratogenic responses.	151

Table 11	Selected polymorphic enzymes associated with altered drug response.	159
Table 12	Toxicogenomic Standards and their organizations	162
Table 13	Drug metabolizing enzyme markers predictive of adverse drug reactions.	185

List of Abbreviations

Abbreviation	Stands For
¹H NMR	High Resolution NMR Spectroscopy
2D-PAGE	2 Dimensional Polyacrylamide Gel Electrophoresis
ACeDB	A. C. elegans Database
<i>Acly</i>	ATP-Citrate Lyase Gene
ACOX	Acyl-Coa Oxidase,
Acs11	Acyl-Coa Synthetase Long-Chain Family Member 1
ADME/Tox	Absorption, Distribution, Metabolism, Excretion and Toxicity
AHH	Aryl Hydrocarbon Hydroxylase
AhR	Arylhydrocarbon Receptor
Aldh3a2	Aldehyde Dehydrogenase Family 3 , Subfamily A2
<i>Anxa2</i>	Calpactin I Heavy Chain Gene
<i>Anxa5</i>	Annexin A5
APAP	Acetaminophen

Apoc2	Apolipoprotein C2
APOJ	Apolipoprotein J
<i>A-raf-1</i>	A-Raf Proto-Oncogene Serine/Threonine-Protein Kinase -1
ATP	Adenosine Triphosphate
BALF	Bronchoalveolar Lavage Fluid
<i>BAX</i>	Bcl2-Associated X Protein
BLAST	Basic Alignment Search Tool
CAR	Constitutive Androstane Receptor
Cd36	CD36 Antigen (Collagen Type I Receptor, Thrombospondin Receptor)
CD4	Cluster Of Differentiation 4
<i>CDK5</i>	Cyclin-Dependent Kinase 5
cDNA	Complementary Deoxyribonucleic Acid
CE-LIF	Capillary Electrophoresis-Laser-Induced Fluorescence
CE-MS	Capillary Electrophoresis– Mass Spectrometry
c-fos	FOS: V-Fos FBJ murine Osteosarcoma viral Oncogene
<i>CIP1</i>	Cop1-Interactive Protein 1

CLO	Clofibrate
<i>Clu</i>	Clusterin Gene
c-myc	Avian Myelocytomatosis Viral Oncogene Homolog
<i>Colla1</i>	Collagen Type 1, Alpha 1 Gene
COT	Cancer Osaka Thyroid) Oncogene
CSeco	3 β -Hydroxy-5-Oxo-5,6-Secocholestan-6-Al
CSF	Cerebrospinal Fluid
CTD	Comparative Toxicogenomics Database
CVD	Cardiovascular Disease
CYP450	Cytochrome P450s
cyt-c	Cytochromes C
DD	Differential Display
DIMS	Direct Injection Mass Spectroscopy
<i>DraI</i>	Restriction Enzyme Source: A <i>E. Coli</i> Strain That Carries The DraI Gene From <i>Deinococcus Radiophilus</i>
ECVAM	European Center for Validation of Alternative Methods
<i>Egf</i>	Epidermal Growth Factor Gene

EGR-1	Early Growth Response Protein-1
Ehhadh	Enoyl-CoA Hydratase / β -Hydroxyacyl -CoA Dehydrogenase
ELSI	Ethical, Legal And Social Implications
ENCODE	Encyclopedia of DNA Elements
EP300	E1A Binding Protein P300
ER	Estrogen Receptor
<i>Erk-3</i>	Extracellular Signal-Regulated Kinase 3
EST	Expressed Sequence Tag
FABP	Fatty Acid Binding Protein
<i>Fasn</i>	Fatty Acid Synthase Gene
FDA	Food and Drug Administration
FT-IR	Fourier Transformed Infrared Spectroscopy
<i>G6pc</i>	Glucose-6-Phosphatase Gene
GADD153	Growth Arrest and DNA Damage Response
GC–MS	Gas Chromatography–Mass Spectrometry
<i>Ghr</i>	Growth Hormone Receptor Gene

GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GSH	Glutathione
GST Ya	Glutathione S-Transferase Ya
<i>Gstm2</i>	Glutathione <i>S</i> -Transferase, Mu 2 Gene
<i>Gstp2</i>	Glutathione <i>S</i> -Transferase, Pi 2 Gene
GTX	Genotoxic Carcinogens
GZMB	Granzyme B
HGP	Human Genome Project
HIF	Hypoxia-Inducible Factor
HLA-DR	Human Leucocytic Antigen-Dr
HNE	4-Hydroxy-2,3-Trans-Nonenal,
HRV	Heart Rate Variability
HSP-10	Heat-Shock Protein-10
HUGO	Human Genome Organization
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
<i>Id1</i>	Inhibitor Of DNA Binding 1