TNFalpha-signaling in drug-induced liver injury

Fredriksson, L.E.

LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AIF	Apoptosis-inducing factor
AMAP	3'-hydroxyacetanilide
AMI	Amiodarone
AnxV	Annexin V
APAF1	Apoptosis protease-activating factor 1
APAP	Acetaminophen; paracetamol
ATF4	Activating transcription factor 4
ATF6	Activating transcription factor 6
AUC	Area under curve
BAC	Bacterial artificial chromosome
CBZ	Carbamazepine
cFLIP	Cellular FLICE inhibitory protein
CHOP	C/EBP-homologous protein
CLZ	Clozapine
CYLD	Cylidromatosis
CYP450	Cytochrome P450
DCF	Diclofenac
DILI	Drug-induced liver injury
DMSO	Dimethyl sulfoxide
EIF	Eukaryotic translation initiation factor
ESI	Electrospray ionization
ER	Endoplasmic reticulum
FADD	Fas-associated death domain
GFP	Green fluorescent protein
GPX	Glutathione peroxidase
GRP	Glucose-regulated protein
GSH	Glutathione
GST	Glutathione S-transferase
HLA	Human leukocyte antigen
HMGB1	High mobility group box 1
HSP	Heatshock protein
IAP	Inhibitor of apoptosis protein
iDILI	idiosyncratic drug-induced liver injury
IFN-γ	Interferon-γ
IκB	Inhibitor of κB
IKK	IκB kinase
IL-1β	Interleukin-1β
IL-6	Interleukin-6
INH	Isoniazid

IPA®	Ingenuity Pathway Analysis
IRE-1α	Inositol-requiring enzyme 1α
JNK	c-Jun N-terminal kinase
Keap1	Kelch-like ECH-associated protein 1
KTZ	Ketoconazol
LDH	Lactate dehydrogenase
LPS	Lipopolysaccharide
MAPK	Mitogen activated protein kinases
MHC	Major histocompatibility complex
MOMP	Mitochondrial outer membrane permeabilization
mPT	Mitochondrial membrane permeability transition
MTX	Methotrexate
NEMO	NF-κB essential modifier
NF-κB	Nuclear factor κB
NFZ	Nefazodone
NIK	NF-κB inducing kinase
NPX	Naproxen
Nrf2	Nuclear factor-erythroid 2 (NF-E2)-related factor 2
NSAID	Non-steroidal anti-inflammatory drug
NTF	Nitrofurantoin
OFX	Ofloxacin
PARP	Poly (ADP)-ribose) polymerase
PERK	Protein kinase R-like ER kinase
PUMA	p53 up-regulated modulator of apoptosis
RAIDD	RIP-associated protein with a death domain
RIP	Receptor-interacting protein
RNAi	RNA interference
ROS	Reactive oxygen species
shRNA	short hairpin RNA
siRNA	short interfering RNA
SN	Simvastatin
SOD	Superoxide dismutase
SRXN1	Sulfiredoxin 1
TAK1	TGFβ-activated kinase 1
TGZ	Troglitazone
TNFα	Tumor necrosis factor α
TNFR	TNF receptor
TRADD	TNF receptor-associated death domain
TRAF	TNF receptor associated factor
UGT	Uridine diphosphate glucuronosyl-transferase
UPR	Unfolded protein response
XBP1	X-box binding protein 1

CURRICULUM VITAE

Lisa Fredriksson was born the 1st of January 1984 in Uppsala, Sweden. In June 2002 she completed her secondary education at Katedralskolan in Uppsala, with a major in natural science. A bit more than half a year later, in January 2003, she began her university studies to become a pharmacist. In 2007 she obtained her Master of Science in Pharmacy degree at the University of Uppsala after a six-month internship at the Division of Toxicology, Leiden University, under the supervision of Dr. Erik Danen. During this internship she investigated the role of integrins and oncogenes in chemosensitivity, work that later inspired to a publication. After another six-month internship at a pharmacy in Malmö, Sweden, she obtained her license to work as a pharmacist in 2008. However, the internship in Leiden had made her interested in pharmaceutical research and in April 2008 she began her PhD under the supervision of Prof. Bob van de Water. During her PhD she has investigated the role of inflammatory and drug-induced intracellular stress in the development of drug-induced liver injury. She has throughout this period learnt to master several new techniques such as high content confocal microscopy, high throughput siRNA screening as well as pathway analysis of gene expression data. Currently, she is working as a postdoc in the same lab to finalize the publications that will come as a result of her work.

LIST OF PUBLICATIONS

A live-cell imaging-based NF-κB nuclear translocation RNAi screen identifies novel regulators of TNFα-induced apoptosis through control of the (de)ubiquitinase A20
Fredriksson L*, Herpers B*, Benedetti G*, Di Z, de Bont H, Meerman JHN, de Graauw M, van de Water B.
Manuscript in preparation

Translation initiation factor EIF4A1 determines TNFα-mediated apoptosis in drug-induced liver injury through the stress protein CHOP
Fredriksson L*, Herpers B*, Wink S, Benedetti G, de Bont H, Danen EH, Luijten M, de Graauw M, Meerman JHN, van de Water B.
Submitted to Hepatology

High content imaging of Nrf2 and NF-κB activation as markers for the prediction of adverse drug-induced liver toxicity
Fredriksson L*, Herpers B¬*, Di Z, Hendriks G, Vrieling H, de Bont H, van de Water B.
Ready to be submitted to Journal of Hepatology

Automated analysis of NF-κB nuclear translocation kinetics in high-throughput screening
Di Z, Herpers B, **Fredriksson L**, Yan K, van de Water B, Verbeek FJ, Meerman JHN.
Under revision, PlosONE

TNFα-mediated NF-κB survival signaling impairment by cisplatin enhances JNK activation allowing synergistic apoptosis of renal proximal tubular cells
Benedetti G, **Fredriksson L**, Herpers B, Meerman JHN, van de Water B, de Graauw M
Accepted for publication, Biochemical Pharmacology

Diclofenac inhibits tumor necrosis factor-α-induced nuclear factor-κB activation causing synergistic hepatocyte apoptosis
Fredriksson L*, Herpers B*, Benedetti G, Matadin Q, Puigvert JC, de Bont H, Dragovic S, Vermeulen NP, Commandeur JN, Danen E, de Graauw M, van de Water B.
Hepatology. 2011

Cross-talk between integrins and oncogenes modulates chemosensitivity
Puigvert JC, Huveneers S, **Fredriksson L**, op het Veld M, van de Water B, Danen EH.
Molecular Pharmacology, 2009

* These authors contributed equally to the study.

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It has now been a bit more than 4 years since I started this journey, a journey towards a PhD diploma, and now I have reached the final destination.

When I had half a year left of my masters to become a pharmacist, I had no plans to pursue a career in research. After only a few hours in the lab per week, with doing mostly pure chemistry work, there was nothing about research that attracted me. However, my determination to do the internship for my master thesis abroad, made me change my mind. At first I knew that I wanted to go to a big city, but when my professor in Toxicology told me about a cute little town in the Netherlands, a country that I barely heard about before, let alone visited, I thought that this option sounded even better. The fact that my present professor, Bob van de Water, was so quick and friendly in his way of answering the e-mails we exchanged made the choice even easier. Going for my master internship to Leiden was the best thing that I could ever have done, and this decision literally changed my life.

My first supervisors were Stephan Huveneers and Erik Danen. Without them agreeing with taking on a Swedish master student, I would never have made it to Leiden, and if that had not happened I would never have written this thesis. Thank you for accepting me as a student, for including parts of my work in your thesis Stephan, and for publishing the same work, together with Jordi Carreras Puigvert, leading to my first scientific article.

In relation to the above I would also like to show my gratitude to the complete "old" TOX-team for making my master experience so nice that I in the end decided that I wanted to do a PhD in the same lab. Marja Moerkens Noordzij, I am so very grateful for you being such great support, both in and outside the lab, already back then!

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