Exposure to genotoxic chemicals and cancer

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Evolution of the Department of Genetic Toxicology and Cancer Biology

- Department GEN was born in 1996 and is Tamara’s child.

- She was leading GEN for 8 years (1996-2005).

- In 2002 to GEN joined the researchers from the Department Ecotoxicology and Ecotoxinology.

- In 2005 Tamara trusted the management of GEN to me.

- Now after 20 years GEN is a well recognized research group at national and international level.
P1-0245: Ecotoxicology, toxicogenomics and cancer research (PI: Tamara Lah Turnšek; 1999-2018)

**Genetic toxicology:**
- Genotoxins in environment and food: toxins, metals, pesticides, pharmaceuticals, nanoparticles...
- Anticarcinogens: xanthohmol, ...
- New methods in toxicology

**Cancer biology:**
- Mechanisms of cancer development and progression
- Diagnostic & prognostic markers
- New therapeutic approaches: mesenchimal stem cells

**Ecotoxicology:**
- Effects of cyanobacterial toxins and other pollutants on biodiversity
- Ecological monitoring of surface waters (Water directive 2000/06/EU)

**Effects of humans on environment and environment on human health**
Genotoxic chemicals

<table>
<thead>
<tr>
<th>Sources of exposure</th>
<th>Consequences</th>
<th>Measures to reduce consequences</th>
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<tbody>
<tr>
<td>grilled meat</td>
<td></td>
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<tr>
<td>heterocyclic amines</td>
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<tr>
<td>polyaromatic hydrocarbons</td>
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<tr>
<td>cigarette smoke</td>
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<tr>
<td>heavy metals</td>
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<td></td>
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<tr>
<td>arsenic, cadmium, mercury...</td>
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<td></td>
</tr>
<tr>
<td>nanoparticles</td>
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<tr>
<td>pesticides</td>
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<tr>
<td>side products of chlorination</td>
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<tr>
<td>contaminated fruit, vegetables, grains</td>
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<tr>
<td>natural toxins (aflatoxin, mikrocystins)</td>
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<tr>
<td>contaminated water</td>
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<tr>
<td>fish</td>
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<td></td>
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<tr>
<td>contaminated fish</td>
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<tr>
<td>contaminated drink</td>
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- Identification
  - Chemical analyses
  - Genotoxicity testing
  - In vitro, in vivo

- Mechanisms of action
  - Molecular mechanistic studies

- Exposure assessment
  - Biomarkers

- Risk assessment
- Risk management
  - Prevention of exposure
  - Chemoprevention
Cadmium - mechanisms of genotoxicity

- Past wide use, environmental contamination, still problems (certain populations in EU exposed to excessive concentrations (EFSA)).
- Human carcinogen (IARC, EPA, ECHA).
- Mechanism of genotoxic activity: formation of ROS, inhibition of DNA repair.

TWI 2.5/ug/kg bw.
Cyanobacterial toxins

- Products of toxic cyanobacteria.
- The role of cyanotoxins in aquatic ecosystems (dr. Sedmak).
- Genotoxicity studies - dr. Bojana Žegura
  - Promotor (PP1 and PP2A inhibitor)
  - Initiator (oxidative DNA damage: ROS formation, depletion of antioxidants)

- Cylindrospermopsin - an emerging cyanotoxin
  - Induces direct DNA damage
  - Higher genotoxic potential than MCLR
- More hazardous than MCLR?
  - Our studies cited in “Health effects support document for cylindrospermopsin” published by EPA 2015

Mikrocistin LR possible human carcinogen (IARC: Group 2B)
- Promotor (PP1 and PP2A inhibitor)
- Initiator (oxidative DNA damage: ROS formation, depletion of antioxidants)

- Genotoxicity and potential carcinogenicity of cyanobacterial toxins – a review
- Mikrocistin LR possible human carcinogen (IARC: Group 2B)
  - Promotor (PP1 and PP2A inhibitor)
  - Initiator (oxidative DNA damage: ROS formation, depletion of antioxidants)

Cylindrospermopsin induced DNA damage and alteration in the expression of genes involved in the response to DNA damage, apoptosis and oxidative stress
Anticancer drugs in the environment
EU FP7 project - Cytothreat

- Expected concentrations in the environment are low compared to many other drugs (i.e. blood-pressure and lipid regulators, NSAIDs.....)
- Due to their mechanism of action – interference with the genetic material and cell signaling systems - most of the anti-cancer drugs belong to the group of highly dangerous compounds (CMRs) for which no safe level of exposure can be established.
- Do residues of anti-cancer drugs represent environmental risk?

Adverse effects at 10 ng/L

All samples reduced reproduction of C. dubia.
All but one sample induced DNA damage in ZFL cells.
Correlations with anticancer drugs were detected for both bioassays.
Chemoprevention: xanthohumol

- Differential toxicity against cancer and normal cells.
- Protective effect against genotoxicity of dietary carcinogens (HCA) via inhibition of their metabolic activation and induction of detoxification.
- Inhibition of the induction of HCA induced DNA damage and pre-carcinogenic lesions in rat colon and liver at low doses (corresponding to 5 mg/day in a 70 kg person).

Xanthohumol is one of the most promising chemopreventive agents
HepG2CDKN1A–DsRed biosensor system for rapid and simple detection of genotoxic agents

→ High throughput genotoxicity screening tool: pharmaceutical and chemical industry, environmental monitoring


**Response** | **Known genotoxicity activity**
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Positive (25) | Negative (12)
Positve | 21/25 | 1/12
Negative | 4/25 | 11/12

**Sensitivity** (correct prediction of genotoxic compound): 84%
**Specificity** (correct prediction of non-genotoxic compound): 92%
Mesenchymal stem cell derived metabolically active progeny hepatic cells for genotoxicity testing

Day 1                     Day 24

AMC                       PHC

Albumin expression
Glycogen storage

% tail DNA

BaP µM

% tail DNA

AFB1 µM

TBHP µM

% tail DNA

Control

BAp

AFB1

mRNA expression

Cytochrome P450 (CYP3A4, CYP1A1)
NAT2
SULT1A1
GSTP1
UGT1A1

% tail DNA

Immortaliz. PHC
After induction & maturation
After maturation

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Thank's and see you later