In-depth investigation of diet-related DNA adduct formation *via* DNA adductomics: To eat or not to eat red meat!?

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1. Introduction

In 2015, the International Agency for Research on Cancer and the World Health Organization issued that red meat is 'probably carcinogenic to humans' and processed meat is 'carcinogenic to humans'. Epidemiological research has demonstrated that red meat consumption significantly contributes to colorectal cancer (CRC) risk. Different hypotheses have been put forward to explain this causal relationship but the heme hypothesis, stating that heme iron in red meat stimulates the formation of genotoxic N-nitroso compounds (NOCs) and lipid peroxidation products (LPOs), has received the most support. Both NOCs and LPOs can exert DNA damaging effects like e.g. DNA adduct formation. DNA adduct formation is believed to be the first step in chemically induced carcinogenesis.

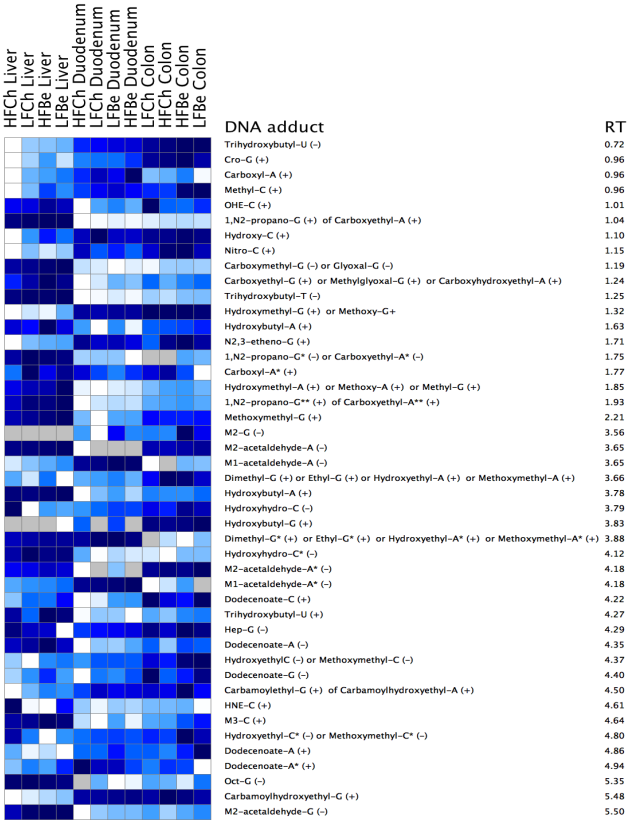

Figure 1. Heat map of DNA adducts in the liver, duodenum and colon of rats fed a high or low fat chicken or beef diet (HF = high fat, LF = low fat, Ch = chicken, Be = beef). Darker shades of blue represent higher DNA adduct levels.

2. Approach

DNA adductomics is a fairly recently breached branch of metabolomics that accommodates the assessment of the environmental exposure to genotoxic chemicals. We developed a novel DNA adductomics methodology to enable a more in-depth investigation of diet-, and more specifically, NOC- and LPO-related DNA adduct formation. More specifically, an in-house diet-related DNA adduct database and a high resolution mass spectrometry (HRMS) based methodology were established. After successful validation (1), the state-of-the-art DNA adductomics platform was implemented to investigate the genotoxic effects of red vs. white meat digestion. Beef (model for red meat) and chicken (model for white meat) were digested *in vitro* (static model) as well as *in vivo* (Sprague-Dawley rats), after which the DNA adductome of digestion samples (*in vitro* setups) and tissues (*in vivo* setup) was mapped. Data processing and statistical interpretation was executed with Xcalibur™, SPSS, SIEVE™, and SIMCA™.

3. Results

Combining the results from 3 independent *in vitro* and 1 *in vivo* digestion experiment(s), 7 DNA adduct types, including O^6-carboxymethylguanine, dimethyl- or ethylthymine, methylguanine, heptanalguanine, a malondialdehyde-guanine adduct, and a malondialdehyde-cytosine adduct could be singled out as potential red meat digestion markers (2).

4. Discussion

The discovery of red meat digestion related DNA adduct markers is highly relevant to the red meat-CRC hypothesis because their formation may be linked to DNA alkylation and/or oxidation by e.g. NOCs and/or LPOs. Follow-up research should further investigate the role of DNA adduct formation in the red meat-CRC pathway as well as the mutagenic potential and human *in vivo* relevance of the proposed DNA adduct markers. In addition, these results demonstrate that the in-house DNA adductomics platform offers new and highly promising perspectives for the assessment of the genotoxic effects of environmental chemicals.

References

1. L.Y. Hemeryck, A.I. Decloedt, J. Vanden Bussche, K. Geboes and L. Vanhaecke. "High resolution mass spectrometry based profiling of diet-related deoxyribonucleic acid adducts". *Analytica Chimica Acta* 892: 123-131, 2015.
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