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DNA ADDUCTOMICS TO UNRAVEL THE POTENTIAL CAUSAL ASSOCIATION BETWEEN RED MEAT DIGESTION AND COLORECTAL CANCER

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Epidemiological research has demonstrated that red meat consumption contributes to colorectal cancer (CRC) risk. The main hypothesis; the heme hypothesis, states that the ingestion of heme iron, which is more abundant in red compared to white meat, stimulates the formation of N-nitroso compounds (NOCs) and lipid peroxidation products (LPOs). Both NOCs and LPOs can exert geno- as well as cytotoxic effects, hence contributing to carcinogenesis. In this study, 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) to investigate gastrointestinal DNA adduct formation upon red *vs.* white meat digestion. DNA adduct formation was assessed by means of a state-of-the-art UHPLC-HRMS DNA adductomics platform, after which univariate (e.g. t-test) as well as multivariate (e.g. OPLS-DA) statistics were employed for red meat associated DNA adduct marker discovery. 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. This is highly relevant to the red meat-CRC hypothesis because the formation of the retrieved DNA adduct types may be linked to DNA alkylation and/or oxidation by e.g. NOCs and/or LPOs. Follow-up research will focus on 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.