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Finding Intermediate DNA Methylation Biomarkers of Early Life Exposures and Later Life Obesity

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Objectives: Many early life exposures have been associated with childhood adiposity, however the mechanisms remain largely unresolved. DNA methylation is hypothesised to be a potential mechanism underlying this phenomenon, with differences in DNA methylation having been associated with adiposity. However evidence linking exposures with both methylation and adiposity is limited. Thus our aim was to investigate the associations between the early life factors, blood DNA methylation, and subsequent adiposity outcomes.

Methods: Using data from the Avon Longitudinal study of parents and children (ALSPAC), associations between early life exposures and methylation at individual CpG sites (at ages 7.5 and 17) were investigated. Exposures investigated included older maternal age at birth, rapid weight gain (RWG), adversity and antibiotic exposure in the first year. DNA methylation for 1,000 study members was measured using the *Infinium* HumanMethylation450 BeadChip (at ages 7.5 and 17). Epigenome-wide association studies were carried out for each exposure with independent surrogate variable analysis. Associations between overweight/obese (OW/OB) and the CpG loci with significant methylation differences were investigated using logistic regression adjusted for confounders.

Results: RWG was associated with differential methylation in childhood for one CpG (5% false discovery rate correction). The significant loci was annotated to upstream of the gene encoding a 5' nucleotidase that localizes to the mitochondrial matrix (NT5M). The mean difference between those who were exposed compared to unexposed was 1% increase in methylation. Methylation at this loci was not associated with OW/OB in childhood in adjusted regression analyses, however there was an association between methylation at this loci at age 17 and OWOB at age 17. Validation of this target in other populations is ongoing. No other early life exposures demonstrated significant associations with DNA methylation in childhood or adolescence.

Conclusion: Overall there were few early life exposures associated with changes in methylation in childhood in this cohort. This study identified a small but significant increase in methylation at one CpG site in blood in childhood in association with early life rapid weight gain. The significant CpG loci could be a potential biomarker of exposure predictive of later life adiposity pending further study.

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Understanding the Bioactivity of Pomegranate Ellagitannins in Humans: Results of a Literature Review

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Objectives: There is strong evidence in animal models suggesting that pomegranate fruit exerts health benefits relating to their antioxidant and anti-inflammatory properties [1]. Beneficial effects are certainly the consequence of the presence of the pomegranate polyphenols, mostly consisting of ellagitannins (ETs). However, studies in humans often failed to show clear associations between pomegranate intake and health outcomes, possibly due to inter-individual variation in absorption, distribution, metabolism, and excretion (ADME) of ETs.

Methods: A literature review was conducted using the PubMed and Scopus databases including all original research articles on the relationship between inter-individual variability and ADME of ETs in humans. Data were summarized in a tabulated summary containing: study design, population, description of the intervention, duration, outcomes relevant to inter-individual variability in bioavailability and metabolism of ETs.

Results: From 2004 to date, most of the research studies are mainly related to cardiometabolic risk biomarkers. Intervention studies are carried out using pomegranate juice or phenolic extracts at different doses of ETs. Additionally, the study designs used differ for each trial. Data on the four criteria ADME were not available in all publications. Results showed that urolithins are the predominant metabolites following pomegranate consumption. Anyhow, few works are still focused on the bioconversion of pomegranate ETs to their active metabolites.

Conclusions: Urolithins are colonic microbiota metabolites of ETs and are considered responsible for *in vivo* health effects. The recently discovered existence of human metabolic phenotypes or metabotypes [2] could explain the variability seen in diet intervention studies. An understanding of the ADME of ETs in relation to the inter-individual variability is crucial for the elucidation of the mechanisms responsible for the health benefits of pomegranate and other ET-rich foods.

Acknowledgments: This study was supported by the SIR programme (no. RBSI14LHMB) granted by the Italian Ministry of Education, University and Research.

References

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