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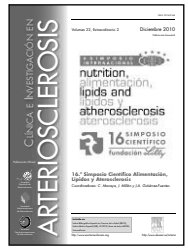

16.º SIMPOSIO CIENTÍFICO ALIMENTACIÓN, LÍPIDOS Y ATEROSCLEROSIS

Human microbiome evolution, health and predisposition to disease

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Understanding the contribution of gene-environment interactions in the aetiology of cardiovascular disease, and particularly the role of nutrition as a driver for adverse or protective effects, is of prime importance if we are to reduce the global burden of disease in ageing western populations. To this end, an array of post-genomic technologies (transcriptomics, proteomics, metabonomics, etc.) have been applied to characterizing heart disease in order to improve our understanding of the aetiology and to discover diagnostic or prognostic biomarkers of the disease.

Of the 'omics' technologies, metabonomics provides the most accessible window on investigating the impact of nutritional interventions on cardiovascular health since metabolic profiles of easily obtainable biofluids such as blood plasma and urine carry information relating both to genetic and environmental influences[1]. Metabonomics relies upon the use of high resolution spectroscopic techniques, typically either nuclear magnetic resonance (NMR) spectroscopy or mass spectrometry, to generate comprehensive low molecular weight profiles of biofluids, tissues or cells, which can be subsequently modelled and interpreted using multivariate statistics. By comparison of metabolic profiles from samples obtained from groups of individuals under different physiological or pathological conditions, for example atherosclerosis versus healthy, metabolites that systematically differentiate two or more conditions can be obtained and used in a diagnostic capacity or to improve mechanistic understanding. Although a few preliminary metabonomic studies have been conducted to characterize the metabolic consequences of atherosclerosis either in animal models[2] or in humans[3,4], the technology has not yet been fully exploited with respect to interrogating the mechanisms of cardiovascular disease. However, even from the limited number of studies undertaken to date, evidence suggests that there is a definitive metabolic signature associated with the disease and that this metabolic signature can be modulated by dietary intervention.

In a recent study, in which a metabolic profiling strategy was applied to a large scale epidemiological study on the impact of diet on hypertension (the INTERMAP study; International Collaborative Study of Macronutrients, Micronutrients and Blood Pressure), a range of metabolites were identified that differentiated populations with vastly differing blood pressure levels and lifestyles[5]. This metabolome wide association study (MWAS) approach harnesses the power of large epidemiological cohorts and high throughput metabolic profiling to generate associations between metabolism, lifestyle and disease in complex free living populations. Amongst the candidate biomarkers of hypertension derived from this study several of the strongest were metabolites involved in gut microbial metabolism or mammalian-microbial co-metabolism and included hippurate (inversely associated with BP), phenylactetylglutamine and formate.

The role of the gut microbiota either in the aetiology and development of disease, or as factors to be considered in calculating disease risk, is currently under scrutiny. Co-evolution has influenced the microbiome of organisms such that metabolic complementarity exists within the microbiota and that critical biosynthetic pathways are provided for the host that significantly extend host metabolic capacity. In addition to their primary function in host immunity the microbiota are known to be associated with harvesting of energy, metabolism of xenobiotics and have been implicated in metabolic signaling. Landmark studies in both animal models and humans, such as those

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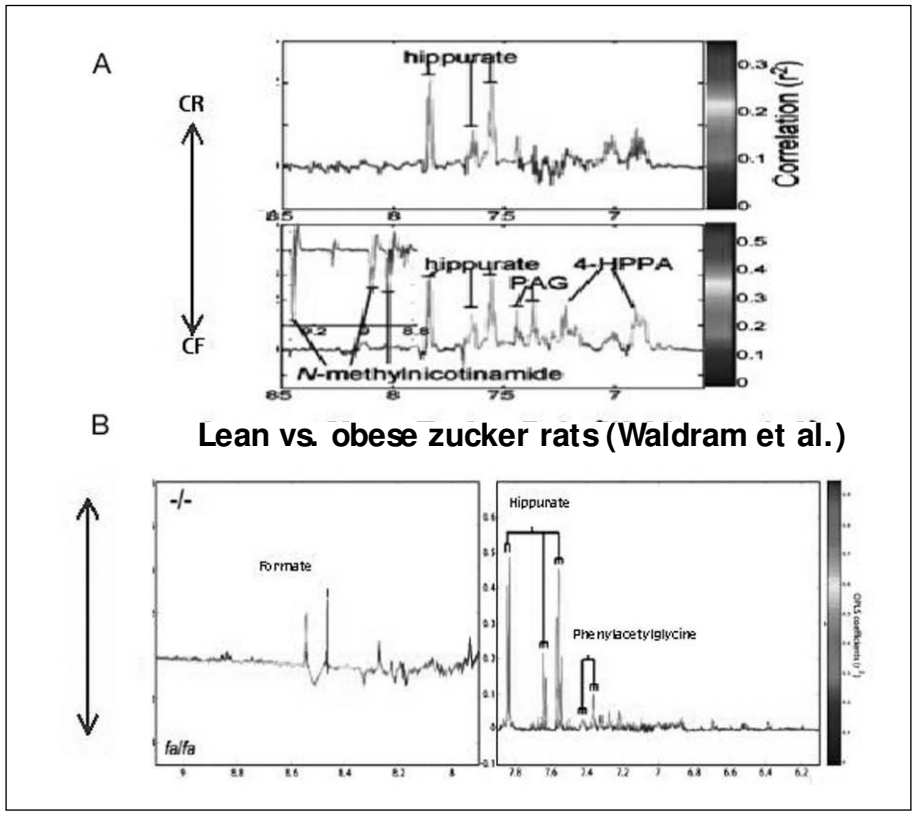

Figure 1 A) Control fed (CF) vs. caloric restricted (CR) dogs (Wang et al). B) Lean vs. obese Zucker rats (Waldram et al).

from Gordon's group, have shown that obese and lean individuals carry a different gut microbial composition[6,7]. In addition to providing a means of investigating mammalian biochemical pathways, metabolic profiles can also reflect gut microbial composition or activity. Clear differences in microbially-derived metabolites have been shown in urinary, fecal and plasma profiles from obese individuals with metabolites such as hippurate (glycine conjugate of benzoic acid) and phenylacetylglutamine being associated with leaner phenotypes in a range of animal models and in man[8,9]. Bariatric surgery is increasingly utilized as a therapeutic intervention for morbid obesity and is also known to cure type 2 diabetes in the majority of cases. Metagenomic profiling of fecal samples post bariatric surgery have shown a shift towards increased numbers of proteobacteria[9] and in a separate study focusing on the plasma metabolite profile, an increase in 4-cresyl sulfate, a microbial metabolite known to be produced by several species of Clostridia was recorded consistent with a modified microbiome post surgery[10]. Collectively the evidence points towards the gut microbiota playing a significant role in conditions associated with cardiovascular health. One of the most promising developments in this respect is the ability to statistically integrate metabolic profiles with metagenomic profiles in order to extract correlations between particular bacterial species or families and metabolites. This has been achieved using correlation methods[11] or bidirectional linear projection methods[12] to derive core microbial-metabolite associations. There is much to be learned from this line of investigation and a series of studies focussing on the effect of nutritional interventions on metabolic profiles with respect to obesity and metabolic syndrome have shown that it is possible to modify the metabolic signature relating to microbial metabolism, and to link this to phenotypic changes, for example weight loss[13]. Transgenomic interactions have been identified following the implementation of high fat diets, with particular effect on the gut microbial products of choline metabolism such as methylamines[14], whilst administration of pre- and pro-biotics have been shown to alter plasma lipids favourably, in addition to inducing changes in a range of urinary gut microbial metabolites including microbially modulated bile acids[15]. New research indicates that in both germ free and antibiotic models of microbial depletion the bile acid profiles of several tissues, including that of the liver, kidney and heart is significantly different from conventional animals, containing a substantially higher percentage of tauro-conjugated bile acid species (Jonathan Swann unpublished observation). This indicates that the presence of microbiota influences the global metabolism of the host and may impact on the development of heart disease and metabolic disorders.

Metabolic profiling is now widely accepted as a clinically relevant tool for investigating disease and is gaining credibility in probing transgenomic interactions between the gut microflora and the host. The true impact of the microbiota on cardiovascular disease is yet to be elucidated but evidence points to a contribution at multiple levels ranging from lipid metabolism to generating toxic metabolites from putrefaction of proteins. Further

investigation of this mammalian-microbial interaction will promote a deeper understanding of the pathology and may ultimately result in the discovery of new drug targets.

Conflict of interest

The author declares she has not any conflict of interest.

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