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Diet is increasingly appreciated as one of the most important environmental factors for maintaining health and preventing disease throughout the life span. The field of nutritional sciences is currently undergoing a period of unprecedented growth and maturation, as understanding the complexity underpinning the molecular basis of individual responses to dietary exposures is now within reach. Technological advances and omics approaches are yielding a comprehensive understanding of the interactions among human genetics, epigenetics, and the microbiome, and their collective contributions to variations in human dietary needs during all stages of human growth, development, and aging. Furthermore, investigations into unique responses of embryonic and adult stem cells to their nutritional milieu hold promise for understanding the plasticity and programming of biological networks that permit adaptation to nutrient exposures, and informing novel nutritional and other therapeutic approaches to healthy aging. Nutrition research is rapidly evolving from using mostly linear and descriptive approaches to a more quantitative and systems-level science. Such approaches are essential to address effectively the increasing incidence of nutrition- and lifestyle-related chronic diseases at both individual and population levels.

This volume brings together leading experts in the areas of nutrition, nutrigenomics, metabolic programming, food-based bioactive dietary components, and the gut microbiome, as well as those experts in the application of innovative tools and methods for statistical and biological network analysis, which are now at the forefront of nutritional and biomedical sciences. The chapters provide a roadmap for the integration of normative science methods and approaches with more comprehensive systems biology-based investigations that deploy a multitude of omic platforms. This integration is essential to escape the bottleneck in knowledge generation by applying decades of knowledge about nutrients and their function to comprehensive omics and clinical data acquisition, processing, visualization, and interpretation. Achieving a systems-level understanding of nutrient function in health and disease will usher in an age of precision nutrition in support of maximizing human health and potential.

Martin Kussmann
Patrick J. Stover
Biography of Martin Kussmann

Martin has been recruited as “Professor of Systems Biology in Nutrition and Health” at the Liggins Institute, University of Auckland, New Zealand. He has also been appointed Chief Scientist of the NZ “National Science Challenge” on “High-Value Nutrition”.

In February 2011, Martin joined the Nestlé Institute of Health Sciences (NIHS) on the campus of the Ecole Polytechnique Fédérale Lausanne (EPFL), Switzerland, as Head of the “Molecular Biomarkers Core”, which he has built from scratch. This core facility and program had initially covered five platforms and teams, i.e. proteomics, metabonomics, lipidomics, micronutrient analysis and diagnostics. Over the first five years of NIHS, Martin seeded lipidomics, micronutrient analysis and diagnostics in his team, and then been spun these out into other research cores, according to their main applications.

Proteomics and metabonomics served as the key molecular phenotyping platforms in Martin’s latest “Systems Nutrition Group” which has developed and conducted systems biology-oriented nutrition and health research in the context of healthy ageing with a focus on cognitive, metabolic and intestinal health.

In June 2009, Martin was appointed Honorary Professor for Nutritional Science at the Faculty of Science, Aarhus University, Denmark. Since June 2012, he has been Lecturer (Maître d’Enseignement et Recherche, MER) at the Faculty of Life Sciences, EPFL. From March 2003 to January 2011, Martin was leading the Functional Genomics Group at the Nestlé Research Centre, Lausanne, and was responsible for nutrigenomics and nutri(epi)genetics.

Being educated and trained as an analytical biochemist, Martin has acquired research experience in the pharmaceutical, biotech start-up and nutritional industry. Martin holds a B.Sc. from the Univ. Aachen, Germany, and a M.Sc. from the Univ. Konstanz, Germany. He performed his doctoral research in Konstanz and at the University of California, San Francisco, USA. During his doctorate and post-doctorate, he has specialised in mass spectrometry, proteomics and genomics.

Martin has (co-)authored >130 publications, edited books and journal issues, and is an internationally requested author and speaker. He serves on the Scientific Advisory Boards of Keystone Symposia, the Human Proteome Organisation (HUPO), and the OMICS Group. He is an Editorial Board Member of e.g. Frontiers; Genes and Nutrition; Applied and
Translational Genomics; Journal of Proteomics; OMICS Journal of Integrated Biology; and Journal of Integrated Omics.

**Competences**

- Nutrigenomics & Personalized Nutrition
- Proteomics, Metabonomics, Lipidomics
- Essential and Micro-Nutrients
- Molecular Diagnostics
- Metabolic, Gastrointestinal and Immune Health
Section I  Genes, Proteins, and Nutrition
1 The use of transcriptomics as a tool to identify differences in the response to diet

Juri C. Matualatupauw and Lydia A. Afman

1.1 New concepts in nutrition research

The role of nutrition in the pathogenesis of metabolic diseases, such as type 2 diabetes and cardiovascular disease, is clearly recognized. In the past, nutritional research was aimed at providing general dietary advice with the goal of improving population health. A problem with this approach is that even though dietary changes may be of great benefit at the population level, the effects at the individual level are very small and hardly noticeable [1]. The ultimate way to improve health is by providing personalized dietary advice. New approaches and methodologies are essential if we want to demonstrate nutritional effects on health at the individual level. The main challenges that we are facing within the nutrition field are the high variability in response to nutrition between subjects, the relatively small effects of nutrition, and the long period it may take before effects become evident. One of the key issues with the high variability in response is that not only non-mutable factors such as age, gender, and genotype affect the response but also changeable factors such as health status affect the response to nutrition. The drawback with the latter is the lack of appropriate biomarkers to characterize individual health status. The markers used to show efficacy of interventions are often late single biomarkers of disease state. These biomarkers are relevant to demonstrate the efficacy of pharmacological interventions but are less applicable to show the efficacy of nutritional interventions, which are mostly performed in a relatively healthy population.

1.2 Comprehensive phenotyping

A new concept in nutrition research is the measurement of a wide range of markers to characterize health, which is called “comprehensive phenotyping” [2]. The arrival of comprehensive genomics techniques in the last decade drove this development, as it allowed the measurement of the expression of thousands of genes, proteins, and metabolites in one sample. These techniques can be applied to a range of samples, including blood, urine, cells,
and tissue biopsies, that can be collected fairly easily during dietary intervention studies in healthy volunteers. In the last few years, we have demonstrated the sensitivity of these techniques by showing nutritional effects on health where classical approaches failed [3,4]. Comprehensive phenotyping not only includes omics techniques but also requires the measurement of classical markers and intermediary endpoint measures that have been shown to be associated with disease. Better characterization of health status by using a comprehensive phenotyping approach not only helps to demonstrate the efficacy of a nutritional intervention but also supports the identification of people at risk for disease development who can still profit from dietary advice.

Comprehensive phenotyping is still in an early phase, and very few studies have been published so far that integrated omics techniques with functional and classical markers in the field of nutrition. Recently, a study has been published in which a huge amount of data was integrated to characterize individual responses to nutrition [5]. The ultimate goal was to develop a machine-learning algorithm that predicts personal postprandial glycemic responses to real-life meals. Week-long glucose levels and responses to 46,898 meals were continuously measured in a cohort of 800 people. This study adopted a comprehensive phenotyping approach by integrating the glucose responses with blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota. The predictions of postprandial glycemic responses were validated in an independent 100-person cohort. Furthermore, a blinded randomized controlled dietary intervention based on this algorithm resulted in significantly lower postprandial glucose responses and consistent alterations to gut microbiota composition. This study shows that with the use of comprehensive phenotyping and adequate data integration, personalized nutrition is potentially within our reach.

1.3 Phenotypic flexibility

Another new development within the nutrition field is the measurement of an individual’s capacity to adapt to dietary challenges, which is called “phenotypic flexibility” [2,6,7]. A dietary challenge, such as a high-fat challenge or an oral glucose tolerance test (OGTT), triggers the adaptation capacity of organs, cells, and tissues and challenges metabolic and inflammatory homeostasis. For example, oral high-fat challenges have been used to study postprandial lipid metabolism, showing a high variation in individual responses. Individuals with a more pronounced postprandial response were at an increased risk of developing CVD. Similarly, an OGTT is used to evaluate insulin resistance. At fasting, insulin insensitivity may not be detectable, but after an OGTT, insulin insensitivity becomes apparent. Phenotypic flexibility can be an important indicator of individual health status, as it might reflect the (dys-)functioning of metabolic organs, such as liver and adipose tissue. It might therefore be able to characterize health status better or reveal effects of nutrition on health that otherwise would have remained undetected.

The combination of both approaches, comprehensive phenotyping and phenotypic flexibility, will result in a dynamic biomarker profile as outcome measure. This profile is expected to provide more information on health status and thus the efficacy of dietary interventions than the static single biomarkers that have been used so far.

Studies using a comprehensive phenotyping approach to characterize individual responses to diet are rare. Most studies that examined individual responses to diet using comprehensive omics techniques performed these analyses retrospectively and only few studies stratified
groups beforehand. The same scarcity accounts for studies that used challenge tests in combination with omics techniques to characterize individual responses based on phenotype.

In this chapter, we summarize the studies that either used non-mutable factors such as age, gender, and genotype or mutable factors such as health status to characterize individual response to diet, in the long or medium term or after a nutritional challenge, with a specific focus on studies that used the comprehensive-omics technique transcriptomics as the outcome measure.

1.4 Factors that influence the transcriptome response to diet

Transcriptomics was one of the first of the omics technologies to be used in nutrition-related research in humans. Much of the research has been focused on examining changes in gene expression patterns using microarrays, upon either acute challenges or longer-term dietary interventions. One of the types of cells that is frequently used to assess transcriptome profiles is blood cells, which are easy and non-invasive to harvest in humans. A subpopulation of blood immune cells regularly studied are peripheral blood mononuclear cells (PBMCs). Subcutaneous adipose tissue is also often studied in human nutrigenomics investigations, because it is relatively non-invasive to take biopsies from this tissue and adipose tissue is known to play a key role in the pathogenesis of metabolic diseases. Lastly, skeletal muscle has also been examined in some studies.

Several studies that investigated the change in whole-genome gene expression upon a nutritional intervention observed large inter-individual differences in response to a dietary intervention [8–11]. The reasons for these large inter-individual differences are not yet fully understood, but can include genetic, phenotypic, or environmental differences between individuals. Of particular interest in the context of personalized nutrition are the studies that identified factors that have an interaction effect on the response to diet. This chapter focuses on studies that examined this interaction effect using transcriptomics as outcome measure. Factors that are discussed are gender, age, genotype, anthropometric measurements, plasma biochemical markers and gut microbiota. Furthermore, we discuss some studies that used other outcome measures to identify responders and non-responders to diet and subsequently used transcriptomics to examine mechanistically the differences between these two groups.

1.4.1 Gender

Gender is one of the most obvious phenotypes for which a difference in response to diet can be expected. However, the number of studies that investigated the difference in gene expression response to diet between men and women is limited. One study examined the postprandial changes in PBMC gene expression after a breakfast based on olive oil with a high or low amount of phenol compounds [12]. Microarray analysis demonstrated a significant change in expression of 98 genes between the high- and low-phenol breakfasts. However, on performing additional separate analyses for men and women, they found a higher number of differentially expressed genes: 250 and 143, respectively. Only 32 genes were differentially expressed in both men and women, indicating that the effect of the phenols on PBMC gene expression might be affected by gender.
Rudkowska et al. [13] examined the effects of 6 weeks of supplementation with n-3 polyunsaturated fatty acids (PUFAs) on PBMC gene expression in 29 overweight and obese men and women. Microarrays showed that 170 transcripts were differentially expressed upon n-3 PUFAs on examining gene expression changes in the total study population. However, when separate analyses for men (n = 12) and women (n = 17) were performed, 610 transcripts were differentially expressed in men and 205 in women. Only nine transcripts overlapped between men and women, indicating that the gene expression response in PBMCs to n-3 PUFAs may be different between men and women. Pathways differentially expressed between men and women were related to oxidative stress, peroxisome proliferator-activated receptor alpha (PPAR-alpha) signaling, and nuclear factor kappa B (NF-κB) signaling. Expression of genes in the oxidative stress and PPAR-alpha signaling pathways were downregulated in men and upregulated in women, whereas genes in the NF-κB signaling pathway were downregulated in men only.

Taken together, these two studies indicate that the gene expression response to certain nutrients is influenced by gender. Even though this seems to be a very plausible assertion, many studies do not differentiate between men and women and the studies described above that examined this aspect only did so in a secondary analysis.

### 1.4.2 Age

Another obvious factor that may cause a difference in response to diet is age. Many studies have already taken age into account by selecting subjects only in certain age groups. We identified only one study that actually examined the effect of age on the whole-genome gene expression response to diet. In that study, Thalacker-Mercer et al. [14] performed a crossover trial in which 12 younger (21–43 years) and 10 older (63–79 years) healthy men were given a controlled diet containing a high, medium, or low amount of protein for three 18-day periods. Microarrays were performed on skeletal muscle biopsies that were taken on day 12 of each intervention period. A significant interaction between diet and age was observed for 853 genes. With increasing protein in the diet, expression of genes related to protein metabolism was found to increase in younger subjects and decrease in older subjects. Moreover, older men had an increased expression of genes related to protein catabolism on the low-protein diet. Previously, older subjects showed a reduced anabolic response in skeletal muscle to increased protein intake compared with younger subjects [15]. It is known that protein needs are indeed different between young and old. Using transcriptomics, Thalacker-Mercer et al. tried to identify processes that take place in the muscle that may be responsible for this. In addition to the effects of protein in muscle, it is conceivable that age may also affect the response to other nutrients and on other tissues.

### 1.4.3 Genotype

One of the most studied feature of personalized nutrition is gene–diet interactions, where researchers examine the effects of gene variants on the response to diet. This area of research is referred to as nutrigenetics. It is clear that some of the individual differences in the response to diet are caused by genetic differences. Research has been focused on examining
the effects of variants of several genes, some of the most studied genes being APOA5, APOE, GST, MTHFR, and PLIN [16]. These studies, however, were focused mostly on the effects of these gene variants on blood biomarkers or disease outcomes. Omics technologies may be very useful for the better characterization of the effects of some of these gene variants and to understand the underlying mechanisms [17]. However, to our knowledge, no studies have investigated gene–diet interactions using a transcriptomics approach.

### 1.4.4 Anthropometric measurements

In addition to non-changeable phenotypes such as gender, age, and genotype, other factors may also affect the response to diet. One of these factors is body mass index (BMI). We performed a study in which the effect of BMI on the postprandial transcription response to a high-fat shake was examined [18]. In a crossover design, 17 lean and 15 obese subjects consumed shakes containing 95 g of fat, enriched in either saturated fatty acids (SFAs) or monounsaturated fatty acids (MUFAs). Microarrays were used to examine changes in whole-genome gene expression in PBMCs before and after intake of the two shakes. We observed marked differences in the response to these high-fat challenges on comparing obese with lean subjects, with 607 and 2516 genes being differentially expressed after the SFA-shake and the MUFA-shake, respectively. In response to the SFA challenge, genes related to platelet activation were upregulated in obese and downregulated in lean subjects. In response to the MUFA challenge, genes related to post-translational protein modification were upregulated in obese and downregulated in lean subjects. Genes related to G-protein-coupled receptors were downregulated in obese and upregulated in lean subjects.

Another study examined the effect of BMI on postprandial gene expression response to a high-fat challenge and a high-glucose challenge [19]. In this crossover study, a subgroup of 23 subjects underwent both the high-fat and the high-glucose challenge. PBMC gene expression profiles were determined before and after both challenges. It was found that some genes showed a consistent response regardless of BMI. However, a considerable number of genes responded in a BMI-dependent manner: 760 genes for the high-fat and 269 for the high-glucose challenge. These genes were related to T-cell receptor-mediated inflammatory signaling and cell adhesion pathways, with some of these genes being downregulated and some upregulated with increasing BMI. Moreover, the effect of BMI on the gene expression profiles was larger for the high-fat than the high-glucose challenge.

In addition to these acute challenge studies, the effects of BMI on mid- to long-term dietary interventions have also been investigated. Pasman et al. [20] studied the effects of BMI on adipose tissue gene expression profiles during 4 weeks of high versus low vegetable consumption. Ten lean and ten obese subjects consumed 200 or 50 g of vegetables daily in a crossover study design. On comparing the high and low vegetable intakes, 532 genes were found to be differentially expressed in lean subjects and 323 in obese subjects. In lean subjects, enriched pathways were related to inflammation, with an increase in gene expression of interleukin 8 (IL-8) and NFKB2 and a decrease in gene expression of complement component 3 and NFKB inhibitor. In the group of obese subjects, inter-individual variation in response was found to be high and consequently no pathways were found to be enriched.
In one study, a short-term intervention was performed to examine the effect of BMI on the gene expression response in adipose tissue to a 9-day nutritional intervention [21]. In a crossover study design, subjects consumed 40 g/day of either an intervention spread, containing increased amounts of medium-chain triglycerides, PUFAs, and conjugated linoleic acid, or a control spread. The intervention decreased the expression of genes related to energy metabolism in lean subjects only. Obese subjects showed a downregulation of inflammatory genes and an upregulation of lipid metabolism-related genes. Interestingly, interindividual variation in the gene expression response in the obese subjects was found to be fairly high. The authors performed an additional analysis, in which they found that expression of genes related to mitochondrion, cell adhesion, extracellular matrix, immune response, and inflammatory response correlated better with waist-to-hip ratio and fat percentage than BMI.

In addition to BMI, the amount of fat tissue or body fat distribution may be important in determining the response to diet. In a small crossover study, Radonjic et al. [22] examined the effect of body fat distribution on the whole-genome gene expression response to two dietary fat interventions. Microarrays were performed on adipose tissue samples before and after interventions. The authors compared subjects with upper body obesity (waist-to-hip ratio >1) with those with lower body obesity (waist-to-hip ratio <1). The intervention diets contained either predominantly long-chain PUFAs or medium-chain fatty acids. On comparing the effects of the two interventions on gene expression, they found more genes to be differentially expressed in upper-body obese subjects (239 genes) than in lower-body obese subjects (73 genes). A subsequent analysis on pathway level showed that with increasing waist-to-hip ratio, expression of immune response and apoptosis-related genes increased and that of metabolism-related genes decreased on comparing the medium-chain fatty acid- with the PUFA-enriched diet. This study shows that there may be differences in the gene expression response to dietary fatty acids between upper- and lower-body obese subjects. However, the number of subjects in this study was small, with five upper-body obese subjects and six lower-body obese subjects, so care should be taken with the interpretation of the results.

In summary, BMI has been shown to affect the acute postprandial gene expression response to different types of acute challenges in PBMCs. These effects were mainly observed in pathways related to inflammation and cell adhesion. Moreover, the effect of BMI on gene expression changes was found to be stronger for a fatty acid challenge than a glucose challenge. For short- to medium-term dietary interventions, there is some evidence that both BMI and body fat distribution may affect the response of the subcutaneous adipose tissue to diets containing different types and amounts of fatty acids. Lastly, waist-to-hip ratio and fat percentage may explain a larger proportion of the inter-individual differences in response to nutritional interventions than BMI.

1.4.5 Plasma biochemical markers

High levels of triglycerides, LDL-cholesterol and total cholesterol and also low levels of HDL-cholesterol in the blood are associated with an increased risk of CVD. Understanding how persons with different levels of these biomarkers respond to dietary interventions could be very useful in preventing disease. One study used a transcriptomic approach to examine the effects of 12 weeks of fish-oil and corn-oil supplementation in normo- and dyslipidemic men (total cholesterol >200 mg/dl, LDL-cholesterol >130 mg/dl, triglycerides >150 g/dl) [23].
Microarrays were used to study whole blood cell gene expression. Substantially more genes were differentially expressed by 12 weeks’ consumption of both types of oils in dyslipidemic men than in normolipidemic men. Fish-oil supplementation regulated genes related to immune system, inflammation, lipid metabolism, and cardiovascular disease in the dyslipidemic subjects. Expression of several genes related to fatty acid metabolism were downregulated, emphasizing the potential beneficial value of n-3 PUFAs in dyslipidemic persons.

1.4.6 Gut microbiota

The link between the gut microbiota and the development of obesity, CVD, and type 2 diabetes has attracted much attention in recent years [24]. It has become clear that the microbes in the gut can affect the way in which we respond to nutrients. One of the nutrients that has been studied in relation to the gut microbiome is isoflavones. Isoflavones are compounds that are naturally present in soy and are structurally very similar to the 17β-estradiol hormone. The effects of isoflavones are mediated, in part, by their binding to estrogen receptors [25]. Therefore, isoflavone supplementation might be of interest during and after menopause. In women, isoflavones are thought to have positive health effects with regard to menopausal complaints, such as hot flashes [26]. One of the major soy isoflavones, daidzein, is converted to equol by intestinal bacteria. Of all humans, 30–60% carry these bacteria and are equol producers. Equol has a higher estrogenic and antioxidant activity than daidzein and other isoflavones. Owing to these properties, it is hypothesized that supplementation with isoflavones is especially beneficial in equol producers [27].

Niculescu et al. [28] performed a study that was designed to examine the effect of equol producer status on isoflavone supplementation-induced changes in gene expression in blood lymphocytes. Postmenopausal equol-producing and non-producing women showed a similar number of differentially expressed genes after 84 days of soy isoflavone supplementation compared with placebo: 319 versus 322, respectively. However, equol-producing women had an increased expression of estrogen-responsive genes compared with non-producers, illustrating the importance of equol-producer status in modulating estrogen-related actions of isoflavones.

We also studied the effect of equol-producer status on whole-genome gene expression in the adipose tissue of post-menopausal women following 8 weeks’ consumption of two different commercially available isoflavone supplements that were either low or high in genistein [29]. For the low-genistein supplements, 883 and 1169 genes were differentially regulated in non-equol and equol producers, respectively, whereas for the high-genistein supplements, 547 and 631 genes were differentially regulated for non-equol and equol producers, respectively. Independent of supplement type, expression of energy metabolism-related genes was downregulated in equol producers and upregulated in non-producers after supplementation. Furthermore, equol producers showed an anti-inflammatory gene expression response to the two types of isoflavone supplements whereas this response was not observed in non-producers.

In summary, the effects of the gut microbiome on whole-genome gene expression have been studied only in the specific case of equol-producing bacteria. The transcriptomics studies point towards more pronounced effects of isoflavones in equol-producing post-menopausal women. Much remains to be studied with regard to gut microbiome–diet interactions.
1.5 Using transcriptomics to explain the mechanism behind differences in response to diet

Transcriptomics has also been used to understand better the differences between responders and non-responders to interventions. Shike et al. [30] studied the effects of soy supplementation on gene expression in patients with invasive breast cancer. Patients were randomly assigned to soy supplementation (n=70) or placebo (n=70) for the period from diagnosis until surgery, which ranged from 7 to 30 days. Genome-wide gene expression was measured post-treatment in surgically resected tumor samples of a larger group (n=35) of patients using microarrays. In a secondary analysis, they compared the gene expression response between high and low responders to the intervention based on serum genistein levels. They compared tumor gene expression in a high-genistein level subset of patients (n=12) with that in a subset of patients with low genistein levels (n=23). A total of 126 genes were differentially expressed between these two groups and pathway analysis revealed an increased expression of pathways related to cell growth and proliferation in the tumors of the high-genistein patients. Moreover, expression of FGFR2, a known oncogene and marker of poor prognosis in breast cancer [31], was increased in the high-genistein compared with the low-genistein group. Overall, this study provides indications that soy supplementation may not be beneficial in all breast cancer patients and identifies a subgroup of patients who show a high-genistein response in which soy supplementation may actually be harmful.

Rudkowska et al. [32] compared PBMC transcriptomic profiles of responders and non-responders to 6 weeks of n-3 PUFA supplementation. Six subjects in whom plasma triglycerides were lowered by n-3 PUFAs (responders) were matched to six subjects in which they were not (non-responders). Several genes related to lipid metabolism were differentially expressed between responders and non-responders. These results indicate that there may be some differences in the way in which lipids are handled between the two groups.

Mutch et al. [33] investigated differences in gene expression profiles between subjects who maintained weight loss versus those who regained weight after a period of caloric restriction. They compared changes in whole-genome gene expression profiles in subcutaneous adipose tissue upon caloric restriction in the two groups and found 1291 and 1298 genes differentially expressed by caloric restriction within weight maintainers and weight regainers, respectively. Weight maintainers showed decreases in expression of genes related to extracellular matrix, whereas the weight regainers showed increased expression in these genes. Moreover, weight maintainers increased their expression of genes related to apoptosis and p53, whereas the weight regainers showed no change in expression of these genes. In conclusion, this study reveals differences in gene expression profiles between weight maintainers and regainers and provides some leads in understanding the causes of successful weight maintenance.

In summary, these studies show that gene expression profiles can be used to understand better why some persons do respond favorably to a dietary intervention and others do not.

1.6 Conclusion

In this chapter, we have discussed studies that used transcriptomics for studying differences in responses to diet (Table 1.1 and Table 1.2). These studies point towards clear differences in the gene expression response to diet based on phenotypic measurements.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of intervention</th>
<th>Population</th>
<th>No. and gender</th>
<th>Study design</th>
<th>Duration</th>
<th>Tissue</th>
<th>Gene expression analysis methodology</th>
<th>No. for gene expression analysis</th>
<th>Factor influencing the response to intervention</th>
<th>Processes or genes identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camargo et al. (2010) [12]</td>
<td>Olive oil-based breakfast, high (398 ppm) or low (70 ppm) in phenolic compounds</td>
<td>20 subjects with metabolic syndrome</td>
<td>9 males, 11 females</td>
<td>Randomized, controlled, double blind, crossover study</td>
<td>4 h</td>
<td>PBMCs</td>
<td>Microarrays (Agilent)</td>
<td>20</td>
<td>Gender</td>
<td>–</td>
</tr>
<tr>
<td>Rudkowska et al. (2013) [13]</td>
<td>Fish oil (n-3 PUFA) 3 g/day</td>
<td>30 healthy subjects, BMI 25–40</td>
<td>13 males, 17 females</td>
<td>One arm 6 weeks PBMCs</td>
<td>Microarrays (Illumina)</td>
<td>30</td>
<td>Gender</td>
<td>Oxidative stress, PPAR-alpha signaling and NF-κB signaling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalacker-Mercer et al. (2010) [14]</td>
<td>Protein (0.5, 0.75, or 1.0 g/kg/day)</td>
<td>12 younger (22–43 years) and 10 older men (63–79 years)</td>
<td>22 males</td>
<td>Randomized, controlled, crossover study</td>
<td>18 days (muscle biopsy on day 12)</td>
<td>Skeletal muscle (Vastus Lateralis)</td>
<td>Microarrays (Affymetrix)</td>
<td>22</td>
<td>Age</td>
<td>Protein metabolism</td>
</tr>
<tr>
<td>Van Erk et al. (2008) [21]</td>
<td>Spread (containing increased levels of medium-chain triglycerides, PUFAs, and conjugated linoleic acid) or control</td>
<td>Lean and overweight</td>
<td>20 males</td>
<td>Randomized, controlled, double blind, crossover study</td>
<td>9 days</td>
<td>Adipose tissue</td>
<td>Microarrays (Affymetrix)</td>
<td>10 lean, 10 overweight</td>
<td>BMI</td>
<td>Energy metabolism, inflammation, lipid metabolism</td>
</tr>
</tbody>
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(continued)
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<thead>
<tr>
<th>Study</th>
<th>Type of intervention</th>
<th>Population</th>
<th>No. and gender</th>
<th>Study design</th>
<th>Tissue</th>
<th>Gene expression analysis methodology</th>
<th>No. for gene expression analysis</th>
<th>Gene expression analysis methodology</th>
<th>Processes or genes identified</th>
<th>Factor influencing the response to intervention</th>
<th>Processes or genes identified</th>
<th>Factor influencing the response to intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esser et al. (2015) [18]</td>
<td>95 g of fat (SFA and MUFA)</td>
<td>Lean and obese</td>
<td>18 lean males, 18 obese males</td>
<td>Randomized, double blind, crossover study</td>
<td>4 h PBMCs</td>
<td>Microarrays (Affymetrix)</td>
<td>17 lean, 15 obese</td>
<td>BM</td>
<td>Immune response, apoptosis, metabolism</td>
<td>BMI</td>
<td>Immune response, apoptosis, metabolism</td>
<td>BMI</td>
</tr>
<tr>
<td>Matoine et al. (2015) [19]</td>
<td>75 g of glucose, 54 g of fat</td>
<td>Lean and obese</td>
<td>7 males, 16 females</td>
<td>Randomized, controlled, crossover study</td>
<td>1 h PBMCs</td>
<td>Microarrays (Affymetrix)</td>
<td>23 lean, 21 obese</td>
<td>BM</td>
<td>BMI</td>
<td>BMI</td>
<td>BMI</td>
<td>BMI</td>
</tr>
<tr>
<td>Posman et al. (2013) [20]</td>
<td>Vegetables (50, 200 g)</td>
<td>Lean and obese</td>
<td>32 males</td>
<td>Randomized, controlled, crossover study</td>
<td>4 weeks (adipose tissue biopsy after 4 h of fat)</td>
<td>Microarrays (Illumina)</td>
<td>10 lean, 10 obese</td>
<td>BM</td>
<td>BMI</td>
<td>6 lower body obese men, 5 upper body obese men</td>
<td>BMI</td>
<td>6 lower body obese men, 5 upper body obese men</td>
</tr>
<tr>
<td>Radijic et al. (2009) [22]</td>
<td>Spread containing predominantly medium-chain triglycerides (60 g/day)</td>
<td>Lean and obese</td>
<td>12 males</td>
<td>Randomized, controlled, double blind, crossover study</td>
<td>2.5 weeks adipose tissue</td>
<td>Microarrays (Affilgen)</td>
<td>10 lean, 10 obese</td>
<td>BM</td>
<td>BMI</td>
<td>BMI</td>
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<td>BMI</td>
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<tr>
<td>Schmidt et al. (2012) [23]</td>
<td>Fish oil 2.3 g/day, placebo oil</td>
<td>Lean and obese</td>
<td>20 normo- and dyslipidemic men</td>
<td>Randomized, controlled, 4-arm, parallel study</td>
<td>12 weeks whole blood</td>
<td>Microarrays (Phalanx Biotech Group)</td>
<td>10 lean, 10 obese</td>
<td>BM</td>
<td>BM</td>
<td>9, 6, 8, and 7 subjects BMI, body fat distribution</td>
<td>Bitmap</td>
<td>9, 6, 8, and 7 subjects BMI, body fat distribution</td>
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