Chapter 2

The Omics of Obesity

Darren Henstridge and Kiymet Bozaoglu

Additional information is available at the end of the chapter

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Abstract

Obesity is a complex multi-faceted disease affecting billions of people worldwide. Traditionally, obesity was thought to be a consequence of having access to energy dense food and busy lifestyles that do not factor in sufficient physical activity. Although diet and exercise play a major role in obesity development, these are not the only contributors. It is widely accepted that genetic and epigenetic factors also play a major role in obesity development and these in turn affect the lipidome, metabolome and proteome. With new technological advances, it is now possible to delve into these specific areas to further understand the mechanisms involved in obesity development. These technologies are collectively termed "omics" technologies, and this chapter will summarise the recent advances in obesity and metabolism research and describe new technologies that have been used to identify mechanisms that play a major role in the development of obesity. In particular, we will examine the different omics platforms that are available and have been used to study obesity. Collectively, these studies will be fundamental in identifying new and effective treatment strategies.

Keywords: obesity, genomics, epigenomics, lipidomics, proteomics, metabolomics

1. Introduction

Obesity is a global epidemic and is on the rise at an alarming rate. It is estimated that 2.1 billion people worldwide are either obese or overweight, which is almost 30% of the world's population [1]. This increase in obesity also predisposes individuals to other comorbidities such as cardiovascular disease, type 2 diabetes and metabolic syndrome [2] and therefore is a major public health concern. Obesity has traditionally been thought of as a consequence of a "bad diet" (high energy intake) and/or a sedentary lifestyle (low energy expenditure) resulting in a positive energy balance that manifests itself in the form of energy storage within adipose tissue. While this is true, it is now apparent that this is a simplistic view, and there are many contributing factors that impact energy storage and utilisation. In recent years, signifi-

cant advances in the understanding of obesity and metabolism have been made using "omic" technologies. "Omic" techniques involve the detection and identification of molecules within a given biological sample, whether it is derived from cells, a tissue sample or indeed an entire organ or organism. Primarily, omics studies have aimed to identify the genes (genomics), messenger RNA (mRNA) (transcriptomics), proteins (proteomics) and metabolites (metabolomics that encompasses lipids (lipidomics)) of a sample or a group of samples and how they differ from another sample or group. Other omics platforms are also important in the regulation of these pathways including the effect of epigenetics (the epigenome/epigenomics) on the function of genes and the role of the gut microbiota within a host (the microbiome/microbiomics) on metabolite production and energy harvest from food. "Omic" platforms are being utilised by researchers around the world to identify mechanisms that contribute to the development and maintenance of obesity, the evolution of obesity to metabolic diseases such as type 2 diabetes and to try and identify possible therapeutic avenues to treat obesity (**Figure 1**). This chapter focuses on discussing obesity from the level of the genes associated with obesity and their regulation by the epigenome right through to the proteomic, lipidomic and metabolomic level in studies from both human cohorts as well as studies conducted in pre-clinical models.

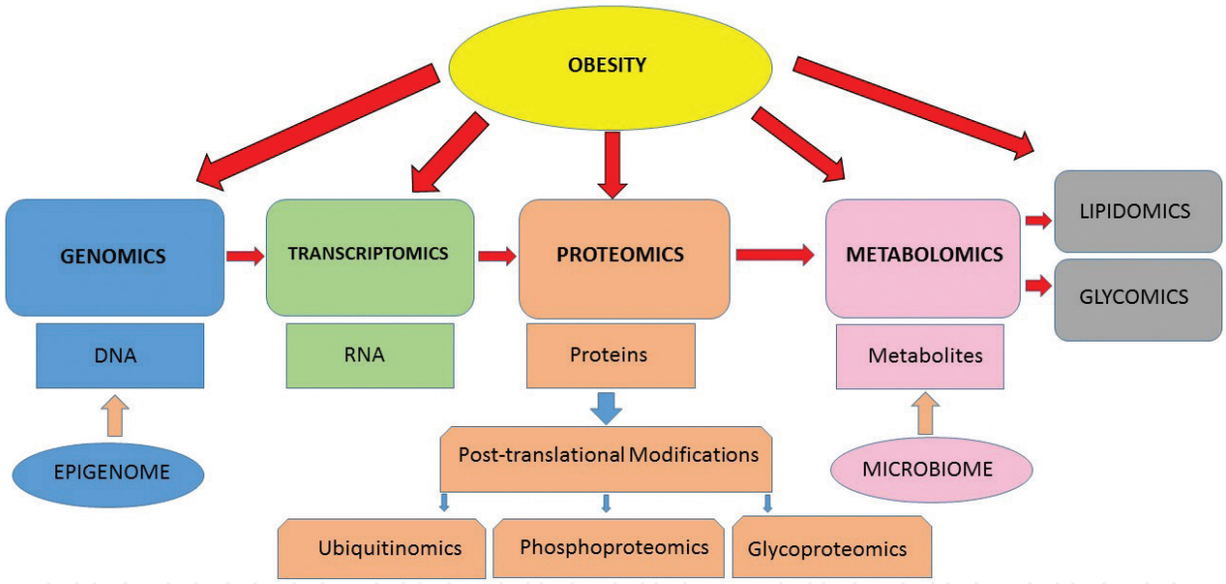

Figure 1. Flow chart representation of the various "omic" platforms used to study obesity. Further understanding of each of these stages will not only lead to a greater understanding of the pathogenesis of obesity and identification of therapeutic targets, but could potentially be used for prescription of personalized medicine (prevention and treatment). Data such as what is able to be obtained from lipidomic analysis may be utilized in the clinic to evaluate risk and monitor disease severity and provide prognostic information.

2. Genomics

While the global incidence of obesity is on the rise and is thought to be predominantly due to poor diet and sedentary lifestyles, it is also widely accepted that genetic and epigenetic factors also play an important role in obesity development. Twin studies have demonstrated that the heritability of obesity ranges from 40 to 70% [3], which clearly shows an important role of

genetics in obesity and could depict which individuals are at higher risk of developing the disease. Therefore, it is empirical that we identify and understand the genetic regulation of obesity which will potentially lead to more targeted therapies to help stem this obesity epidemic.

2.1. Genome-wide association studies in obesity

With the completion of the Human Genome Project, it has been established that there are 20,000–25,000 genes within the human genome [4]. High-throughput genotyping technology coupled with The HapMap project [5] and 1000 Genomes Project [6] has made it possible to conduct genome-wide association studies (GWASs) to identify common variations in the genome that may be linked to diseases. The basis of GWAS is the detection of association of linkage disequilibrium (LD) between the causal variants and single-nucleotide polymorphisms (SNPs), which reduces the number of SNPs required to cover the whole genome. However, this is also a limitation as in the analyses a minor allele frequency of >5% is required, which means that only common SNPs will be identified. The very first large-scale SNP chip GWAS was performed by the Wellcome Trust Case Control Consortium in 1,924 type 2 diabetic (T2D) cases and 2,938 population controls from European samples and identified several variants associated with T2D phenotypes [7]. They also identified a novel gene, which was associated with obesity, fat mass associated with obesity (*FTO*). *FTO* has been shown to exert its primary effect on T2D risk through its impact on adiposity [8]. Following on from the discovery of *FTO*, a meta-analysis was performed in 16,876 European subjects and replicated the associations between variants in *FTO* and obesity, and also identified variants within the melanocortin-4 receptor (*MC4R*) to be associated with fat mass, weight and obesity risk, which have been previously shown to be the leading cause of monogenic severe childhood-onset obesity [9]. This underscores the merit of GWAS meta-analyses to validate previous associations as well as identify new regions that may be associated with obesity-related phenotypes. Since these two studies, there has been a boom in GWAS studies and subsequent obesity susceptibility loci identified. To date, ~200 variants associated with obesity-related phenotypes have been identified; however, it is postulated that these loci only account for <10% of the variance [10–15]. Although this is quite low, and means that 90% of variance remains to

Study population	Number of samples	Loci identified	Reference
European and African Americans	100,716	12 BMI loci identified; 4 were novel	[15]
European	52,140	6 loci associated with leptin, 5 independent of BMI	[14]
European	339,224	97 BMI loci identified	[11]
European, East Asian, South Asian, and African American	224,459	49 BMI loci identified; 33 were novel	[12]
European	47,541	3 new BMI loci	[13]
European	226,911	2 known and 6 novel BMI associated loci	[10]

Table 1. Summary of recent genome-wide meta-analyses of obesity.

be explained, they have provided us with an emerging wealth of knowledge of the genomic localisation, frequency and effect sizes, and potential functional implications that these loci may have. More recently, a number of meta-analyses of GWAS data have been performed and have identified new loci associated with body mass index (BMI) (**Table 1**). Surprisingly, these meta-analyses also replicated previously identified loci, which validate that these loci may be contributing to obesity and underscore the importance of performing GWASs in the first place.

3. Epigenomics

Epigenomics is the study of alterations to the transcriptional activity of genes in response to environmental stimuli *without* altering the DNA sequence. These alterations include methylation, histone modification as well as other changes in the chromatin structure that may affect the transcriptional regulation of a given gene. Importantly, these epigenetic modifications are thought to be an important link in the "missing heritability" hypothesis [16-18]. The concept of epigenetic regulation of obesity has become of great interest over the last decade and several studies have demonstrated that epigenetic modifications can occur very early in life which may predispose individuals to obesity later in life.

3.1. Early life epigenetic programming

In the late 1980s, Barker and Osmond were the first to describe that early life exposure to certain adverse conditions including over or under nutrition and stress may increase susceptibility to disease later in life [19]. Since then, there have been many studies, particular animal studies that have verified this hypothesis and have demonstrated that malnutrition (both excess and deprivation) during pregnancy is associated with increased fat deposition in the offspring and may also directly impact the oocytes in females and primordial germ cells of male foetuses [20, 21]. Furthermore, there is evidence that *in utero* over or under nutrition can affect DNA methylation, histone post-translational modification as well as gene expression of target genes involved in insulin signalling and fatty acid metabolism [22, 23]. Hence, this predisposes the offspring and the grand-offspring to obesity and related disorders. Therefore, epigenetic modifications are hypothesised to be trans-generational and have been shown to be reversible whereby specific epigenetic marks can be turned on or off depending on the stimuli (Bishop et al). Most of these studies have been performed in animal models including mice [24, 25], rats [26, 27], Macaque [28], drosophila [29] and sheep [23, 30, 31]. The effects of the *in utero* environment on foetal programming in humans have not been well explored. Two recent studies have investigated the effects of maternal nutrition before and during pregnancy on DNA methylation on the offspring. The first study, the Dutch Hunger Winter Study [22], examined the effects of prenatal exposure to famine on DNA methylation and was able to show an increased methylation in *LEP* and *IL10* and decreased methylation in *IGF2* and *INSIGF*; however, these subjects were obese, and therefore, it is not clear whether these changes occurred due to the maternal famine exposure or a response to increased BMI. The second study, the Gambian mother-child cohort, was a large randomised control trial

which examined the effects of DNA methylation in response to maternal nutrition at conception and have demonstrated altered methylation in the offspring of these mothers and that these epigenetic changes were sex specific [32, 33]. A more recent randomised controlled study examined the effects of double blind peri-conceptional micronutrient supplementation in cord blood and observed sex-specific methylation changes which further supports the importance of *in utero* nutrition and the potential effects it may have on adiposity later in life (Dominguez-Salas, Moore et al. 2014). Another study, the AVON Longitudinal Study of parents and children, performed an epigenome-wide association analysis in 1,108 patients and found that the maternal underweight condition may be more influential on the DNA methylation of the offspring compared to the offspring from the maternal overweight mothers, while weight gain during pregnancy did not have much effect on DNA methylation in the offspring [34]. Although there is growing evidence of the effects of maternal nutrition on fatty acid metabolism and insulin signalling in humans later in life, there still remains some uncertainty and replication in large-scale population cohorts are warranted. The early detection of changes in the expression and epigenetic changes of candidate genes may provide biomarkers that will prevent or delay the onset of disease.

3.2. Human epigenome-wide association studies

Stemming from the animal epigenetic studies, there has been a recent incline in epigenome-wide association studies (EWAS) across different human populations. Most studies have focused more on site-specific differences in DNA methylation and its association with metabolic phenotypes, as it has been proposed to be a potential biomarker for clinical diagnosis and prognosis of disease [35]. A number of epigenetic marks related to obesity have been identified and replicated in other populations.

A study by Aslibeykan et al. (2015) performed an EWAS in CD4+ cells from frozen buffy coats from 991 healthy participants from the used Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study which identified eight differentially methylated sites associated with BMI, including cg00574958 (*CPT1A*), cg04332373 (*CD38*), cg17287155 (*AHRR*), cg26164488 (NA), cg07504977 (NA), cg14476101 (*PHGDH*), cg26680760 (NA) and cg26140475 (NA). They also identified four differentially methylated sites associated with waist circumference Cg00574958 (*CPT1A*), Cg04332373 (*CD38*), Cg14476101 (*PHGDH*) and cg25349939 (*GTDC1*) [36]. They replicated these methylation sites in whole blood from two independent cohorts—the Framingham Heart Study (FHS) (n = 1,935 case: control study, and n = 442 random samples) and the Atherosclerosis Risk in Communities (ARIC) study (n = 2,015 samples). A follow-up study in the ARIC study identified 76 BMI-related and 164 WC-related epigenetic marks mainly in *HIF3A*, *CPT1A* and *ABCG1* [37]. Thirty-seven of the BMI and one waist circumference mark were replicated in the GOLDN (n = 991 samples) and FHS (n = 2,377 samples) cohort. Another study identified 982 individual differentially methylated CpG sites between the insulin sensitive (IS) and insulin resistant (IR) groups. Of these sites, 538 were associated with unique genes with functions in cell adhesion, signal transduction and regulation of transcription and include *ADAM2, IGF2BP1, TBX5, HDACM, CD44* and *ZNF711*. These data are supportive of the close link between obesity and T2D and suggest the existence

of a methylome map within Visceral adipose tissue (VAT) that may predispose individuals to IR and T2D [38].

Family studies are beneficial as they have the potential to identify causative candidate regions of differential DNA methylation. A study by Ali et al. (2016) used a discovery approach in 192 subjects from seven families from the Take off Pounds Sensibly Family Study of Epigenetics (TFSE), and then validated the initial differential methylation marks in an extended cohort of 1,052 subjects [39]. They identified and replicated three loci where methylation status was associated with BMI%, and these were located in the body of suppressor of cytokine signalling (*SOCS3*), 3′ untranslated region of the zinc finger protein 771 (*ZNF771*) and at the transcription start site of LIM domain containing 2 (*LIMD2*) gene. Functional analyses were then performed in 330 subjects from the methylation analyses [39].

Examining promoter methylation patterns is thought to be a promising strategy for the use of early detection of disease (Laird 2003). Given that TNF*a* is pro-inflammatory cytokine elevated in obese subjects, Campion et al. (2009) investigated methylation patterns in the promoter region of TNF*a*. Methylation was measured in baseline peripheral blood mononuclear cells (PBMCs) from 24 patients who were put on an 8-week calorie restricted diet. Two differentially methylated promoter regions were assessed according to previous literature. The group of men who lost weight with the low calorie diet showed a significantly lower TNF*a* promoter methylation and that their baseline circulating TNF*a* levels were positively associated with total promoter methylation (Campion, Milagro et al. 2009). This demonstrates that examining promoter methylation may well be an important aspect in early detection and prognosis of disease.

3.3. Can PBMCs be used as a surrogate for epigenetic studies?

Despite progress in the epigenetic marks of obesity, there still remain some controversy in the use of peripheral blood mononuclear cells (PBMCs) as a surrogate for identification of epigenetic marks that may contribute to obesity development as there may be site-specific marks that may be missed. However, it is important to consider that with human studies, we are limited to tissues that we can readily access and the most commonly and easily accessible tissue to examine epigenetic modifications in humans is whole blood or PBMCs. This has been thought to have limitations in itself as it may not explain tissue-specific modifications that may be present. In light of this, many recent studies have examined epigenetic profiles in both PBMCs as well as subcutaneous adipose tissue (SAT). Once such study was from Arner et al. 2016, where they performed and EWAS using PBMCs, SAT and VAT in 80 obese women of which 40 insulin resistant and 40 insulin sensitive (Arner, Sahlqvist et al. 2016). They wanted to determine similarities of methylation status between the tissues and to determine whether PBMCs could be used as a marker of systemic IR. They were not able to show similar methylation sites between the PBMCs and adipose tissue and therefore concluded that CpG methylation in PBMCs does not reflect differential methylation sites in white adipose tissue (WAT). These data suggest that PBMCs may not be a suitable tissue for metabolic phenotyping of obese individuals. However, another study by Demarath et al. (2015) (described above) also measured methylation markers in SAT from their ARIC cohort and replicated 16 of these BMI

markers (Demerath, Guan et al. 2015). Given that these associations remained in different ethnic cohorts as well as different tissue samples (whole blood vs. CD4 cells from buffy coat vs. adipose tissue) demonstrate that adiposity traits are associated with different methylation sites independent of tissue type or ethnicity. It is clear that more thorough investigations into tissue differences are required; however, this may not always be possible in some settings such as brain- or heart-related disorders.

3.4. Epigenetics and intervention studies

The variation in epigenetic patterns with obesity has raised some interest in the field. There have been several intervention studies that have investigated the role of obesity and weight-loss interventions on global and promoter specific DNA methylation patterns. A 6-month exercise intervention study using adipose tissue from 23 healthy men with a family history (or not) of T2D demonstrated a global increase of adipose tissue DNA methylation in response to the exercise intervention (Ronn, Volkov et al. 2013). Interestingly, the subjects with a family history of T2D had less CpG sites with a significant difference in methylation patterns in obesity-related genes in response to the 6-month exercise intervention (Ronn, Volkov et al. 2013). Another study examined methylation changes in subjects that underwent gastric band surgery and were able to demonstrate significant effects on promoter methylation. More interestingly, before the patients underwent surgery, they observed significant methylation changes in genes involved in metabolic pathways and mitochondrial function, however after surgery and subsequent weight loss, the expression of these same genes normalised to similar levels to non-obese subjects (Barres, Kirchner et al. 2013). An additional study examined epigenetic changes in a normal weight, obese and successful weight loss maintainers (maintained weight for 9 years) that consisted of 48 males and females and demonstrated that the successful weight-loss maintainer group had methylation patterns that resembled the normal weight group rather than the obese group, which shows that methylation changes can be reversed (Huang, Maccani et al. 2015).

In summary, these studies collectively validate an important role for epigenetic regulation in metabolic processes. Furthermore, epigenetic marks coupled with gene expression in candidate genes may offer new pharmacological targets to counteract these modifications and potentially help avert obesity and associated diseases.

4. Proteomics

While genetic regulation in a biological system is unequivocally vital to health and disease, mRNA transcript levels generally only partially correlate with protein expression [16]. Typically, transcript abundance explains approximately one- to two-thirds of the variance in protein levels, depending on the organism [16]. This is due to the fact that it is not only the transcription that determines protein abundance but also post-transcriptional factors such as RNA processing and stability, translation, protein stability/turnover and protein modification. So while transcription data can provide a starting point as to whether or not a protein will be found and its likely level of abundance in a given sample, changes in expression levels may

not correlate to changes in protein levels. Consequently, proteomics is an important area of research to enable the characterisation of the proteome. Traditionally, the expression of individual proteins has been quantified using antibodies and techniques such as western blotting but today many proteins and the whole proteome of a sample can be assessed at once by using various mass spectrometry approaches. Proteins are regulated by a wide variety of chemical alterations after they have been translated. These post-translational modifications can include but is not limited to phosphorylation, ubiquitination, acetylation, glycosylation, nitrosylation, acetylation and methylation, and consequently, these are all sub-branches of proteomics.

4.1. Proteomic analysis in adipocyte cell culture models

Insulin plays a major role in the regulation of metabolic homeostasis. In adipose tissue, insulin-stimulated glucose uptake and the inhibition of lipolysis are two major functions of insulin. Quantitative phosphoproteomics using stable isotope labelling with amino acids in cell culture (SILAC) was used to interrogate the insulin signalling network in response to insulin stimulation in the 3T3-L1 adipocytes cell culture model [17]. The phosphoproteomics identified 37,248 phosphorylation sites that spanned 5705 proteins. Of these, around 15% were regulated by insulin demonstrating the complexity of the insulin signalling network in adipose cells [17]. A time course analysis also revealed a large variation in when phosphorylation events occur following insulin treatment, demonstrating the dynamic nature of the pathways. Novel mechanisms of the AKT-mTORC2 were also identified leading to the identification of SIN1 as an Akt substrate that contributes to the regulation of mTORC2 activity [17]. Proteomic analysis has also been useful in determining that large-scale changes to proteins that occur in 3T3-L1 cells during adipogenesis [18]. Wilson-Fritch et al. used mass spectrometry and database correlation analysis to describe a 20–30-fold increase in mitochondrial proteins during adipogenesis including proteins involved in fatty acid metabolism and those that are mitochondrial chaperones [18]. Further analysis revealed that the insulin-sensitising drug rosiglitazone (belonging to the thiazolidinedione (TZD) class of drug) also changes expression of mitochondria-related proteins which makes sense considering it is a known adipogenesis-inducing agent.

4.2. Proteomic changes in human obesity

The characterisation of protein expression in organs during obesity can help scientist unveil the biological impact of obesity and lead to a greater understanding of the condition. An interesting area of adipocyte biology is how the subcutaneous adipose tissue (fat found under the skin and largely around the hips, thighs and buttocks) is thought to be the more metabolically active and metabolically healthy type of fat and the visceral adipose tissue (central obesity) which is associated with metabolic dysfunction and disease differs. Via 2D-DIGE and mass spectrometry analysis, Perez-Perez and team investigated the protein differences in omental and subcutaneous adipose tissue of healthy obese individuals. These results identified 43 differentially expressed proteins including those that have been linked to lipid and glucose metabolism, lipid transport, protein synthesis and folding inflammation and the cellular stress response [19]. One way of getting proteomic information without the invasiveness of using adipose biopsies is to use peripheral blood mononuclear cells (PBMCs) as

a surrogate tissue. Abu-Farha and colleagues utilised shotgun proteomics to examine the PBMC proteome in lean versus obese individuals [20]. About 1063 proteins were identified as common proteins between both groups (lean and obese participants), and of these, 47 were differentially expressed (by at least 1.5-fold). Of these 47, 18 were increased and 29 decreased in the obese group compared to lean. As adipose tissue is an endocrine organ that secretes substances (adipokines) that impact metabolism in other tissues, proteomic analysis of these factors is of interest. Human primary subcutaneous adipose tissue cells were cultured and tandem mass spectrometry used to analyse the secretome of the cells [21]. As well as the detection of a number of well-characterised adipokines-like adiponectin (validating the technique), this method leads to the identification of multiple serine protease inhibitors (called serpins) [21]. Using this proteomics approach and exposing the adipose cells to different metabolic states and treatments, may be a way to further elucidate the factors that are released by adipocytes, the quantities by which they are released and under which conditions they are released. This could pave the way for a greater understanding as to the endocrine effects of the adipocyte.

4.3. Animal models of obesity and alterations to the proteome

One way to look at the way obesity impacts biology and metabolism is to look at and study the white adipose tissue (WAT) itself. A global label-free phosphoproteomic screen of WAT in mice discordant for obesity due to high-fat feeding detected and quantified a total of 7696 peptides. Differential phosphorylation levels between groups were found at 282 phosphosites from 191 different proteins [22]. This data set identified phosphorylation changes in enzymes involved in metabolic pathways such as glucose and lipid homeostasis pathways, linking these proteins to disturbed metabolism [22]. Importantly, the authors were able to further dissect out the likely impact of adiposity by using the data set to provide predictions on upstream kinases that are likely affected. These predictions revealed well-known kinase families such as AMPK and AKT that have been heavily studied in metabolic dysregulation verifying their approach. It also identified others such as MRCKα and PAK 1 and 2 whose role is unknown in relation to obesity [22]. Thus, this sort of analysis has the potential to uncover novel pathways altered with obesity and how this alters adipocyte function.

We all know that some individuals seem to put on weight even though they consume a healthy, low-fat diet, whereas others eat all of the energy-dense junk food that they want and do not have any impact on their waistlines. As this would rule out calorie content as the driving force for this type of accumulation of adiposity, it is likely that there is an underlying susceptibility in these individuals. Xie and colleagues tried to replicate this in an animal study where they performed proteomic analysis on mice that were either obesity resistant or obesity prone [23]. Results indicated that ubiquinol-cytochrome c reductase core protein 1 (Uqcrc1) and Enolase 3 were decreased and monoglyceride lipase (MGLL) and glucose-6-phosphate dehydrogenase (G6PDH) were increased in the visceral adipose tissue of obesity-prone mice compared to obesity-resistant mice [23]. These proteins involved in energy metabolism, glycolysis and fat synthesis may provide a clue as to why visceral adipose tissue is more or less likely to store energy and expand.

Though adipose tissue is obviously important to study, other metabolic organs are also too important to study. Baiges et al. [24] investigated the effects of a high-fat diet (HFD) on the rat liver proteome. Analysis identified 1,131 liver proteins and demonstrated that a high-fat diet changed the expression of 90 of these proteins. As one would have hypothesised, many of these proteins are involved in glucose and lipid metabolism [24]. Proteomics can also be further enhanced by analysing sub-cellular compartments such as mitochondria. In a study comparing lean versus obese mice, Nesteruk et al. [25] purified isolated mitochondria from both liver and skeletal muscle and analysed mitochondrial-associated proteins via mass spectrometry. Analysis identified 1,675 liver and 704 muscle mitochondria-associated proteins and of these, 221 liver and 44 muscle proteins were differentially expressed between the lean and obese groups [25]. Analysis of"sub-proteomes" such as the ones at the mitochondrial proteome may be used more in the future to identify cellular compartment-specific changes associated with obesity. This type of analysis is also beneficial in the sense that it can increase the sensitivity of the process and allow the detection of lowly expressed proteins.

Looking into the future, the combination and integration of proteomics analysis with other"omic" platform analysis such as genomics, transcriptomics and metabolomics may provide a useful systems biology approach to further understand the regulation of whole-body fat mass.

5. Metabolomics

Metabolites are small molecules that can be measured in bodily fluids including blood and urine as well as in tissue samples. Of particular interest are low-molecular-weight metabolites that are involved in metabolic pathways where they act as substrates, intermediates or products. Such metabolites include hormones, fatty acids and amino acids [26]. Metabolomics therefore is the analysis of the metabolite profile in a given sample, cell or organ. There are a number of different subtypes of metabolomics including lipidomics, glycomics, fluxomics and peptidomics. While the genome and in turn the proteome set the scene as to what biological processes take place or are dominant in a cell, the actual activity and function encoded by the genes and proteins is carried out via metabolites [26]. Consequently, the metabolome is impacted by the accumulation of all the genetic variation, epigenetic status, gene and protein expression, enzymatic activity and environmental factors that are expressed in or exerted on an organism. Given that the large array of metabolites are formed in biological systems, this is a complex task. Most often, the techniques used to profile metabolomics are nuclear magnetic resonance spectroscopy (NMR) and gas chromatography mass spectrometry (GC-MS). In general, metabolomics is a high-throughput technology and while initial start-up costs of purchasing equipment and providing the infrastructure is expensive, once established, on a per-sample basis, it is relatively inexpensive. Short of this, there are many centres that specialise in metabolomic measures set up throughout the world. These centres often will provide metabolomics data on samples for a fee-for-service arrangement.

5.1. Metabolomic analysis in obese humans

For an in-depth description of the amino acid metabolism, lipid metabolism, carbohydrate metabolism and nucleotide metabolism-related metabolites that have been shown to be altered in the setting of obesity or diabetes or obesity with diabetes, we refer the readers to the review by Park et al. [27]. Herein, we will discuss some of these changes and provide a separate section on a popular sub-branch of metabolomics that concentrates on studying lipids (lipidomics). In the 1970s, it was demonstrated that obese individuals have higher circulating levels of numerous amino acids including branched-chain amino acids (BCAAs) [28]. Recently, utilising new analytical techniques, a number of studies have confirmed and expanded on these findings. In a study, utilising metabolomics and lipidomics of blood plasma and urine to investigate association of metabolites with adiposity, it was demonstrated that there were seven metabolites that were important in predicting visceral fat levels, which included the amino acids tyrosine and glutamine and the lipid species PC-O 44:6, PC-O 44:4, PC-O 42:4, PC-O 40:4 and PC-O 40:3 [29]. In an alternative study conducted in obese Japanese individuals, plasma levels of amino acids are found to be associated with visceral fat accumulation. These amino acids included levels of alanine, glycine, glutamate, tryptophan and tyrosine [30]. In a metabolomic profiling study of 74 obese and 67 lean individuals, a number of differences in fatty and amino acids were reported [31]. Levels of free fatty acids C14:0, C16:0, C16:1, C18:1, C20:4 remained elevated in obese as compared to lean subjects. Levels of eight amino acids increased in obese as compared to lean individuals including alanine, arginine, asparagine, glutamine, leucine, phenylalanine, tyrosine and valine while conversely one decreased (glycine). Four acylcarnitine species (C3, C5, C6 and C8:1) were higher in the samples from obese individuals [31]. The data suggested the existence of a (BCAA)-related metabolic signature in obesity and linking this to metabolic dysregulation, these changes were associated with insulin resistance [31].

Metabolomic profiling may assist in distinguishing different types of obesity. As metabolic abnormalities are associated with central obesity more so than they are with peripheral obesity, Gao et al. set out to identify via metabolomics whether serum metabolic markers differ in those with central versus peripheral obesity [32]. Five types of metabolites were verified to be higher in the central obesity group after multiple testing adjustments. These included the BCAAs leucine, isoleucine and valine as well as alpha-aminoadipic acid and propionylcarnitine (C3 acylcarnitine) [32]. These metabolites may provide a useful mechanistic insight into determining the difference between metabolically healthy peripheral obesity and metabolically unhealthy central obesity. Another way to discriminate against metabolically healthy obesity and metabolically abnormal obesity is to divide patients on the basis of whether they have any form of hyperglycemia, hypertension or dyslipidemia. Chen et al. conducted such study in obese individuals from a weight-loss clinic and could indeed identify differential metabolic profiles and metabolic pathways [33]. These groups differed in L-kynurenine, glycerophosphocholine (GPC), glycerol 1-phosphate, glycolic acid, tagatose, methyl palmitate and uric acid. The pathways that could distinguish between the obese metabolically healthy and unhealthy groups were pathways involved in fatty acid biosynthesis, phenylalanine metabolism, and valine, leucine and isoleucine degradation pathway [33].

Variants in the fat mass and obesity-associated gene FTO has been identified as a risk factor for the accumulation of fat mass and the development of obesity [8, 34]. By correlating metabolites after stratification for whether or not an individual is a carrier of the FTO risk allele, genetic FTO-induced changes in the metabolome can be assessed. Via utilising samples obtained as part of a Korean community-based cohort (KARE cohort), Kim et al. [35] used serum metabolite quantification by targeted metabolomics to correlate FTO-genotype with alterations to metabolites. This resulted in the analysis of 134 different metabolites (78 glycerophospholipids, 21 amino acids, 12 sphingolipids, 12 acylcarnitines, 10 biogenic amines and 1 hexose). Of these metabolites, the authors found that seven metabolites were associated with increased risk of obesity due to the presence of the rs9939609 FTO risk allele [35]. Most notably, of these seven metabolites, five were phosphatidylcholines (PCs) (C36:5, C36:6, C38:5, C38:5, C38:6 and C40:6) and these showed the strongest effect, while the monosaccharide (hexose) and amino acid (valine) were also associated. Similar future studies investigating the impact of genetic risk factors on the metabolome can provide insight into how genes impact metabolism and contribute to the development of obesity.

5.2. Metabolomic and obesity in animal models

Using mouse models that have had a genetic manipulation (knock-out, knock-down overexpression), metabolomics can be used to gain an idea as to the impact a genetic modification has on obesity or metabolic pathways. Neuroblast differentiation-associated protein AHNAK knock-out mice (AHNAK(-/-)) have been reported as having a phenotype whereby they have a strong resistance to high-fat diet-induced obesity. Consequently, Kim et al. [36] applied (1) H NMR-based metabolomics to compare the altered metabolites in the urine from high-fat diet (HFD) fed wild-type and AHNAK(-/-) mice. The profiling identified that the urinary metabolites of HFD-fed AHNAK(-/-) mice gave higher levels of methionine, putrescine, tartrate, urocanate, sucrose, glucose, threonine and 3-hydroxyisovalerate compared to wild-type mice suggesting that the resistance to the HFD-induced obesity may arise from alterations in amino acids [36]. Likewise, human ataxin-2 (ATXN2) knock-out mice display obesity, insulin resistance and dyslipidemia [37]. To understand the effects of the loss of ATXN2, Meierhofer and team used unbiased profiling approaches to quantify the global metabolome of ATXN2 knock-out mice with label-free mass spectrometry [38]. Significant down-regulated pathways for branched chain and other amino acid metabolism, fatty acids and citric acid cycle provided evidence for the biological function of ATXN2 and the potential mechanism via which the lean phenotype is maintained [38]. Thus, metabolomics used in combination with genetic models offers a viable way to determine biological significance of genes and improve understanding of cellular pathways.

6. Lipidomics

Lipidomic measurement is a sub-branch of metabolomics where the identification of lipid classes and species is made. Given obesity is a disease whereby lipids accumulate in adipose tissue to make large adipose tissue depots, lipidomics is an extremely relevant platform for

the field. Typically, analysis can identify not only the different classes of lipid that are in a given sample, but also the molecular species that make up those different classes. Multiple approaches to performing lipidomics are available. Shotgun lipidomics refers to the process of identifying the lipidome of biological lipid extracts directly without the need for chromatographic purification. Targeted lipidomics involves the combination of liquid chromatography and stable isotope or non-physiological internal standards to provide quantification to hundreds of lipids. While untargeted lipidomics refers to the combination of liquid chromatography with high mass analysis to detect lipid species [39]. Numerous studies have investigated the lipidomic signature that is associated with increased fat mass in animal and human models.

6.1. Insights into human obesity from plasma lipidomics

Plasma lipidomic screening has been used to characterise the circulating lipids in obese compared to lean individuals to gain an insight into how obesity alters this parameter. In a study of monozygotic twins who differed in body weight by 10–25 kg, characterisation of lipid species in serum samples identified that obesity, independent of genetic influences, was associated with increases in lysophosphatidylcholine (LPC) lipids and decreases in ether phospholipids [40]. In an alternative study looking for plasma lipidomic associations with waist circumference used as a marker of central obesity, it was noted that dihydroceramides were associated with waist circumference, particularly the species 18:0, 20:0, 22:0 and 24:1, while two sphingomyelin species 31:1 and 41:1 were inversely associated with waist circumference [41]. In a study of 1,176 young individuals (20 years of age) in which 175 different plasma lipid metabolites were analysed, a positive association was found between waist circumference and seven sphingomyelins and five diacylphosphatidylcholines and negative association with two LPCs [42] while another study also demonstrated a reduction in numerous LPC species in the plasma of obese individuals [43]. Differences observed between studies could be due to the type of obesity in the different cohorts sampled. For example, obesity due to a high caloric intake could potentially result in a different lipidomic profile than what is observed in individuals who are obese due to a sedentary lifestyle. Other factors such as diet, sample preparation and age could also have an effect.

One potential use of plasma lipidomics is to use it as a diagnostic tool or monitoring tool in obese patients. By measuring the plasma lipidomic signature and correlating levels of various lipid species to risk factors of further disease such as region-specific adiposity or liver dysfunction, a panel of lipids may be identified to stratify at-risk patients [44]. A serum biomarker that predicts ectopic fat levels could be utilised in the clinic to track ectopic fat levels or conversely to track the effectiveness of interventions to decrease it. Currently, it is necessary to use expensive large-scale imaging technology to investigate ectopic lipid deposition. Even so, this only detects levels of triacylglycerols (TAGs) rather than other lipid metabolites that are found in lower abundance that have been implicated in causing metabolic dysfunction such as ceramides and diacylglycerols (DAGs). Alternatively, invasive biopsy procedures with analytical analysis can be used to identify the relative expression of these lipids. Given the relative ease of blood collection, plasma lipid profiling may provide an alternative avenue to provide a picture of tissue lipid levels if a predictor(s) can be identified.

In one study using shotgun lipidomics that captured 252 individual lipid species over 14 different classes, the authors aimed to link the circulating levels of blood plasma lipids to fat accumulated in various parts of the body including visceral adiposity and epicardial adipose tissue (EAT) (which are both cardiac disease risk factors) [44]. Via modelling analysis, a strong association was identified between visceral adiposity and plasma diacylglycerol (DAG) and EAT and triacylglycerol (TAG) (both DAG and TAG are composed of saturated fatty acids) [44]. In this study, EAT is also correlated with increased levels of phosphatidylglycerol (PG) species including PG 20:3/20:3 and PG 22:5/18:1 and with decreased levels of ether phosphatidylethanolamine (PE-O) lipid species that are mainly composed of plasmalogens [44]. Additionally, Perreault and colleagues set out to determine the ability of lipidomics performed in the serum to predict ectopic lipid accumulation in skeletal muscle, in particular, the ability to predict TAG, DAG and ceramide. After analysis of 215 serum lipids, they found that in obese individuals, ganglioside C22:0 and lactosylceramide C14:0 levels in the serum predicted muscle TAG levels while serum DAG C36:1 and free fatty acid (FFA) C18:4 could predict muscle TAG levels. Furthermore, serum TAG C58:5, cholesterol ester C24:1, phosphatidylcholine C38:1 and FFA C14:2 were good predictors of the ceramide levels in muscle. Moving forward, confirmation of such findings could allow for a panel of plasma lipids to accurately depict the state of ectopic lipid deposition in peripheral tissues such as skeletal muscle and prove useful in the clinical setting [45].

6.2. Tissue lipidomics in human obesity

While plasma is an obvious location to identify a prognostic marker, studying the lipidomic profile in adipose tissue itself or in other metabolic organs is of great interest to understand the biology of the condition. In a study of 20 obese, but otherwise healthy women, lipidomics was carried out on subcutaneous adipose tissue samples. Participants were divided into those with high content of liver fat or those with a low content of liver fat to determine if adipose tissue is altered in those discordant for intrahepatic lipid content. Analysis of 154 lipid species revealed increased concentrations of TAGs particularly long chain, and ceramides, specifically Cer (d18:1/24:1) in the group with more liver fat [46]. In another study carried out in obese insulin-resistant women compared to obese women with normal insulin levels, lipid profiling revealed an increase in G_{M3} ganglioside and phosphatidylethanolamine (PE) lipid species in omental adipose tissue [47]. These findings corresponded to an increase in ST3GAL5, the synthesis enzyme for G_{M3} ganglioside, and a decrease in phosphatidylethanolamine methyl transferase (PEMT), the degradation enzyme of PEs [47]. Thus, these changes may contribute to the obesity-induced insulin-resistant state.

In a human lipidomics screening of plasma and skeletal muscle samples comparing lean individuals with those who were obese or overweight but insulin sensitive (as defined by glucose infusion rate during a hyperinsulinemic-euglycemic clamp) and those who were obese and overweight but insulin resistant, demonstrated that there was no defining difference in the skeletal muscle of those who were lean as compared to those that were overweight or obese [48]. The plasma samples did demonstrate a higher quantity of TAG and lower plasmalogen species in those who were overweight or obese compared to lean. However, in individuals who were overweight or had obesity but were discordant for insulin resistance those who

were insulin-resistant had higher levels of C18:0 sphingolipids in skeletal muscle and higher levels of DAG and cholesterol ester (CE) and a decrease in LPC and lysoalklphosphatidycholine in the plasma [48]. This suggested that insulin resistance has a greater impact within the obese setting on the lipidomic profile than what obesity has on the profile in comparison to those that are lean.

6.3. Plasma lipidomics in obese rodent models

Plasma lipidomics has been assessed in various rodent models of obesity and to investigate the effect on the lipidome of various intervention studies. Barber and colleagues performed lipidomics in plasma samples from mice fed a high-fat diet for 12 weeks. Compared to low-fat diet control mice, these mice had increased levels of TAG, DAG and sphingolipid species, while there was a reduction in LPC levels [43]. To describe these LPC effects further, a high-fat feeding time course study was completed which noted an increase in LPC 18:0 and 20:0 after just 1 week of high-fat feeding. However, LPC 15:0, 16:1, 18:1, 18:2, 20:1 and 20:5 were all significantly decreased from baseline at 1 week and continued to be decreased out to 6 weeks of high-fat feeding [43]. While most of the LPC species were decreased some species such as 18:0 were elevated. Also utilising a high-fat diet to induce obesity, Li and colleagues identified LPC 18:0 as a potential biomarker of obesity [49] confirming the findings of Barber and authors.

6.4. Lipidomic analysis in tissues from rodents

Gaining access to rodent organ samples is far more convenient than human tissues and thus can be used more readily to access intra-tissue lipid content. Sixteen-week old wild type (WT) and the leptin-deficient *ob*/*ob* mice, a genetic model of obesity that becomes overweight due to hyperphagia, were studied for their hepatic lipidomic profiles using non-targeted analysis via ultra-performance liquid chromatography (UPLC) coupled to quadrupole mass spectrometry (MS). The obese mice had an increased level of TAG and DAG lipid species in the liver as well as diacylphosphoglycerols and ceramide species, while there was a decrease in the sphingomyelins [50]. Using high-fat feeding to induce obesity, Turner et al. performed a tissue lipid profiling study over a course of time of the high-fat dietary intervention [51]. Liver TAG was increased after 1 week of high-fat feeding and peaked at 16 weeks of high-fat feeding whilst numerous DAG species were elevated in the liver at 1, 3 and 16 weeks of feeding. Hepatic ceramide content was unchanged after 1 week of high-fat feeding, the 20:0 and 22:0 species elevated at 3 weeks of feeding and the 18:0 and 20:0 species increased at 16 weeks of high-fat feeding. Whilst these species were increased with high-fat feeding, the 24:1 and 24:0 species were significantly decreased at both 3 and 16 weeks of high-fat feeding [51]. In the epididymal adipose tissue, TAG levels and numerous DAG species were elevated at 16 weeks of high-fat feeding. Ceramide and sphingomyelin species were increased at both 1 and 16 weeks of high-fat feeding. Analysis of the skeletal muscle revealed an increase in TAG and DAG levels at 3 and 16 weeks post-high-fat feeding, whilst in terms of ceramide levels, only the 18:0 ceramide species was increased at 3 and 16 weeks [51]. These studies have highlighted the lipid changes that occur in tissues during obesity induced by different means.

The use of metabolomics and lipidomics is set to continue as they may prove useful in providing indications of metabolic health in the obese setting. Identification of metabolites as"biomarkers" may make it possible to identify individuals at risk of developing obesity, which could be useful as a way of tracking disease progression and provide a predictive tool for diseases associated with obesity. These measures could also theoretically be used to give an indication of the effectiveness of new weight-loss therapies and their impact on metabolism. Studies have already taken place investigating bariatric surgery, in particular, Roux-en-Y gastric bypass surgery. How this type of surgery impacts the metabolome was not very well described so Arora et al. analysed the plasma metabolome and lipidome of morbidly obese individuals prior to and after surgery to describe the effects of surgery [52]. From 96 metabolites and 192 molecular lipid species compared, the factors that were most different at 42 days post-surgery were decanoic acid and octanoic acid whose levels increased and the sphingomyelins 18:1, 21:0 and 18:1, 22:3 whose levels decreased [52]. Moving forward, it is likely that a greater understanding of fluxomics will be utilised. Fluxomics is an analytical method that describes the rates of metabolic reactions within a sample. This is important as metabolism is a dynamic process, and metabolomics and lipidomics analysis will only provide a snapshot or static picture of the metabolic reactions in the cell. It could be stated well that it is not the quantity of metabolites that is important in the obese setting but the rates at which they undergo metabolic reactions.

7. Microbiomics

Metagenomics is a broad term used for the study of genetic material collected from environmental samples including but not limited to soil, sediment and water and in particular relevance to obesity, the gut. The gut microbiota contains all the organisms within the gut and the gut microbiome contains the genome that is within these organisms. Measuring the microbiomic status of the gut environment allows for the study of the composition of all microbes in that ecosystem. Whilst the microbiota consists of all bacteria, fungi, archea, viruses and other microbes, most of the research effort in relation to gut microbiota has been focused on the bacteria portion. This is no surprise given the widespread dominance of bacteria in and on the human body and indeed throughout all ecosystems on Earth. Also no surprise given the location of this ecosystem is the findings over the last decade that the composition of the gut microbiota is altered with obesity and is impacted by the diet of the host. The relationship between the composition and activity of the resident gut microbiota and the effect that this has on the metabolism of the host is currently being delicately teased out and it is an area that has really benefitted from the modern sequencing methods and analytical techniques. By identifying the microbiome and comparing results to electronic databases, an understanding can be formed on the species of bacteria that compose a microbiota community. Like other"omes" mentioned throughout this discussion, modern advances in technology regarding sequencing has allowed further insight into the precise make-up of the gut microbiota and how it is altered under different pathological conditions. At the forefront of these, analysis has been the use of highly conserved 16S sRNA genes as a molecular marker for microbial diversity (proxies for different species). With the development of sequencing technologies it

has become possible to analyse all 16S rRNA genes in a sample and compare it with relevant databases that have been complied [53].

7.1. Gut microbiota and obesity in humans

Human gut microbiota composition is formed in early life with colonisation occurring over the first 3–5 years until it reaches a more stable, adult-like microbiota configuration [54]. However, in adulthood, alterations in this composition of bacteria can be observed in individuals with varying degrees of adiposity or metabolic health. Differences in the distal gut microbiota of obese versus lean humans has been demonstrated with the relative proportion of the phylum of bacteria named bacteroidetes found to be decreased in obese individuals compared to lean individuals, along with the finding that the bacteroidetes abundance increase as obese individuals lose weight [55]. These findings must be noted as somewhat controversial given other studies have shown no difference between obese and non-obese groups in relation to the proportion of bacteroidetes nor any change in the proportion of bacteroidetes measured in faeces once obese individuals lose weight [56]. These observed differences could come down to the way in which the samples were obtained, the methods involved in measuring the bacteria or the differing diets that the obese individuals recruited to the study were consuming. In this latter study, it was observed that the phylum of bacteria called Firmicutes was reduced in faecal samples from obese subjects on weight-loss diets, correlating changes in gut bacteria species to changes in adiposity [56]. It is difficult to distinguish whether changes in gut microbiota are just a response to obesity or weight loss are actually a causative factor.

One way to test whether human gut microbiota composition is causative in inducing an obesity-associated phenotype is to take gut microbiota from humans and populate the gut of germ-free mice (mice raised in an isolator so as to never be exposed to microorganisms) who have no gut microbiota. Although there are of course some species differences, on a whole, mice and humans share most of the same genes (~99%) and similar microbiota profiles making this type of experimental setup relevant for the evaluation of microbiota-induced physiological effects on the host [57]. Utilising faecal samples obtained from adult human female twins that were discordant for obesity, Ridaura et al. were able to demonstrate that an obesity phenotype is transmissible from human to rodent [58]. In these studies, germ-free mice were transplanted with the faecal matter of either the lean or obese human twin resulting in an increase in total body weight and fat mass in the mice receiving the microbiota from the obese twin. Intriguingly, if mice with the lean twin's microbiota and mice with the obese twin's microbiota were housed together (mice are coprophagic so will eat their cage mates' faeces), a recolonisation process occurred where bacteroidetes species from the lean microbiota invaded into the obese microbiota and this correlated with a protective metabolic phenotype where obesity-related traits were no longer observed. This raises the possibility of a potential protective effect on obesity of these bacteroidetes species [58].

7.2. Gut microbiota and obesity in animal models

Other studies utilising germ-free mice have demonstrated that microorganisms may have a role to play in dictating body weight. Germ-free mice have less body fat than regularly raised

mice despite the fact they actually eat more and take in more calories which should oppose this affect [59]. Further studies in germ-free mice have demonstrated that an obese phenotype is transmissible from mouse to mouse via the gut microbiota. Germ-free mice receiving microbiota transplants by oral gavage with microbiota either sourced from genetically obese *ob*/*ob* mice or lean mice have demonstrated that recipients of the *ob*/*ob* microbiota put on more body fat in the weeks after being inoculated as compared to those who received the "lean" microbiota transplant [60]. 16S-rRNA-gene-sequence-based analysis of samples obtained in this study demonstrated that the *ob*/*ob* donor microbiota samples had a greater abundance of firmicutes bacteria compared with that of the lean donor microbiota samples [60] indicating the possibility that enriching the gut with firmicutes may drive the body weight phenotype. Indeed a number of rodent studies have raised the possibility that the ratio of the phyla bacteroidetes to that of the phyla firmicutes is associated with obesity. In comparison with lean mice, *ob*/*ob* mice have a ~50% reduction in the abundance of bacteroidetes and an increase in firmicutes [61]. High-fat feeding studies utilised to induce obesity via a dietary means also have found an increase in the firmicutes species [62] indicating that both obesity induced by hyperphagia (*ob*/*ob* mice) and obesity induced by energy dense food (high-fat diet) is associated with an increase in firmicutes. As differences in gut microbiota communities may impact obesity and the metabolism of the host mouse, this should be considered a confounding factor when comparing different mouse strains, or the same mouse strain but from different mouse vendors or animal facilities as each facility is likely to harbour its own unique microbiota signature.

7.3. How would the gut microbiota cause obesity or contribute to obesity progression?

There are many possible reasons as to why the gut microbiota composition may impact the host and result in the development of obesity. First, certain types of gut microbiota may be more efficient in extracting energy out of food that passes through the gut and therefore make available more energy for the host in which they reside. Bomb calorimetry analysis measuring the energy content of faeces revealed that *ob*/*ob* mice have significantly less energy remaining in their faeces relative to their lean littermates suggestive that the microbiota within *ob*/*ob* mice are better at harvesting and extracting energy from the food within their digestive tract [60]. Other possibilities include the role of inflammation. Obesity has been associated with a type of chronic low-grade inflammation and modification of the gut microbiota has been suggested to increase the leakiness of the gut barrier resulting in the increased appearance of microbial products such as lipopolysaccharide (LPS) (endotoxin) in the circulation [63, 64]. These products could potential cause peripheral tissue inflammation and impede normal metabolism. Yet another possibility is the fact that the gut microbiota is responsible for the production of metabolites such as short-chain fatty acids (SCFAs) that are produced by the fermentation of dietary fibres by the bacteria in the gut [65]. SCFAs are organic acids with an aliphatic tail of less than six carbons and comprise of acetate, propionate, butyrate and valerate and are used by the host as an energy source. It is hypothesised that alterations in the production of these SCFAs with obesity could adversely affect satiety, hepatic glucose and lipid production as well as inflammatory processes and contribute to the progression of obesity and related conditions [66]. Thus, the microbiome composition can have an impact

on another one of the"omes" the metabolome of the host and alter physiological processes via this mechanism. An interaction between the microbiome and the lipidome may also be at play. This is evident in a study of 893 individuals which identified 34 bacterial taxa associated with body mass index and blood lipids [67]. Cross-validation analysis revealed that the microbiota present explains 4.5% of the variance in body mass index observed and 6% of the plasma triglycerides variance and this was independent of factors such as age and sex that were taken into consideration in the analysis [67].

The gut microbiota may play an important role in the balance between metabolic health and disease. If a characteristic microbiota signature can be described and confirmed in obesity (or in specific types of obesity) then the potential exists to modify this composition and improve health. Whilst the simplest solution to restore the composition of the microbiota would be a change in diet, other avenues such as prebiotic, probiotics and microbiota transplants are also being explored.

8. Conclusion

Herein, we have provided a review of the information that has been sourced from the study of the various"omes" in relation to obesity—from the genome and epigenome that provided the initial coding information regarding body weight regulation right through to the functional"omes" the proteome and metabolome that carry out the physiological cellular functions of these codes. As further investment is made in technologies to increase the capability and detection of these"omic" molecules, a multi-disciplinary team approach will be required to extract the most information and perhaps more importantly, the most relevant physiological information in relation to obesity. A systems biology approach is needed to understand the complexity of the physiology of all the reactions that take place due to the interaction between all of the genetic, proteomic and metabolomic information. Engineers are vitally important in furthering the technological capacities of machinery and bioinformaticians in developing ways to explore these complicated data sets to ensure that the data are collected and analysed in a meaningful way. Graphical representation of the data in a digestible fashion is essential to foster understanding of these findings of scientists of different fields. Cell biologists, biochemists and physiologists will play an important role in characterising these findings in proof-of-concept experiments in laboratory, and health and medical practitioners armed with these findings will ultimately deliver knowledge and hopefully personalised treatment strategies to the obese patients in the clinic.

Author details

Darren Henstridge and Kiymet Bozaoglu*

*Address all correspondence to: Kiymet.bozaoglu@bakeridi.edu.au

Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

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