Cutting-edge epigenetics research reveals new genes linked to metabolic syndrome in humans

Metabolic syndrome refers to a cluster of symptoms such as obesity, insulin resistance, and high blood pressure. The syndrome greatly increases the risk for developing type 2 diabetes, atherosclerosis, and heart failure. Dr Matteo Pellegrini, Professor of Molecular, Cell, and Developmental Biology at the University of California, Los Angeles, leads a diverse team of scientists who are striving to understand the basis of metabolic syndrome by exploring certain modifications to our DNA, known as epigenetic changes. The group hopes to expand the basic knowledge in this area and potentially identify new diagnostic strategies for metabolic disorders such as type 2 diabetes.

In multicellular organisms e.g., humans, other animals, and plants, almost every cell contains identical genetic information. However, not all cell types behave in the same way. For example, white blood cells are distinct from bone cells in appearance and function. Chromatin is a dense complex found in the nucleus of the cell that contains the majority of our DNA, along with RNA and associated proteins. It plays a critical role in establishing and maintaining these intracellular differences (or phenotypes) by regulating cell-specific gene expression.

**EPGENETICS AND THE EPIGENOME**

Epigenetics refers to the study of heritable changes in gene expression that do not involve changes to an individual’s DNA sequence. These changes result in new phenotypes without any change in genotype (e.g., without mutations or structural chromosomal alterations). Epigenetic changes or modifications, which occur within the chromatin, are influenced by multiple factors including age, the surrounding environment and lifestyle habits e.g., smoking and diet, and the presence of disease. While our genome (DNA sequence) remains relatively stable throughout our lives, our epigenome (the entire set of epigenetic changes within our cells) is highly dynamic and undergoes significant changes in response to the factors mentioned above. Normal or healthy epigenetic changes contribute to important events such as terminal cell differentiation to produce brain cells, pancreatic cells, blood cells, and other cell types. However, epigenetic modifications can also have profound negative impacts on gene expression, contributing to a range of diseases, including cancers, metabolic syndrome, and diseases marked by intellectual disabilities. While the epigenetics field is rapidly evolving, DNA methylation remains a major focus area, and this is the subject of Professor Pellegrini’s research.

**DNA METHYLATION**

There are many players involved in maintaining the state of chromatin, one of which is DNA methylation. This is a specific DNA modification where a component of DNA, known as cytosine, is methylated by a specialised enzyme in a certain position. This heritable modification, known as 5mC, is widespread among humans, other animals, plants, bacteria, and certain fungi. In mammals, DNA methylation is instrumental in the following processes: imprinting, where genes are expressed in a parent-derived specific manner e.g., the maternal gene for a given trait is expressed (turned on) while the corresponding paternal gene is repressed (turned off); X-chromosome inactivation, a process that occurs very early on in embryonic development to ensure that females possess the correct number of X chromosomes; and regulation of gene expression. Defects in DNA methylation are associated with cancer, ageing and rare imprinting disorders such as Prader-Willi syndrome, a complex disorder that often includes obesity and type 2 diabetes.

**METABOLIC SYNDROME**

Obesity, insulin resistance, dyslipidaemia (an abnormal amount of lipids in the blood), high blood pressure, and high serum triglycerides are among the traits associated with metabolic syndrome, a condition which increases the risk for developing type 2 diabetes, atherosclerosis, and heart failure. Roles for genetics in metabolic syndrome have been established, and an increasing body of evidence suggests that epigenetic modifications are also implicated. For example, changes to the paternal diet during pregnancy can influence DNA methylation levels in the placenta, including changes in the activation of genes that regulate key metabolic pathways. Recent studies also revealed that diet-induced adult obesity affects the methylation state of certain obesity-associated genes. Links have also been found between environmentally induced changes in DNA methylation and fetal origins of adult disease, whereby events that occur during early embryonic development e.g., malnutrition, influence an individual’s future risk for developing adult disease.

Metabolic syndrome is the leading cause of death in Western countries, and in the US, 44% of adults over the age of 50 suffer from one of the conditions mentioned above, greatly increasing their risk for serious conditions such as heart attack, stroke, and type 2 diabetes. Given the apparent but not fully elucidated association between epigenetics and metabolic syndrome, a deeper understanding of how DNA methylation is implicated in these conditions is warranted.

**WHAT IS METABOLIC SYNDROME?**

Metabolic syndrome is a cluster of symptoms such as obesity, insulin resistance, and high blood pressure. The syndrome greatly increases the risk for developing type 2 diabetes, atherosclerosis, and heart failure. Roles for genetics in metabolic syndrome have been established, and an increasing body of evidence suggests that epigenetic modifications are also implicated. For example, changes to the paternal diet during pregnancy can influence DNA methylation levels in the placenta, including changes in the activation of genes that regulate key metabolic pathways. Recent studies also revealed that diet-induced adult obesity affects the methylation state of certain obesity-associated genes. Links have also been found between environmentally induced changes in DNA methylation and fetal origins of adult disease, whereby events that occur during early embryonic development e.g., malnutrition, influence an individual’s future risk for developing adult disease.

**DNA METHYLATION**

There are many players involved in maintaining the state of chromatin, one of which is DNA methylation. This is a specific DNA modification where a component of DNA, known as cytosine, is methylated by a specialised enzyme in a certain position. This heritable modification, known as 5mC, is widespread among humans, other animals, plants, bacteria, and certain fungi. In mammals, DNA methylation is instrumental in the following processes: imprinting, where genes are expressed in a parent-derived specific manner e.g., the maternal gene for a given trait is expressed (turned on) while the corresponding paternal gene is repressed (turned off); X-chromosome inactivation, a process that occurs very early on in embryonic development to ensure that females possess the correct number of X chromosomes; and regulation of gene expression. Defects in DNA methylation are associated with cancer, ageing and rare imprinting disorders such as Prader-Willi syndrome, a complex disorder that often includes obesity and type 2 diabetes.

**METABOLIC SYNDROME**

Obesity, insulin resistance, dyslipidaemia (an abnormal amount of lipids in the blood), high blood pressure, and high serum triglycerides are among the traits associated with metabolic syndrome, a condition which increases the risk for developing type 2 diabetes, atherosclerosis, and heart failure. Roles for genetics in metabolic syndrome have been established, and an increasing body of evidence suggests that epigenetic modifications are also implicated. For example, changes to the paternal diet during pregnancy can influence DNA methylation levels in the placenta, including changes in the activation of genes that regulate key metabolic pathways. Recent studies also revealed that diet-induced adult obesity affects the methylation state of certain obesity-associated genes. Links have also been found between environmentally induced changes in DNA methylation and fetal origins of adult disease, whereby events that occur during early embryonic development e.g., malnutrition, influence an individual’s future risk for developing adult disease.

**WHAT IS METABOLIC SYNDROME?**

Metabolic syndrome is a cluster of symptoms such as obesity, insulin resistance, and high blood pressure. The syndrome greatly increases the risk for developing type 2 diabetes, atherosclerosis, and heart failure. Roles for genetics in metabolic syndrome have been established, and an increasing body of evidence suggests that epigenetic modifications are also implicated. For example, changes to the paternal diet during pregnancy can influence DNA methylation levels in the placenta, including changes in the activation of genes that regulate key metabolic pathways. Recent studies also revealed that diet-induced adult obesity affects the methylation state of certain obesity-associated genes. Links have also been found between environmentally induced changes in DNA methylation and fetal origins of adult disease, whereby events that occur during early embryonic development e.g., malnutrition, influence an individual’s future risk for developing adult disease.

Metabolic syndrome is the leading cause of death in Western countries, and in the US, 44% of adults over the age of 50 suffer from one of the conditions mentioned above, greatly increasing their risk for serious conditions such as heart attack, stroke, and type 2 diabetes. Given the apparent but not fully elucidated association between epigenetics and metabolic syndrome, a deeper understanding of how DNA methylation is implicated in these conditions is warranted.
Most major epigenome studies carried out to date have been conducted in blood samples, primarily because blood is the easiest sample type to collect on a large scale. Given that metabolic syndrome manifests as obesity and that adipose tissue is directly implicated in this process, it is imperative to also study other tissues, such as adipose tissue, to fully unravel the effects of metabolic syndrome on the epigenome. Recently published work from Professor Pellegrini’s group addressed this issue by profiling DNA methylation states in the abdominal adipose tissue that lies just beneath the skin (subcutaneous).

**THE METSIM COHORT**
The Metabolic Syndrome in Men (METSIM) cohort consists of just over 10,000 men aged between 45–73 years in one region in Finland. This cohort includes healthy individuals and those with metabolic syndrome, and was investigated in this study. Professor Pellegrini’s group investigated the association between clinical traits associated with diabetes and obesity, and also include other cohorts of different ethnicities or females. However, these tests could also be ordered by a clinician, to inform treatment options.

**What first made you decide to look at adipose tissue?** Adipose tissue is one of the central mediators of metabolic syndrome, which is characterised by the accumulation of triglycerides in adipocytes. We therefore hypothesised that epigenetic changes to adipocytes may be more dramatic than those observed in blood, or other tissues, that are less directly involved in this syndrome.

**How did you come to use a cohort of Finnish samples for your work in Los Angeles?** My colleague Jake Luis has a long standing collaboration with Markku Laakso, the developer of the METSIM cohort. I am part of a research grant at UCLA that is generating and analysing genomic data from this cohort.

**How far away are we from seeing epigenetic tools at the point-of-care assessment for type 2 diabetes risk?** My guess is that now that direct-to-consumer genetic tests are becoming more popular, epigenetic tests will follow shortly. These tests could be used to monitor an individual’s health (e.g., increasing metabolic health and potentially nutrient deficiencies), and will provide a valuable complement to genetic testing. This may make it possible for the general public to monitor their health without having to go to a doctor’s office. However, these tests could also be ordered by a clinician, to inform treatment options.

**What is next for your work?** We would like to expand our study to profile a larger group of individuals from METSIM, and also include other cohorts of different ancestries and include both sexes. We are also developing cheaper and more efficient profiling approaches based on targeted bisulfite sequencing. Finally, we are also investigating the possibility of commercialising this technology.

Epigenetic tests ... could be used to monitor an individual’s health and will provide a valuable complement to genetic testing.

**WHAT LIES AHEAD** It should be noted that the data acquired from adipose tissues from the METSIM cohort solely represents DNA methylation status of middle-aged Finnish men. The findings may differ in other ethnicities or females. However, the work carried out by Professor Pellegrini’s group illustrates that DNA methylation profiling is a useful tool to characterise the epigenetic and cellular basis of metabolic syndrome in the cohort studied, and that epigenetic studies complement traditional genetic approaches to identifying new candidate genes of clinical relevance.