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Beyond the CpG: an integrative approach to decoding DNA methylation in immunometabolic health

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CHAPTER EIGHT

Appendix

English summary

Introduction

As we get older, many of us face similar challenges. We struggle to stay energetic and active, take longer to recover from illness, and find it harder to maintain a healthy weight. Beneath these everyday experiences lies a biological transition that alters how our bodies respond to the world around us. Two tightly connected aspects of this process are changes to the *immune* system, which detects and eliminates threats, and to our *metabolism*, which controls how we use and store energy. Together, these age-related shifts are called ***immunometabolic dysfunction***, and they can eventually lead to severe age-related diseases, such as cardiovascular disease or type 2 diabetes.

One way to monitor *immunometabolic* health is by measuring levels of ***messenger molecules*** in the blood. These tiny signals allow different tissues to communicate with each other, sharing updates about hunger, stress, and inflammation. *Insulin*, for instance, is released by the pancreas after a meal to indicate energy availability. Other examples include *leptin*, which helps to control appetite by carrying messages from our fat and stomach to our brain, and *interleukin-6*, a danger signal released during infection or injury (**Box 1**). Breakdown in how these *messenger molecules* are produced, transmitted, or received plays a central role in ageing and disease.

Box 1. Key messenger molecules that help measure and maintain immunometabolic health

Insulin is released by the pancreas after a meal in response to rising sugar levels, signalling that your body should use the available sugar as energy or store it for later. In this way, insulin helps keep blood sugar levels within a healthy range.

Interleukin-6 (IL-6) is involved in immune responses and inflammation. Short-term IL-6 signalling helps co-ordinate defence and repair during infections or injury, but prolonged or dysregulated activity is linked to chronic low level inflammation in ageing and disease.

Leptin is produced primarily by fat tissue and helps regulate long-term energy balance. A small portion is also released by the stomach after a meal. It communicates with the brain to control appetite in line with the body's energy stores.

Adiponectin is also released by fat tissue and is associated with beneficial metabolic effects. It enables tissues to respond more effectively to insulin and limits inflammation, thereby supporting immunometabolic health.

Epigenetic control

To produce these *messenger molecules*, our bodies rely on instructional blueprints called ***genes*** encoded in our DNA. Although all tissues carry the same DNA inherited from our parents, they do not transmit the same signals. Instead, they each perform specific roles in the body. Almost all *leptin* comes from fat, while insulin is created exclusively in the pancreas. This is because *containing* a gene is not enough; a tissue must also *activate* it. This is where ***epigenetic control*** comes in.

Epigenetic control determines which *genes* are switched on or off in each tissue, thereby shaping their identity and function. Importantly, it can also change over time in response to diet, exercise, and age. This is why genetics alone does not determine our *immunometabolic* health and ageing trajectory, and why lifestyle can still have a powerful impact. By altering how tissues read their DNA, *epigenetic control* provides a critical connection between lifestyle, biology, and *immunometabolic* health.

Aims of this thesis

This thesis set out to discover whether ***DNA methylation***, a specific form of *epigenetic control*, helps to shape *immunometabolic* health. It examined how *DNA methylation* relates to *messenger molecules* in blood (**Chapters 2 and 3**), whether it can respond to lifestyle changes in older adults (**Chapter 6**), and introduced new tools to support similar work in the future, both in the lab (**Chapter 4**) and using a computer (**Chapter 5**).

Studies in blood

We explored whether *immunometabolic* health was linked to altered *DNA methylation* in blood and, if it was, whether this reflected disruption in the transmission or reception of *messenger molecules*. Our first focus was *interleukin-6 (IL-6)*, a danger signal strongly linked to ageing and inflammatory disease. This revealed that *DNA methylation* was primarily responding to *IL-6* in the blood. Circulating cells spend their lives exposed to *IL-6* and this alters how they read their DNA. We traced a clear path from elevated *IL-6* through *DNA methylation* to obesity and disease, revealing that *DNA methylation* mediates the harmful effects of inflammation.

When we shifted our focus to *adiponectin* and *leptin*, our findings took an unexpected turn. Although these *messenger molecules* are not produced in blood, the signals identified were tied to adiponectin production rather than reception. Crucially, these patterns occurred right next to the adiponectin *gene* and could also be detected in fat. This revealed two important insights. Firstly, *DNA methylation* can influence how adiponectin is produced and this directly shapes immunometabolic health. Secondly, representative signals of molecular changes in fat can also be detected in blood. This finding opens the door to using existing large-scale blood biobanks to study age- and disease-related molecular regulation and *immunometabolic* health throughout the body.

Lifestyle changes

Beyond identifying *DNA methylation* connected to messenger molecules, we also asked whether it could respond when people alter their lifestyles. To answer this, older adults joined the GOTO study where they improved their *immunometabolic* health through a combination of increased physical activity and reduced caloric intake. Samples of their blood, fat, and muscle were collected both before and after the study and showed *DNA methylation* changes in all three tissues. These alterations could also all be linked to observed reductions in body mass index (BMI) and leptin levels.

Combining our findings across studies, we found a similar pattern: *genes* identified in multiple Chapters were involved in insulin signalling and type 2 diabetes, strengthening confidence that *DNA methylation* is biologically relevant for both responding to and driving immunometabolic health. Taken together, this thesis uncovered ***where*** DNA methylation matters, that it ***can*** respond to lifestyle changes, and ***how*** it connects *messenger molecules* to disease. By revealing how lifestyle, biological messages, and epigenetic control intersect, this work helped to lay a foundation for understanding and improving *immunometabolic* health in our ageing populations.