Epigenetics unlock the potential for personalised medicine

The sequencing of the human genome in 2003 signalled the dawn of an exciting new era for genetic medicine. Yet almost 15 years later it has become clear that our genes alone cannot predict our susceptibility to most complex diseases or fully explain fundamental aspects of human development and ageing. Epigenetic factors are rapidly taking the spotlight as major players in the critical pathways that trigger the onset and progression of numerous life-threatening and debilitating genetic diseases. Technologies that harness our growing knowledge of epigenetic mechanisms look set to revolutionise approaches to medicine and healthcare across the globe.

Precise and powerful chemical modifications to our DNA alter the regulation or function of essential genes that influence our development or cause disease. Innovations, such as oxidative bisulfite (oxBS) sequencing enable accurate quantification and mapping of these important epigenetic marks, which cannot be identified and measured using traditional genetic research techniques.

Epigenetic signatures have become valuable biomarkers for disease, inspiring a new generation of medicines and diagnostics that bring precision medicine closer than ever to the patient. In combination with techniques such as liquid biopsy (LQB), epigenetic platforms provide swift and accurate analysis of clinical samples, facilitating early detection of disease with the ultimate aim of improving patient outcomes.

Methylation matters – the importance of DNA modifications

Epigenetic research explores mechanisms of gene regulation that do not alter the underlying DNA sequence. These processes or pathways are typically reversible and include significant chemical changes within nucleotide sequences, such as methylation, as well as histone and RNA modifications. Epigenetic modifications may be inherited or added in response to environmental factors. Lifestyle choices increase exposure to triggers (e.g., pollutants, cigarette smoke) that change our epigenome. Similarly, chemical signals present in the womb during prenatal development or hormones released during puberty lead to epigenetic changes that alter the regulation of particular genes, affecting many vital developmental processes.

A wealth of evidence demonstrates that chemical changes within the DNA, such as 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC), play a pivotal role in the functioning of the genome and the regulation of essential biological pathways. Discovery and measurement of epigenetic modifications have advanced our understanding concerning the genetic origin of many diseases and the factors that influence the epigenome.

By Dr Jason Mellad

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Differential patterns of DNA methylation are associated with abnormal cellular function and disease, particularly cancers. The mechanisms responsible for these critical DNA modifications are a key focus in leading-edge drug development. For example, the Ten-Eleven Translocation (TET) family of enzymes converts 5mC to 5hmC in DNA and aberrant TET function is associated with aggressive cancers. Agents that target this pathway may provide the basis of effective oncology therapies in the future.

Power and influence in the epigenome

Epigenetic patterns or signatures change throughout our lifetime. Our environment, medicines and even our diets can trigger epigenetic changes that modify and shape our phenotype. These changes may have a positive physiological or evolutionary impact, allowing us to adapt to our environment, or they may be considered harmful, leading to processes that make us more vulnerable to disease and affect our well-being.

Studies involving monozygotic or ‘identical’ twins have provided intriguing insights concerning the genetic and environmental factors that regulate epigenetic pathways or mechanisms, confirming that our genes cannot be wholly responsible for regulating development of complex phenotypic traits. Identical twins often display disparities in the incidence of conditions such as diabetes, autism and certain types of cancer, despite the inheritance of identical genetic material and consistency of environment during early development. Variability in DNA methylation patterns between monozygotic twins tends to increase with age and become more pronounced in adult twins with divergent medical histories, indicating that lifestyle choices and environmental differences play a considerable role in modifying the epigenome.

A number of well-characterised epigenetic modifications are highly stable over time and have demonstrated inheritability across generations. Studies in individuals who were prenatally exposed to famine conditions during the Dutch Hunger Winter (1944-45) have revealed shared patterns of DNA methylation within a number of genes associated with growth and the development of metabolic disease. These modifications disrupt normal gene expression and continue to be detected in the same individuals decades later. The impact of these changes on the epidemiology of certain diseases is even evident in subsequent generations; incidence of cardiovascular and metabolic conditions is increased in the children and grandchildren of men and women exposed to the Dutch Hunger Winter.

References
The promise of epigenetic biomarkers

The epigenetics arena has become a rich and exciting global research environment, inspiring collaborations between commercial and academic partners that have identified many significant epigenetic biomarkers for a wide range of serious and debilitating diseases. Precise mapping and measurement of epigenetic biomarkers will improve clinical practice by enabling diagnosis during early stages of disease development, even before genetic changes have taken place. Research in glioblastoma shows that epigenetic alterations associated with tumorigenesis can be detected in neighbouring non-tumour cells, even though they appear to be genetically "normal". Researchers have also demonstrated that epigenetic changes precede common genetic mutations in an in vitro model of lung cancer. Epigenetic-based diagnostics that can detect early disease signals will provide opportunities for clinical intervention before symptom progression has impacted on quality of life, when patients are still relatively fit and conditions favour treatment success.

Epigenetic biomarkers allow more accurate disease prognosis, particularly in therapeutic areas that are associated with a high degree of variability concerning survival. Further research in glioblastoma and several other cancers shows that levels of 5hmC are important in the regulation of disease-critical genes. Global reduction in 5hmC across the genome is associated with poor clinical outcomes in these patients. These highly-specific biomarkers can help to personalise disease management; allowing treatment response to be monitored more precisely and medications to be adjusted accordingly to optimise treatment outcomes, reduce adverse side-effects associated with some medicines and encourage the appropriate use of healthcare resources.

Patient-centred diagnostics

Epigenetic biomarkers for disease are stable. They can be mapped and measured effectively using

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Epigenetic biomarkers: key features

- Epigenetic signatures, such as 5mC and 5hmC, are stable and can be mapped/measured using techniques such as oxBS.
- Epigenetic modifications occur early in disease development and may precede genetic changes.
- Epigenetic biomarkers are highly tissue- and disease state-specific, aiding timely intervention with appropriately targeted therapies.
- Highly-sensitive analysis platforms enable epigenetic biomarkers to be effectively identified from clinical samples containing exceptionally low concentrations of DNA (eg LQB samples).

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Drug development and personalised approaches to care

Epigenetic changes are intrinsically reversible, making them desirable targets for drug therapy. Disrupting or inhibiting these modifications may hold the key to effective treatment for a broad range of diseases.

Drugs that elicit clinical effects through interactions with epigenetic machinery are already in use. This promising area of research has prompted many pharmaceutical partners to explore agents that target the epigenome in fields such as immuno-oncology and inflammatory disorders.

Medicines that modify the activity of epigenetic enzymes and adapter proteins have provided therapeutic options for many patients living with conditions such as lymphoma or myelodysplastic syndrome (MDS). Methylation inhibitors (or hypomethylating agents), such as the DNA methyltransferase inhibitor (DNMTi) 5-azacytidine, are cytotoxic cancer treatments that have been available for many years. However, these ‘first-generation’ epigenetic drugs can be relatively unstable and associated with unpleasant side-effects. Much research has focused on development of ‘second-generation’ epigenetic medicines that promise a greater degree of selectivity, providing effective management of disease alongside a more acceptable tolerability profile.

Drugs that are designed to influence epigenetic status provide potential options for novel and more precisely-targeted approaches that cannot be achieved through traditional medicines. Multicomponent treatment regimens that combine epigenetic drugs with other therapeutic compounds may allow multiple cellular pathways to be targeted, optimising disease management. This exciting new area of development includes the emergence of polypharmacology drug delivery systems, in which epigenetic agents are fused with other medicines to form a single multitarget drug that promotes synergistic mechanisms of action between constituent drugs. This approach may offer a more favourable pharmacokinetic profile compared with concomitant administration of individual treatments and could reduce toxicity issues.

A focus on the future – delivering through partnership

Collaboration and partnership are key to realising the potential of epigenetic research within the clinical setting, for the benefit of patients. Commercial partners and academic experts bring unique and valuable insights to these collaborations, with the
necessary investment to package and deliver new technologies appropriately.

Many companies around the world, including Cambridge Epigenetix, are at the forefront of epigenetic discovery, particularly concerning the mapping of 5mC and 5hmC modifications, analysis of LQB samples and identification of new therapeutic targets. These organisations are applying in-house expertise and working collaboratively with commercial and academic partners to drive fresh innovations that may improve identification and management of disease.

Working alongside academic institutions to support development of novel techniques for detection and mapping of epigenetic modifications and biomarker discovery enables commercial organisations to keep abreast of the very latest research and innovations in this area. Knowledge sharing with other experts, for example in the field of LQB, further supports efficient and rapid biomarker discovery. Collaborative approaches with pharmaceutical partners will enable application of these biomarkers across platforms for companion diagnostics, new therapies and technologies that support personalised medicine.

As our understanding of the epigenome continues to deepen and evolve, the opportunities for innovation and application of this knowledge in the clinical setting are expanding considerably. In the future, these advances may help to shape our long-term approach to the management of human health and well-being; enabling ongoing monitoring of our epigenome and opportunities to implement clinical interventions early in disease development or adapt our lifestyles appropriately to avoid health issues. It is our vision that, through advancing epigenetic discovery, we will be able to make disease optional, not inevitable.

Dr Jason Mellad is the Chief Executive Officer at Cambridge Epigenetix. Jason has a BSc in Molecular Biology and Chemistry from Tulane University and was a Marshall Scholar at the University of Cambridge where he completed a PhD in Medicine.

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