The inherent nature of disease

Canada Research Chair in Epigenetics, Reproduction and Development **Dr Sarah Kimmins** discusses her groundbreaking work into epigenetics and how it is informing new theories about the importance of parental health and nutrition

What is the overarching aim of your work?

One of the most prevalent beliefs in society with regard to health is that disease is largely dependent on the DNA you inherit from your parents. However, it has become increasingly clear that health is also influenced by the environment. Our research focus is on understanding how a parent's environment, including diet and obesity, influence the health and development of his/her offspring. Your lifestyle choices and exposure to certain foods, stresses, exercise and toxicants all have an enormous impact on whether or not you will contract a disease. In recent years we have found that the impact of the environment on health has extended beyond the individual's health to span generations. This means that the lifestyle choices a parent makes and the toxic environmental exposures they encounter have the possibility to impact their children, and possibly even their grandchildren.

Can you explain what is meant by the term epigenetics?

It is commonly believed that inheritance is entirely dependent on DNA alone. However, in addition to DNA there is another layer of heritable information known as the epigenome. The epigenetic information is directly associated with DNA and controls how it is used to impact gene expression. Epigenetics includes biochemical information in the form of DNA methylation at specific regions of the genome and also includes proteins known as histones, which influence the organisation of the DNA and its access to genes by the transcriptional machinery. Epigenetic factors work in concert to influence the stability of the chromosomes and control levels of gene expression.

How is epigenetics involved in inheritance and disease?

The epigenome is passed from generation to generation, in a process called epigenetic inheritance. Remarkably, the epigenome has a memory and contains information about a parent's lifetime experiences, such as exposure to poor diet or toxicants. Epigenetic inheritance may explain, in part, the development and risks of complex diseases such as diabetes, cardiovascular disease, behavioural disorders and cancer.

What makes your research so novel?

In society the reproductive health of the mother has long been emphasised while that of the father has been comparatively ignored. The novelty of our study is that it is the first to show that the folate status of the father, not just the mother, may be of equal importance in determining reproductive success in terms of having healthy babies. Importantly, our work indicates that there are environmentally sensitive regions of the sperm epigenome that respond to diet and transfer a so-called modulated epigenomic map influencing development and, perhaps in the long-term, metabolism and disease in offspring.

How do you predict epigenetic research will evolve over the coming years?

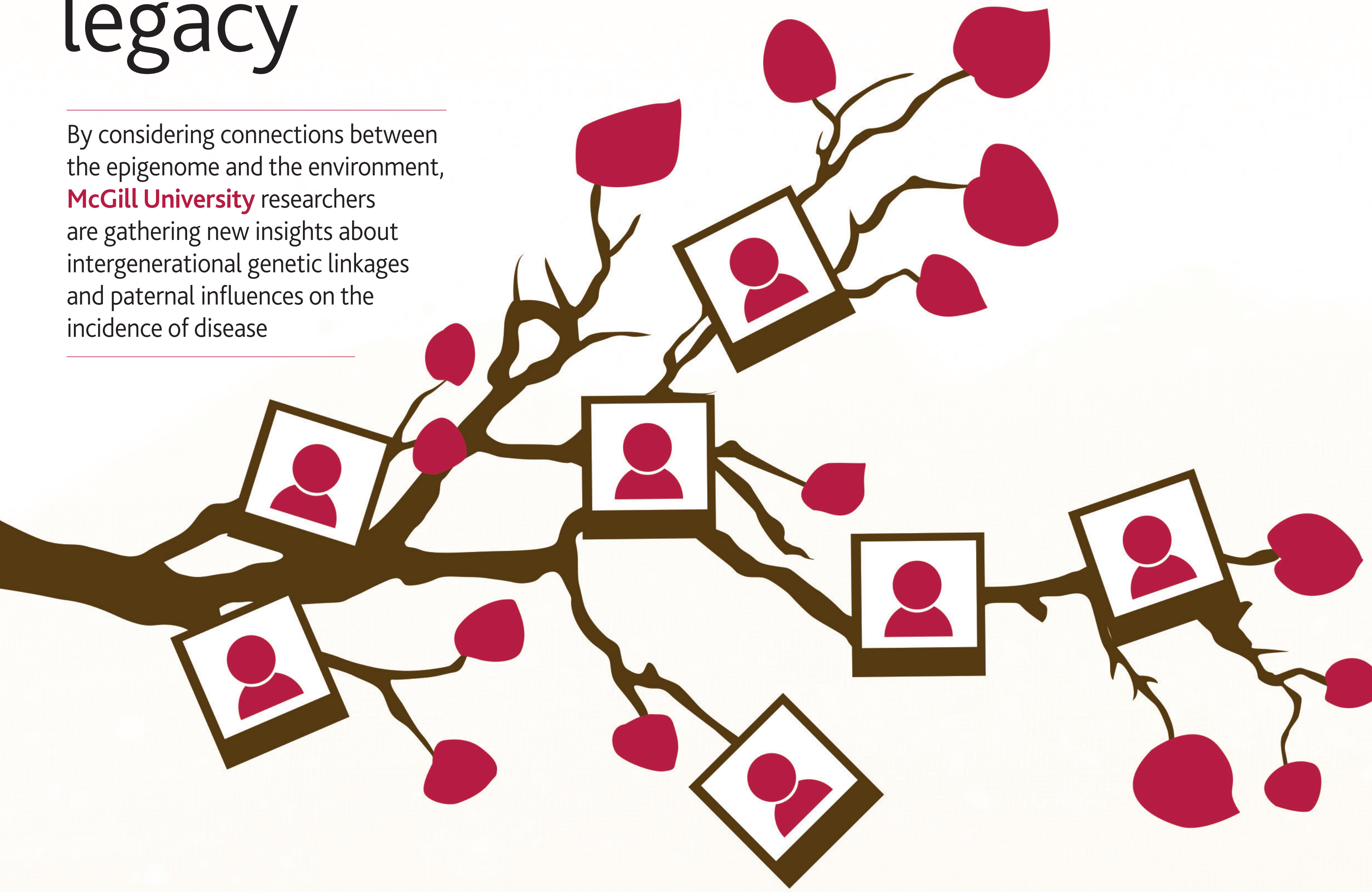
Up until now the real limitations in this field have been accessibility to methods as well as the difficulties that are typical when conducting research. This is still an emergent area with significant gaps in knowledge and techniques. In the past year strides have been made in determining the most reliable methods, but now we face new challenges imposed by the shrinking funding for health and basic research. This is hard to accept. As a researcher you can work to overcome technical obstacles, but it's more difficult to accept that while you may have some great research avenues to pursue there is a general lack of funding to allow you to undertake these investigations.

Are there wider social and health applications of your findings?

We now have data to suggest that everyday experiences, such as diet, can influence the setting of the sperm epigenome. This information opens up new avenues for understanding and preventing paternal routes to developmental defects in offspring and the potential mechanisms underlying intergenerational disease transmission. In the future we would like to provide information that can be used as guidelines to advise men about the importance of preconception health and the impact of nutrition and other environmental exposures.

Biological legacy

By considering connections between the epigenome and the environment, **McGill University** researchers are gathering new insights about intergenerational genetic linkages and paternal influences on the incidence of disease



THE EMERGENCE OF the field of epigenetics brought with it the opportunity to delve more deeply into how lifestyle choices and environmental factors can influence an individual's genetic code and that of his/her offspring. Understanding epigenetic mechanisms is particularly important for epidemiology and pathology as it attributes probable causes of disease. Reigniting the Nature versus nurture debate, this new discipline offers timely information to healthcare professionals. Research scientists at McGill University pay attention to the epigenetic-nutrient interactions that are present in the germline (the germ cells capable of passing on genetic material to the next generation) for this very purpose.

The research currently underway is directed by Dr Sarah Kimmins, Canada Research Chair in Epigenetics, Reproduction and Development, who is an Associate Professor in the Departments of Animal Science and Pharmacology and Therapeutics. The overall goal is to explore and analyse the molecular mechanisms which enable environmental exposure imprinting upon a sperm and egg and how this evolves in the developing embryo: "We are exploring how nutrients, for instance, impact heritable information in the sperm and therefore influence embryo gene expression, and ultimately health," explains Kimmins. Sperm are produced every day, so they are sensitive to subtle changes in diet, etc. It is therefore of particular importance to study susceptibility as there is a shortage of data on men's reproductive health and its long-term consequences for offspring. From Kimmin's perspective there is a lack of appreciation for the influence of male lifestyle choices and progeny health: "This needs to change and I hope that the knowledge contributed through our research will lead to healthier children".

THE ROLE OF EPIMUTATIONS

Previous research has highlighted that the epigenome has a memory capable of passing on information to offspring (epigenetic inheritance) and it has also been shown that this process may be linked to a range of diseases and syndromes, including cancer and behavioural disorders. One area of research considered to be especially important is the identification of epimutations, which, as the name suggests, involves the alteration of epigenetic marks that can influence the expression of genetic material. If an epimutation occurs during sperm or egg development this could lead to deleterious traits being passed on to the offspring. "Our research is suggesting that epimutations induced in sperm can have dire consequences for development," explains Kimmins.

The team at McGill used transgenic and environmental exposure animal models in combination with epigenomic sequencing techniques to identify regions of the sperm epigenome that, when altered, can influence embryo development. "One of our most exciting studies has shown that a father's diet can influence the setting of the sperm epigenome," notes Kimmins, leading to reduced fertility or jeopardised development. Deficiencies in diet, such as a lack of folate – a water soluble B vitamin found naturally in vegetables, meats and grains – can have a critical impact on offspring development. In particular, the group's latest research suggests a father's levels may influence the epigenetic patterns in sperm at genes associated with chronic disease and embryo development.

EXPLORING TRANSFER MECHANISMS

It is essential to build the knowledge base that parental choices, such as diet and environmental factors may have long-term consequences on child health, as prevention is better than cure; intervening before mutations take hold and disease ensues is imperative. This is being achieved by moving from animal models to humans and looking more closely at how a father's diet can affect his child's development, how this is connected to the sperm epigenome and the ways in which environmental memory is transmitted.

Epigenome-wide methods identified genes which had significantly altered methylation in sperm in response to a folate deficient diet. Moreover, fathers with an altered sperm epigenome had these changes at genes linked with development and sired offspring with increased birth defects. This suggests that epigenetic transmission is responsible for transferring the environmental memory from the father to the embryo via the altered sperm epigenome. Kimmins explains: "This study is the first to establish a link between paternal diet, the composition of the sperm epigenome, and consequent altered phenotype in the offspring". The work indicates the need to look much more carefully at the linkages between father's diet and embryonic development.

FOSTERING VALUABLE PARTNERSHIPS

This research relies on experts from a variety of disciplines, as Kimmins elaborates: "All of our projects require multidisciplinary team-based approaches involving basic science, research clinicians, animal models, computational and systems biology approaches. The types of studies we conduct involve exposure models to diets and transgenic animal models, and are possible through an extensive network of external partnerships that stretch beyond Canadian borders." The group's research projects on exposure models were carried out in collaboration with Drs Jacquetta Trasler and Rima Rozen from McGill who developed the diet exposure animal models. While their ongoing epigenomic analysis in various transgenic and environmental exposure models involves collaboration with Janice Bailey from Laval University, and world-leading scientists in epigenome sequencing and computational analysis based at Genome Quebec and McGill. Kimmins also works closely with Dr Antoine Peters from the Friedrich Miescher Institute (FMI) for Biomedical Research in Basel, Switzerland.

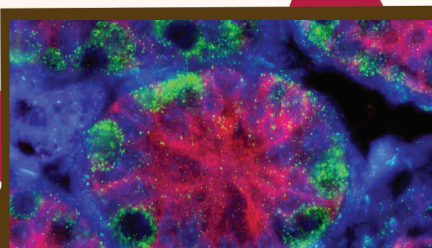
Team members Christine Lafleur (MSc, Research Assistant), Dr Romain Lambrot (PhD, Research Associate) and Keith Siklenka (PhD candidate).

Through the study of a transgenic animal model that involved high-throughput approaches at both the FMI and Genome Québec, Kimmin's group believes it has identified one of the epigenetic mechanisms responsible for transferring heritable information from the father to offspring. This research involved designing a transgenic mouse model whose purpose was to help explain how proteins involved with histones (packaging of DNA) can transmit heritable information and testing heritability by altering epigenome content. "We hypothesised that a specific histone modification contained within the sperm would influence gene expression in the offspring and thus impact development and disease," elucidates Kimmins. The project has great potential for increasing our understanding of the mechanisms that are involved in epigenetic inheritance and for the first time implicates histones in that process.

SHARING KNOWLEDGE

Kimmins has published her research in a number of prestigious internationally peer-reviewed scientific journals, and is currently preparing to publish some new important findings in this field. She is also instrumental in supporting the education of fathers and mothers and has contributed to features aimed at the general public. Kimmins recently wrote an article for *Creating Families* magazine which discussed how fathers' lifestyles influence the health of generations and the ways in which heritable biochemical information can be passed on to future generations.

The international team is now seeking to move onto translational studies to research the applicability of their findings in humans. A number of pilot studies have been planned to look at a range of different health factors, such as obesity and folate status, and how these can impact on the sperm epigenome and the success of pregnancy. Kimmins is particularly enthusiastic about the opportunity to harness their knowledge and develop tools and knowledge that may be used one day in a clinical setting: "We are looking forward in the coming years to working with researchers and clinicians at the Create Fertility Centre in Toronto, Canada as we aim to translate and apply our knowledge to improve pregnancy success".



A cross-section of a postnatal day-10 mouse testis with developing sperm cells (spermatogonia) stained in green. Folate deficiency was associated with a delay in the onset of spermatogenesis.

INTELLIGENCE

EPIGENETIC-NUTRIENT INTERACTIONS IN THE GERMLINE

OBJECTIVES

- To understand how environmental exposures to a parent, such as diets, can alter the epigenome in gametes and to determine the consequences on offspring
- To study the effects of the environment on male germ cell chromatin and generate information that will be of significant consequence for social and health programmes

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