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Editorial

The emerging field of epigenetics and its relevance for the physiotherapy profession

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Physiotherapists are eclectic professionals, capitalising on developments outside the profession. Only a few years ago it was a common belief that pharmacology was not part of their domain, but now physiotherapy is deeply involved in discovering and using pharmacological developments to the advantage of their patients and profession. When Botulinum toxin injection was developed for spasticity, physiotherapists working in neurology researched how its effects could be coordinated with their rehabilitative interventions to maximise the overall benefit,¹ and now clinical physiotherapists regularly coordinate their interventions around the injections. When new mucolytic therapies arose for chronic lung disease, physiotherapists helped to investigate how they might best be coordinated with physiotherapy interventions to enhance the overall benefits.^{2–4} Physiotherapists are now investigating ways that their interventions might best capitalise on developments in pharmacological interventions,^{3,4} hormonal interventions,⁵ and other technological advances.^{6,7}

Epigenetics is a relatively new area of research that might generate findings that could be applied in physiotherapy. Unlike gene therapy, which seeks to amend the genetic code, epigenetics refers to mechanisms that determine a change in gene expression without changing the DNA sequence itself. It is becoming clearer and clearer that most chronic conditions are a consequence of complex gene-environment interaction.^{8–10} The genetic code definitely has some influence in predisposing one individual to certain diseases,^{11,12} but accumulating evidence demonstrates that its relevance is often much smaller than what was thought only a decade ago. Environmental factors such as diet, stressful events, and physical (in)activity are able to change the way a gene works and how it encodes for functional molecules such as functional proteins.^{13–16} This underscores the importance of self-management interventions targeting diet, stress coping and physical activity within a comprehensive physiotherapy program.

Changes in the expression (but not in the structure) of specific genes contribute to the pathogenesis of neurological disorders like Alzheimer's disease,¹⁷ psychiatric illness,¹⁸ and cancer.¹⁹ Higher methylation of DNA (an epigenetic process) of tumour-suppressor genes directly contributes to genetic inactivation of those genes.²⁰ Methylation involves methyl groups being bound to the DNA, which then interferes with the binding of transcription factors, in turn silencing gene expression. DNA methylation can also inactivate genes involved in repairing damaged DNA, thus increasing the chances of mutagenesis.²⁰ The increase in understanding the underlying mechanism of cancer development has led to breakthrough research findings and subsequent innovative treatments (eg, new treatments for leukaemia).¹⁹

Epigenetics is yet to generate clinical implications for physiotherapists; however, many of its discoveries to date suggest that future developments might have applications for physiotherapy practice. Below, we illustrate this using examples from two core features of our profession: pain treatment and exercise therapy.

In relation to pain, a better understanding of nociceptive mechanisms from an epigenetics viewpoint could provide a new paradigm for developing new strategies for pain treatment and might help us to find ways to modify the interventions to make them more effective.

There is evidence that gene-specific DNA methylation of the gene *OPRM1* correlates with post-surgical pain and opioid use after spinal fusion.²¹ *OPRM1* gene encodes the morphine and endorphins receptor MOR, which is the main receptor for opiates. Higher methylation of *OPRM1* would decrease expression of opioid receptors MOR, in turn determining a decreased response to endogenous and exogenous opioids. This suggests a role for opioid release regulation in acute pain, and might help to explain why some subjects respond differently to opioids.

Chronic pain conditions, such as fibromyalgia, osteoarthritis, or peripheral neuropathies, have been associated with alterations of gene expression in several genes.⁹ Notably, those genes control important physiological functions such as learning, inflammation, and neural plasticity.^{15,22} An example of maladaptive neural plasticity is central sensitisation, a state of hyperexcitability of the nervous system that determines stimuli amplification. Central sensitisation has been proposed as a relevant underlying mechanism in many chronic pain conditions.²³ Initial evidence shows its predicting and mediating role in different chronic conditions.²⁴ Initial association has been reported between migraine and methylation of the calcitonin gene-related peptide,²⁵ a peptide that has been well-characterised for its role in neuronal sensitisation.²⁶

Epigenetics might also help physiotherapists to understand new or more detailed mechanisms by which their existing interventions work. Recently, it has been demonstrated for the first time that muscles have an epigenetic memory that influences muscle growth.²⁷ A few weeks of strengthening training increases muscle mass, and reduces methylation levels in a number of genes. Some of them stay hypomethylated for weeks after the end of the training, even when muscle size returns back to baseline. Most importantly, other genes have shown an increased frequency of hypomethylation when muscles are subject to re-loading about 2 months after the first training. Such evidence might have implications for physiotherapists who specialise in preoperative and postoperative care, and shed some light on the mechanisms underlying the importance of an exercise program before undergoing surgery. A relatively short exercise training

program could prime muscles to respond to post-surgical rehabilitation and facilitate recovery. Epigenetic markers could also be used to detect that threshold needed to prime muscles, in order to better predict recovery after surgery.

Regular physical activity also induces significant effects on an array of genes, and seems able to reverse those epigenetic modifications implicated in chronic pain, inflammatory diseases, and other chronic diseases such as diabetes.¹⁵ For instance, a gene named *PGC1-alpha* is rapidly demethylated after a single bout of exercise.²⁸ The same gene is also found hypermethylated in patients with type-2 diabetes mellitus, which suggests a novel mechanism by which exercise might be beneficial for diabetic patients.²⁸ Similarly, regular increases in physical activity improve the profile of circulating cytokines in healthy older people¹⁵ and people with cancer.²⁹ Epigenetic research has discovered that methylation contributes to this improvement. Physical activity has been associated with increased methylation of tumour necrosis factor (a pro-inflammatory cytokine) and decreased methylation of interleukin-10 (an anti-inflammatory one). Already, this evidence confirms the highly relevant impact of exercise on health. On the other hand, we can be speculative and suggest that such results might, in the future, offer avenues for targeting exercise to people at particular genetic risk of cancer recurrence or diabetes because of their genetic makeup or current cytokine profile.

Physiotherapy has always dealt with complexity, aiming to personalise treatments to the single patient. Inherent difficulties have been described in the quest to combine methodologically rigorous research and a patient-centred approach.³⁰ If epigenetic markers can be used to obtain a personalised biological profile of each patient, that in turn would serve to both guide subsequent patient-centred treatment and provide a way to measure its effects.

Physiotherapists working in education and/or research would do well to keep abreast of developments outside of physiotherapy – especially those in epigenetics – and to look for potential ways to apply those discoveries to make our management of patients more effective, or at the very least better understand what we are achieving (in terms of altering the patient's physiology) and the mechanisms underlying those effects.

This editorial is very introductory. Many more aspects of epigenetics and how they might generate future implications and opportunities for physiotherapists could have been given. For example, methylation and gene silencing are not the only epigenetic mechanisms. Other very important mechanisms have been identified, such as histone modifications. Briefly, histones are proteins around which our DNA is wrapped. Their conformation in turn determines whether a certain portion of DNA (eg, a given gene) can be accessed by transcription factors. This is important, as the field is rapidly advancing, and a new group of drugs – so called histone de-acetylase inhibitors – have been designed and tested in pre-clinical and clinical settings to reverse epigenetic modifications.³¹ Physiotherapists seeking a more detailed (but still accessible) explanation of these and other epigenetic mechanisms could start by reading some narrative reviews

specifically developed for clinicians approaching this new and fascinating topic.^{32,33}

In summary, epigenetics is an exciting avenue of research that physiotherapists should get involved in so that we do not miss opportunities to use its new discoveries to the benefit of our patients.

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