Developing epigenetic biomarkers - applications for exercise

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Epigenetics describes the chemical modifications to DNA and its packaging proteins that modify gene expression and perpetuated through cell division. Examples of specific epigenetic modifications include DNA methylation, covalent histone modification and noncoding RNA.

Coordinated changes in epigenetic state drive the cellular specification that accompanies mammalian development, from the early embryo to old age. However, epigenetic state is, to a large extent, plastic and can be influenced by environmental factors, particularly during early development. Such changes can be 'remembered' as cells convert transient changes in gene expression to epigenetic changes that can perpetuate over many cycles of cell division. One of the earliest and well known pieces of evidence for this phenomenon came from a study that showed that DNA methylation changes in the growth factor gene *IGF2* induces by the Dutch Famine at the end of the Second World War persisted for over sixty years (Heijmans *et al.*, 2008). Therefore, it is not surprising that long-lasting epigenetic changes have been observed in skeletal muscle in response to exercise throughout the life course (Grazioli *et al.*, 2017; Fernandes, Arida & Gomez-Pinilla, 2017; Howlett & McGee, 2017). Such changes are likely to regulate specific metabolic pathways. Furthermore, muscle stem cells isolated from individuals with varying levels of physical activity maintain their differential epigenetic state *ex vivo* (Sharples, Stewart CE & Seaborne, 2016).

An active area of research has been to study epigenetic responses to exercise interventions aimed at reducing the risk of chronic diseases such as type 2 diabetes. One such study found exercise-induced epigenetic and changes in the glucose transporter GLUT4 which were accompanied by changes to gene expression (Dos Santos *et al.*, 2015). This shows that exercise-induced epigenetic changes can have direct effects on the metabolic state could potentially protect against type 2 diabetes.

What remains unknown is the extent to which the intensity and duration of physical exercise can drive epigenetic changes in genes associated with risk for cardiometabolic and other age-related diseases. Longitudinal clinical trials of exercise interventions that involve measurement of physiological and epigenetic changes in muscle cells will be necessary to address these questions.

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