Commentary

The emerging field of pain epigenetics

Covalent modification of DNA by methylation is a critical epigenetic mechanism regulating gene expression; increased methylation inhibits and decreased methylation increases gene expression. In this issue of PAIN, two manuscripts provide evidence for a significant contribution of DNA methylation to chronic pain. During gestation, different tissues acquire specific patterns of DNA methylation. These patterns confer cell type identity by regulating genome function. Until recently, these tissue-specific DNA methylation patterns were believed to be fixed in differentiated tissues, particularly since it was assumed that DNA could not lose methyl groups by an active process of demethylation. Because neurons are generally non-dividing, this assumption excluded any possible role for DNA methylation in neuronal plasticity in response to external triggers. However, it is now becoming clear that DNA methylation is, in fact, a reversible biological signal. In addition to innate developmental processes that sculpt the DNA methylation pattern during gestation, DNA methylation patterns can also be altered in response to external signals, such as social exposures early in life. This idea has led to the emergence of the field of “behavioural” epigenetics.

There are fundamental and important differences between genetics and epigenetics that have critical diagnostic and therapeutic implications. In contrast to the genetic code, DNA methylation is influenced by experience and is potentially reversible by pharmacological or therapeutic interventions. DNA methylation is therefore an excellent candidate for both the modulation of chronic pain in response to transient experiential exposures as well as a mechanism underlying inter-individual differences in the susceptibility for developing chronic pain. In support of this hypothesis, Wang et al. recently demonstrated a role for DNA methylation in the spinal cord following nerve injury in rats and Tajerian et al. reported that methylation of the SPARC promoter in intervertebral discs is associated with chronic back pain in both preclinical models and in human patients. The two papers in this issue of PAIN provide further examples of changes in DNA methylation in response to different external exposures that are associated with pain.

Doehring et al. examined the effect of chronic opioid use on DNA methylation in two interesting and complementary human cohorts: drug addicts on methadone replacement therapy and opioid-treated vs. non-opioid-treated chronic pain patients. By using these two cohorts the authors attempt to dissociate the effects of pain from the consequences of exposure to opioids. In their study, the authors examined methylation of the gene encoding the mu-opioid receptor, OPRM1, as well as the repetitive sequence, LINE-1, which is used as a marker of global methylation. Although they found increased methylation of the OPRM1 gene in the opioid-exposed populations, this did not correlate with doses used. However, LINE-1 exhibited increased methylation that associated with both opiate dose and with increased pain. While the study supports a relationship between opiate exposure and global changes in DNA methylation, it is unclear if these changes underlie the increased pain levels reported in the opioid-treated pain patients (i.e. opiate-induced hyperalgesia), or if increased pain severity in this population contributed to increased use of opioids. A prospective study is therefore needed to demonstrate a causal relationship between global methylation and increased pain in opioid-treated chronic pain patients.

An important message of the Doehring et al. study is that chronic drug use is, in effect, an environmental exposure with the potential to impact DNA methylation in different tissues. For example, the anticonvulsant drug valproic acid is now known to inhibit histone deacetylation as well as to induce DNA demethylation. As global changes in DNA methylation are associated with diverse pathologies, such as cancer and lupus, the finding that exposure to medication could have long-lasting and unpredicted epigenetic consequences has profound clinical implications. It is important to note that the changes in DNA methylation that associated with pain were observed in the blood, which, of course, contains cell types not traditionally thought to be involved in pain. It follows that there may be utility in monitoring peripheral DNA methylation, as well as other epigenetic and non-epigenetic modifications, such as telomere length, as potential biomarkers for chronic pain phenotypes.

In the paper by Qi et al., a candidate gene-driven approach is used to illustrate how a peripheral insult (CFA-induced inflammation) triggers DNA demethylation and increased expression of a gene known to be involved in pain. Using a rat model, the authors focus on the gene (cbs) that encodes cystathionine-betaine synthetase (CBS), a hydrogen sulphide (H2S)-producing enzyme in dorsal root ganglion (DRG) neurons. In addition to presenting compelling evidence that the gas molecule H2S is involved in inflammation and nociceptive signalling, the authors demonstrate that the promoter region of the cbs gene is demethylated in DRG samples from inflamed rats vs. controls. The potential causal link between the demethylation event, increased gene expression, and increased pain is clearer in this paper. An interesting aspect of the Qi et al. study is the implication that cbs was demethylated in non-dividing mature neurons. As noted above, demethylation was long considered impossible, yet the idea has recently been gaining acceptance. The current study adds to the growing body of literature supporting the hypothesis that DNA methylation is a reversible biological signal with an important contribution to plasticity.

An open and critical question for both studies involves deciphering the pathways that lead from the exposure to the change in DNA methylation. It stands to reason that the molecular and
cellular pathways leading from chronic drug exposure or tissue injury to pain involve multiple gene networks. The elucidation of these pathways using genome-wide methodologies will allow for a more comprehensive understanding of the pathways leading to chronic pain and to the identification of novel targets for pain therapy. It will also be important to understand whether pain in turn triggers epigenetic alterations in different systems, such as an increase in systemic inflammation or alterations in biological responses to stress, that could impact overall health. Similarly, it will be important to examine how other kinds of exposures, such as social adversity early in life, which is known to cause long-lasting epigenetic alterations and is a well-established risk factor for chronic pain, influence pain chronification. These studies will guide prevention and intervention strategies in the future.

Notwithstanding these unanswered questions, the papers by Doehring et al. and Qi et al. provide a few excellent examples that point to the emergence of the field of “pain epigenetics”. This field has the potential to change the way we understand pain: What are the links between the pain experience and previous environmental exposures, such as from medications or adverse social experiences? What is the impact of chronic pain on downstream health consequences? Can we modulate these links to effect therapeutic benefit? Since epigenetic processes are potentially reversible, it is reasonable to envision novel epigenetic therapeutics that could complement behavioural interventions to alleviate pain. Given that the few currently available epigenetic-based drugs are pharmacologically non-specific, a serious effort will be required to develop more selective targeting of specific DNA methyltransferases and demethylases. At the same time, it is very likely that studies exploring the relationship between epigenetics and chronic pain will uncover differentially regulated genes and pathways that can be more directly targeted.

Conflict of interest statement

The authors have no conflicts of interest.

References


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