Epigenetic regulation of persistent pain

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Persistent or chronic pain is tightly associated with various environmental changes and linked to abnormal gene expression within cells processing nociceptive signaling. Epigenetic regulation governs gene expression in response to environmental cues. Recent animal model and clinical studies indicate that epigenetic regulation plays an important role in the development or maintenance of persistent pain and possibly the transition of acute pain to chronic pain, thus shedding light in a direction for development of new therapeutics for persistent pain. (Translational Research 2015;165:177–199)

Abbreviations: acH3 = acetylated histone 3; acH4 = acetylated histone 4; CCI = chronic constriction injury; CGI = CpG island; DNMT = DNA methyltransferase; DRG = dorsal root ganglion; HAT = histone acetyltransferase; HATi = HAT inhibitor; HDAC = histone deacetylase; HDACi = HDAC inhibitor; 5mC = 5-methylated cytosine; MT = morphine tolerance; ncRNA = noncoding RNA; PSL = partial sciatic nerve ligation; SCN = sciatic nerve; SNPs = single-nucleotide polymorphisms; SNL = spinal nerve ligation; TSS = transcription start sites

INTRODUCTION

Persistent or chronic pain is a complicated clinical condition that impacts the lives of approximately a quarter of the population.[1-7] This clinical condition can be developed from acute pain resulting from tissue damage or be associated with numerous human diseases.[7,8] Similar to varied individual pain sensitivity, there is a large difference in vulnerability of individuals to develop persistent pain.[5-10] Although the mechanisms underlying this variation remain largely unknown, efforts have been made to look for genetic mechanisms and gene expression.

It has been well established from clinical and laboratory studies that under persistent pain conditions cells processing pain signaling, that is, nociceptors in the peripheral nervous system and neurons and glia in the central nervous system (CNS), become sensitized in response to various stimuli. This increased sensitivity is accompanied by functional and structural changes (plasticity).[7,11-14] Multiple molecular mechanisms are likely responsible for these changes. Various chemicals or factors and relevant receptor-signal transduction pathways are proposed to become active during persistent pain.[15,16] Gene-specific and genome-wide association studies further demonstrate that many genes undergo expression changes at mRNA and protein levels in tissues or cells of pain circuitry during the development or maintenance of persistent pain.[17-24]

Cases of single-nucleotide polymorphisms (SNPs) have been found to be risk factors in the development of persistent pain in humans.[25-27] For example, several missense SNPs in the *SCN9A* gene increase activity of its protein product voltage-gated sodium Nav1.7 and are associated with primary erythromelalgia, paroxysmal extreme pain disorder, and osteoarthritic pain.[26,27] In addition to the genetic mechanism that determines and regulates gene expression based on genomic DNA sequences, recently, DNA sequence–independent mechanisms in regulating gene expression, namely epigenetic regulation, have been proposed.[28-34] Primarily, epigenetic mechanisms are involved in gene regulation during early development, in X-chromosome inactivation, and in response to various environmental changes. Epigenetic regulation has been found to

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participate in many physiological and pathologic processes, such as neuronal plasticity and cancer, in which various environmental factors are involved and sometimes, however, no cell division occurs.[28,29,35-37] In most of these cases, genetic mechanisms fail to explain the changes. Environmental factors such as stress, tissues damage, and disease conditions largely impact the vulnerability of individuals to develop persistent pain clearly via DNA sequence–independent mechanism(s). This concept is supported by several lines of evidence. Tissue damage or inflammation is a common environmental event seen in many types of persistent pain. For example, we observed that rats experiencing stimulation by the inflammatory irritant carrageenan to the hindpaw at the first postnatal week exhibited more intense responses when challenged by the same irritant at a young adult age (day 60).[38] Interestingly, mice dams fed with high methyl donor diets during the perinatal period had their male offspring displaying increased mechanical allodynia after skin incision.[39] A number of twin studies have demonstrated the great impact of environmental factors on the development of various pain conditions.[40-42] For example, a study of 33,794 twins indicated that the genetic impact on neck pain development in monozygotic twins diminished following the age when environmental factors become dominant.[40] Environmental factors were involved in interpersonal differences of pain sensitivity and opioid effects.[41] Drug addiction and smoking were associated with epigenetic changes in the nervous system and were found to impact chronic pain.[43] Female smokers reported more chronic pain conditions than nonsmokers.[44] Heroin addicts developed hyperalgesia.[45] It should be also noticed that many diseases involved in epigenetic regulation are associated with persistent pain, such as cancer[32,46,47] and diabetes.[2,48] In those diseases, epigenetic factors may indirectly contribute to the development of persistent pain.

The field of study of epigenetic mechanisms underlying pain or persistent pain has been progressing very rapidly in recent years as reviewed by others.[10,13,49-54] Currently 3 major molecular mechanisms have been proposed for epigenetic regulation, that is, DNA methylation, chromatin remodeling, and noncoding RNA (ncRNA),[33,55,56] although RNA/DNA editing has been proposed as the fourth mechanism.[57] In this review, we will summarize and comment on studies on persistent pain related to these 3 major aspects.

DNA METHYLATION

DNA methylation is the prototype of epigenetic regulation and, in mammalian genomes, occurs mostly on carbon 5 of the pyrimidine ring of the cytosine residue followed by guanine residue, namely CpG dinucleotide.[58,59] In mammalian cells, enzymes to catalyze this reaction are DNA methyltransferase (DNMT)1, 3a, and 3b.[60] In most cases, DNMT1 maintains basic methylation, whereas DNMT3a and 3b are responsible for de novo DNA methylation established during the development and induced by various factors.[60,61] These enzymes do not show obvious tissue specificity, but their expression is regulated. Methylated CpGs are thought to recruit several nuclear proteins known as methylated CpG–binding proteins (MBDs), but repel other transcription factors.[37,60-62] Binding of these proteins may recruit inhibitory transcription factors and produce downregulation or silence of gene transcription.[37]

Functionally, DNA methylation is a complex event because of the nature of CpGs that are unevenly distributed in the genome and differentially methylated among tissues to form the so-called differentially methylated region (DMR).[43,63,64] After evolution, mammalian genomes have developed small guanine-cytosine-rich regions (<1 kb in most cases) that contain clusters of CpGs and are named CpG islands (CGIs).[65] Although the precise definition of a CGI is still in debate, this structure often (about half of the total CGIs) appears near (upstream, overlapping, or downstream) transcription start sites (TSS) of about 72%–76% of protein-encoding genes in humans.[66-70] It was estimated from genome projects that there are close to 29,000 CGIs in human nonrepetitive sequences in which most protein-encoding genes reside.[71,72] Interestingly, a smaller number (21,377) of CGI-like sequences were found in repetitive sequences of humans, although no other protein coding genes except retrotransposons are found in these regions.[72] Sporadic CpGs located within 2 kb sequences distal to CGIs are termed CGI shore and are responsible for most (more than 70%) tissue- (among human brain, liver, and spleen) and cancer-specific DMRs.[73] Because of the nature of CpGs and the means to estimate or evaluate them, there is confusion in the understanding of this structure.[74] Several important issues should be paid attention to before examining and interpreting the data. First, CpGs are distributed within CGIs, CGI shore, repetitive sequences, and intergenic sequences, although only about 16% of human CpGs are found in CGIs.[75] Second, in mature or well-differentiated cells, CpGs in most CGIs are unmethylated[61,76] and only about 5%–8% CGIs have methylated CpGs to form tissue-specific DMRs, most of which are intragenic or intergenic CGIs.[70,77,78] In response to environmental or intrinsic cues, CpGs in CGI, CGI shore, and non-CGI/CpG poor promoters can be methylated in a cell- or tissue-specific manner,[34,79] although approximately 80% of non-CGI