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Epigenetic Modification of Nociceptive Mediators: Implications for the Etiology of Neural Hypersensitivity (Part II)

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SUMMARY Although pain is the most awful feeling for personal perception, it possesses critical benefits for preventing our human being to be injured further. Pain itself forms an overbalanced microenvironment in which people undertakes individualized changes in its neurobiological, psychological, endocrinological and genetic properties especially in the context of chronic pain or when the acute pain transmitted to chronicity. Our previous part (Part I) review the general epigenetic modification of nociceptive contributing factors in the context of chronic pain. Herein (Part II) we paid specific attention on the epigenetic regulation of pain-associated molecules including neurotransmitters and other factors. A detailed understanding of the specific modulating factors that influence individual epigenetic differences contributing to pain sensitivity and responsiveness to analgesics possesses essential implications in clinical pain management. ■

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PAIN IS a don't-want-to-be experience no matter at which context it is, either at the acute postoperative phase or when it becomes chronicity, even though it possesses function of further-injury avoidance. Different types of therapeutic ma-

neuvors, physiologically and physically, have been developed to control the overbalanced pain, whereas the effectiveness of these methods is limited (1, 2). Facilitation and inhibition are two major compositions of the pathway of pain transduction that draws much attention on in the

past decades (3, 4), and great progress was made based on these two “yin” and “yang” systems. However, our patients with pain are still suffering from the “God-made original sinful perception” without efficient conquers. The development of epigenetics promises patients hope for

controlling the pain through modifying the gene expression of pain-related molecules that finally determines the fate of the patient's outcome.

Epigenetic Regulations of Pain

Pain as one of the major stressors can evoke physiological and psychological changes that induce alterations in the expression of pain-associated molecules (5). Under the stimulation of pain, different molecules and proteins showed different levels of expression that finally forms a complex molecular matrix. This is the determinant whether the pain will tend to recover or to get worsened. However, who was the underlying controller of the molecular expression, and further how they reached such a precise interaction? Emerging evidence suggests that epigenetic modulation operates the expression of different genes in the context of pain (6). Given peripheral and central sensitizations are two major parts of the pathogenesis of pain (7, 8), we herein describe their relationship between epigenetic mediation separately, but the de-facto relationship should be in combination.

Epigenetics and Peripheral Sensitization

In most cases, pain derives from peripheral tissue injury or diseases that would unavoidably result in injury on the nociceptors or neural trunks. A series of responses, physically and physiologically, will follow up and then the self-adjustment is activated to avoid further injury and to control the propagation of pain (9). This is the typical process of peripheral injury induced pain. One pivotal step of the pain occurrence is the newly generated mediators that were released by the injured tissues, recruited immune cells and peripheral neurons (10). The injury-induced peripheral pro-analgesic mediators include pro-inflammatory

cytokines (TNF- α , IL-1 β), chemokines (CCL2, CCL3, and CXCL5), prostanoids (PGE₂, PGI₂), nerve growth factor (NGF), bradykinin, histamine, platelet-activating factor, nitric oxide (NO), and proton (H⁺) (11-13). Once these mediators were released due to tissue injury, they will activate and sensitize the nociceptors making them spontaneously active and more readily to be activated by sub-threshold stimuli. We will discuss the epigenetic regulation on these peripheral pain-related mediators.

TNF- α and IL-1 β are two typical pro-inflammatory cytokines believed released and upregulated in response to tissue injury. In arthritic patients, HDAC inhibitors have been observed producing substantial clinical benefits and the levels of both TNF- α and IL-1 β were significantly reduced upon the using of HDAC inhibitors (14, 15) indicating that the expression of peripheral inflammatory cytokines is regulated by epigenetic mechanisms. In further, bindings of IL and TNF- α to their respective receptors lead to H4 hyperacetylation of other factors' promoters via affecting NF- κ B pathway (16, 16). Besides, the recruitment of NF- κ B to pro-inflammatory genes was affected by H3K4 methylation (17). CCL2 excited primary sensory neurons by acting on the biophysical properties of Na(v)1.8 currents via a CCR2/G β y-dependent mechanism (18), and in consideration of the strong association between the changes in function of voltage-gated sodium channels in nociceptive primary sensory neurons participating in the development of peripheral hyper-excitability, and then CCL2 was considered as one important contributor of peripheral sensitization. Meanwhile, CCL2 enhanced striatal dopamine release by cognating to CCR2 receptor through extracellular signal-regulated kinase (ERK), a fundamental enzyme in striatal gene and epigenetic regulation (19), to sensitize cocaine (20)

suggesting that chemokine activation is an essential component of peripheral sensitization that may be closely related to epigenetic regulation. As the target of COX inhibitors, PGE₂ and PGI₂ are two contributors to peripheral hyperalgesia. Emerging evidence showed that epigenetic alterations play a critical role in the regulation of the genes of the COX pathway (21), and also the epigenetic processes underlying expression of the prostanoid receptor EP2 were characterized (22) demonstrating that COX-PGE₂-EP2 pathway is affected by epigenetic modulation. NGF, a small secreted protein, is critical for the growth, maintenance, and survival of target neurons. Brain-derived neurotrophic factor (BDNF) is the most studied NGF, and a large number of data documented its involvement in the regulation of pain (23). However, the expression of BDNF in the CNS was regulated by the interaction between MeCP2 and SIRT1, two critical epigenetic mediators (24), showing that an association between NGF and epigenetic exists. Bradykinin, histamine, platelet-activating factor and NO are four important inflammatory mediators released by injured tissue cell, blood vessels, and blood cells (12), and they contributed to the formation of peripheral inflammation soup around the injured area. Immuno-reactivity of HDAC 8 was detected in the histamine neurons with a pericellular pattern (25), NO itself is an essential mediator of epigenetic gene expression (26) and the NO population was affected by DNA methylation in arginases 1 and 2 (27) suggesting that these tissue-derived mediators also may be regulated by the epigenetic mechanisms. Although we thus far have evidence indicating the epigenetic regulation on the peripheral sensitization, it is still infancy and in-depth work is needed in elucidating the epigenetic modulation on their expression and the potential intertalk amongst them each other.

Epigenetics and Central Sensitization

Central sensitization is defined as an increased response to stimulation that is mediated by amplification of signaling in the CNS (7, 8). Neuroplasticity, glia activation, ion channels' expression and states, and neurotransmitters balance all are critical contributors to the central sensitization (28), a pathological state in which merely the subthreshold stimulation or even no-stimulation (i.e. spontaneously) causes pain. The persistence of pain itself is a risk factor in inducing central sensitization, through which a vicious cycle formed only if when the pain was effectively treated. A great progress has been being made on the understanding of pain mechanisms on the basis of central sensitization, whereas the therapeutic efficacy with currently available methods is limited (29). Traditional concept is that seeking and finding potential contributors to the pathogenesis of pain, and then figuring out activating or inhibiting molecules on the target players. Based on this, over hundreds of molecules were identified over the past decades, but we still cannot reach the ideal purpose – conquer the pain with easy-to-use method. What is the outlet for the next step in pain study? For this question, the epigenetic modulation may give us hope.

Both systemic and spinal administration of HDAC inhibitors produced analgesic effects in inflammatory pain models (30), and such effect resulted from the expression changes of the mGluR2 receptor in both DRG and spinal cord (31). Moreover, pain itself evoked epigenetic changes in pro-analgesic genes. The down-regulation of glutamic acid decarboxylase 65 (GAD65) and hypoacetylation at its promoter were detected when complete Freund's adjuvant (CFA) was injected into rat's paw or the spinal nerve was ligated (32). Chronic pain conditions are strongly associated with the

changes in brain structure and cortical function, but these changes are mediated by the reversible DNA methylation in the mouse prefrontal cortex (33). The increased monocyte chemotactic protein (MCP-3) expression associated with IL-6 dependent epigenetic modification at the MCP-3 promoter after nerve injury plays a critical role in the neuropathic pain-like state (34). Promoter demethylation of cystathionine- β -synthetase gene, the enzyme promoting synthesizing hydrogen sulfide, contributes to inflammatory hyperalgesia through protein kinase A (PKA) pathway (35). Nonetheless, the increased global DNA methylation and methyl-CpG-binding protein 2 (MeCP2) expression in the spinal cord after nerve damage plays an important role in neuropathic pain (36). Hyperacetylation of histone H3 on the promoter regions of macrophage inflammatory protein 2 (MIP-2) and C-X-C chemokine receptor type 2 (CXCR2) evoked chronic neuroinflammation by neutrophil accumulation resulting in neuropathic pain (37). These above-mentioned findings demonstrate that pain can induce DNA or histone methylation and demethylation, or/and histone hyperacetylation and hypoacetylation of specific genes, and then these epigenetic alterations either deteriorate or alleviate pain. What is the final effect therefore depends on the epigenetic balance.

Opioidergic alterations under the chronic pain condition were considered as an essential contributor to central sensitization (38), and corresponding epigenetic modification was proposed to be one of the underlying mechanisms. Chronic use of opioid increased methylation at a CpG rich island in the OPRM1 gene coding for MOP and at a global methylation site (LINE-1) in leukocytes, of which strongly associated with the increased clinical pain (39). However, ultra-low-dose naloxone provides clinical valuable for neuropathic pain management through

regulating global histone methylation suggesting that either the opioid-induced hyperalgesia or pain-induced opioidergic impairment; epigenetic modification is the potential controller (40). Furthermore, epigenetic upregulation of NGF activity in the central nucleus of the amygdala (CeA) promoted the behavior of opioid reward and increased the sensitivity to the rewarding effect of subsequent opioids (41). How to reach the ideal state and how to keep the balance of opioidergic function via adjusting epigenetic regulation and other pain-modulating systems still need to be investigated.

Epigenetic Mechanisms of Pain – Future Directions

Although we so far have evidence for the correlation between epigenetic modification and pain, it just dawns on us. We hereby hypothesized that pain was a three-dimensional bio-phenomenon that includes physical, physiological and psychological changes, in which the tissue injury including chemical, physical, biological and disease-associated ones belongs to the physical dimension, and the molecular and cellular changes including peripheral and central alterations belong to the physiological dimension, and the changes in spiritual and mood belong to the psychological dimension. How to teasing out the precise relationship among these three facets and epigenetic modulation is a thorny challenge for pain scientists.

The interacting matrix among different kinds of pain-related molecules at the peripheral site and in the CNS and different types of epigenetic regulators is the actual situation under the condition of pain. Figuring this complex is as difficult as mapping human disease spectrotyping, while it promises us the final solution of pain therapy. We cannot explore this with a once-for-all pattern, but the step-by-step investigation is

the feasible way in tapping the interactions between two or three these molecules. Good examples are as follows: nerve injury caused a marked reduction in the acetylation of histone H4 at K(v)4.3-neuron-restrictive silencer element (NRSE) through transcriptional suppressor neuron-restrictive silencer factor (NRSF) in the DRG (42), which depicted the crosstalk among histone acetylation, NRSE, K(v)4.3 and nerve injury in DRG; in addition, nerve injury diminished the activity of the big conductance Ca^{2+} -activated K^+ (BK) channel in small and medium DRG neurons by increased BDNF through epigenetic and transcriptional mechanisms (43), which mapped the interaction among BK channel, BDNF, epigenetic modulation and nerve injury in DRG; and further the histone acetyltransferase E1A binding protein p300 epigenetically mediated chronic constriction injury (CCI) induced neuropathic pain via upregulating COX-2 expression in the spinal cord (44), which showed the interrelationship among p300, COX-2, histone acetylation and nerve injury in the spinal cord. Therefore, great efforts are needed to map the complex.

No matter what mechanisms can be explored, the ultimate purpose is to reveal novel targets for pain management. Although the currently approved HDAC inhibitors as drugs like valproic acid for epilepsy and SAHA and FK228 for T cell lymphoma (45, 46) have been tested in animal models of pain, their effects on patients need to be observed at length. These global inhibitors of HDACs would unavoidably produce unexpected side effects, so the risks and benefits should be weighed before giving for pain control. This also raises the question that more specific therapeutics focusing on different epigenetic modulations are necessary for the treatment of pain. For the precise relationship amongst above-mentioned molecules and epigenetic mediators, the methods

from the computational biology, such as molecular docking and packing, quantitative structure-activity relationships (QSAR), Monte Carlo simulated annealing approach, structural bioinformatics, pharmacophore modeling, and signal peptide prediction etc. may provide insights into corresponding molecule-molecule interactions and give hope for the development of novel therapeutics for pain.

In conclusion, the emerging evidence indicates that epigenetic modulation is an essential contributor to the pathogenesis of pain. The study on epigenetic control of pain is still infancy, efforts are needed and a new avenue will be opened along with the progress in the exploration of epigenetic-associated modulation of pain.

Conflict of Interests

None

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References

- Johnson Q, Borsheski RR, Reeves-Viets JL. Pain management mini-series. Part I. A review of management of acute pain. *Mo Med* 2013; 110: 74-79.
- Gilron I, Baron R, Jensen T. Neuropathic Pain: Principles of Diagnosis and Treatment. *Mayo Clin Proc* 2015; 90: 532-545.
- Dubin AE, Patapoutian A. Nociceptors: the sensors of the pain pathway. *J Clin Invest* 2010; 120: 3760-3772.
- Ji RR, Woolf CJ. Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain. *Neurobiol Dis* 2001; 8: 1-10.
- Nishihara M. Psychiatric issues in chronic pain. *Brain Nerve* 2012; 64: 1323-1329.
- Denk F, McMahon SB. Chronic pain: emerging evidence for the involvement of epigenetics. *Neuron* 2012; 73: 435-444.
- Puretić MB, Demarin V. Neuroplasticity mechanisms in the pathophysiology of chronic pain. *Acta Clin Croat* 2012; 51: 425-429.
- Fornasari D. Pain mechanisms in patients with chronic pain. *Clin Drug Investig* 2012; 32 Suppl 1: 45-52.
- DeLeo JA. Basic science of pain. *J Bone Joint Surg Am* 2006; 88 Suppl 2: 58-62.
- Schaible HG. Pathophysiology of pain. *Orthopade* 2007;36: 8, 10-12, 14-16.
- Kiguchi N, Kobayashi Y, Kishioka S. Chemokines and cytokines in neuropathic pain. *Curr Opin Pharmacol* 2012; 12: 55-61.
- Petho G, Reeh PW. Sensory and signaling mechanisms of bradykinin, eicosanoids, platelet-activating factor, and nitric oxide in peripheral nociceptors. *Physiol Rev* 2012; 92: 1699-1775.
- Kress M, Zeilhofer HU. Capsaicin, protons and heat: new excitement about nociceptors. *Trends Pharmacol Sci* 1999; 20: 112-118.
- Vojinovic J, Damjanov N, D'Urzo C, Furlan A, Susic G, Pasic S, Iagaru N, Stefan M, Dinarello CA. Safety and efficacy of an oral histone deacetylase inhibitor in systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum* 2011; 63: 1452-1458.
- Leoni F, Zaliani A, Bertolini G, Porro G, Pagani P, Pozzi P, Donà G, Fossati G, Sozzani S, Azam T, Bufler P, Fantuzzi G, Goncharov I, Kim SH, Pomerantz BJ, Reznikov LL, Siegmund B, Dinarello CA, Mascagni P. The antitumor histone deacetylase inhibitor suberoylanilide hydroxamic acid exhibits antiinflammatory properties via suppression of cytokines. *Proc Natl Acad Sci USA* 2002; 99: 2995-3000.

16. Rahman I, Gilmour PS, Jimenez LA, MacNee W. Oxidative stress and TNF-alpha induce histone acetylation and NF-kappaB/AP-1 activation in alveolar epithelial cells: potential mechanism in gene transcription in lung inflammation. *Mol Cell Biochem* 2002; 234-235: 239-248.
17. Li Y, Reddy MA, Miao F, Shanmugam N, Yee JK, Hawkins D, Ren B, Natarajan R. Role of the histone H3 lysine 4 methyltransferase, SET7/9, in the regulation of NF-kappaB-dependent inflammatory genes. Relevance to diabetes and inflammation. *J Biol Chem*. 2008; 283: 26771-26781.
18. Belkouch M, Dansereau MA, Réaux-Le Goazigo A, Van Steenwinkel J, Beaudet N, Chraïbi A, Melik-Parsadaniantz S, Sarret P. The chemokine CCL2 increases Nav1.8 sodium channel activity in primary sensory neurons through a Gβγ-dependent mechanism. *J Neurosci* 2011; 31: 18381-18390.
19. Trollope AF, Gutiérrez-Mecinas M, Mifsud KR, Collins A, Saunderson EA, Reul JM. Stress, epigenetic control of gene expression and memory formation. *Exp Neurol* 2012; 233: 3-11.
20. Trocello JM, Rostene W, Melik-Parsadaniantz S, Godefroy D, Roze E, Kitabgi P, Kuziel WA, Chalon S, Caboche J, Aparts E. Implication of CCR2 chemokine receptor in cocaine-induced sensitization. *J Mol Neurosci* 2011; 44: 147-151.
21. Cebola I, Peinado MA. Epigenetic deregulation of the COX pathway in cancer. *Prog Lipid Res* 2012; 51: 301-313.
22. To SQ, Takagi K, Miki Y, Suzuki K, Abe E, Yang Y, Sasano H, Simpson ER, Knowler KC, Clyne CD. Epigenetic mechanisms regulate the prostaglandin E receptor 2 in breast cancer. *J Steroid Biochem Mol Biol* 2012; 132: 331-338.
23. Trang T, Beggs S, Salter MW. Brain-derived neurotrophic factor from microglia: A molecular substrate for neuropathic pain. *Neuron Glia Biol* 2011; 7: 99-108.
24. Zocchi L, Sassone-Corsi P. SIRT1-mediated deacetylation of MeCP2 contributes to BDNF expression. *Epigenetics* 2012; 7: 695-700.
25. Takase K, Oda S, Kuroda M, Funato H. Monoaminergic and neuropeptidergic neurons have distinct expression profiles of histone deacetylases. *PLoS One* 2013; 8: e58473.
26. Illi B, Colussi C, Grasselli A, Farsetti A, Capogrossi MC, Gaetano C. NO sparks off chromatin: tales of a multifaceted epigenetic regulator. *Pharmacol Ther* 2009; 123: 344-352.
27. Breton CV, Byun HM, Wang X, Salam MT, Siegmund K, Gilliland FD. DNA methylation in the arginase-nitric oxide synthase pathway is associated with exhaled nitric oxide in children with asthma. *Am J Respir Crit Care Med* 2011; 184: 191-197.
28. van Wilgen CP, Keizer D. The sensitization model to explain how chronic pain exists without tissue damage. *Pain Manag Nurs* 2012; 13: 60-65.
29. Hashizume K. Diagnosis and treatment of chronic pain by pain clinicians. *Brain Nerve* 2012; 64: 1315-1322.
30. Chiechio S, Copani A, Zammataro M, Battaglia G, Gereau RW 4th, Nicoletti F. Transcriptional regulation of type-2 metabotropic glutamate receptors: an epigenetic path to novel treatments for chronic pain. *Trends Pharmacol Sci* 2010; 31: 153-160.
31. Chiechio S, Zammataro M, Morales ME, Busceti CL, Drago F, Gereau RW 4th, Copani A, Nicoletti F. Epigenetic modulation of mGlu2 receptors by histone deacetylase inhibitors in the treatment of inflammatory pain. *Mol Pharmacol* 2009; 75: 1014-1020.
32. Zhang Z, Cai YQ, Zou F, Bie B, Pan ZZ. Epigenetic suppression of GAD65 expression mediates persistent pain. *Nat Med* 2011; 17: 1448-1455.
33. Tajerian M, Alvarado S, Millicamps M, Vachon P, Crosby C, Bushnell MC, Szyf M, Stone LS. Peripheral nerve injury is associated with chronic, reversible changes in global DNA methylation in the mouse prefrontal cortex. *PLoS One* 2013; 8: e55259.
34. Imai S, Ikegami D, Yamashita A, Shimizu T, Narita M, Niikura K, Furuya M, Kobayashi Y, Miyashita K, Okutsu D, Kato A, Nakamura A, Araki A, Omi K, Nakamura M, James Okano H, Okano H, Ando T, Takeshima H, Ushijima T, Kuzumaki N, Suzuki T, Narita M. Epigenetic transcriptional activation of monocyte chemotactic protein 3 contributes to long-lasting neuropathic pain. *Brain* 2013; 136: 828-843.
35. Qi F, Zhou Y, Xiao Y, Tao J, Gu J, Jiang X, Xu GY. Promoter demethylation of cystathionine-β-synthetase gene contributes to inflammatory pain in rats. *Pain* 2013; 154: 34-45.
36. Wang Y, Liu C, Guo QL, Yan JQ, Zhu XY, Huang CS, Zou WY. Intrathecal 5-azacytidine inhibits global DNA methylation and methyl-CpG-binding protein 2 expression and alleviates neuropathic pain in rats following chronic constriction injury. *Brain Res* 2011; 1418: 64-69.
37. Kiguchi N, Kobayashi Y, Maeda T, Fukazawa Y, Tohya K, Kimura M, Kishioka S. Epigenetic augmentation of the macrophage inflammatory protein 2/C-X-C chemokine receptor type 2 axis through histone H3 acetylation in injured peripheral nerves elicits neuropathic pain. *J Pharmacol Exp Ther* 2012; 340: 577-587.
38. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 2011; 14: 145-161.
39. Doehring A, Oertel BG, Sittl R, Lötsch J. Chronic opioid use is associated with increased DNA methylation correlating with increased clinical pain. *Pain* 2013; 154: 15-23.
40. Tsai RY, Shen CH, Feng YP, Chien CC, Lee SO, Tsai WY, Lin YS, Wong CS. Ultra-low-dose naloxone enhances the

- antinociceptive effect of morphine in PTX-treated rats: regulation on global histone methylation. *Acta Anaesthesiol Taiwan* 2012; 50: 106-111.
41. Bie B, Wang Y, Cai YQ, Zhang Z, Hou YY, Pan ZZ. Upregulation of nerve growth factor in central amygdala increases sensitivity to opioid reward. *Neuropsychopharmacology* 2012; 37: 2780-2788.
 42. Uchida H, Sasaki K, Ma L, Ueda H. Neuron-restrictive silencer factor causes epigenetic silencing of Kv4.3 gene after peripheral nerve injury. *Neuroscience* 2010; 166: 1-4.
 43. Cao XH, Chen SR, Li L, Pan HL. Nerve injury increases brain-derived neurotrophic factor levels to suppress BK channel activity in primary sensory neurons. *J Neurochem* 2012; 121: 944-953.
 44. Zhu XY, Huang CS, Li Q, Chang RM, Song ZB, Zou WY, Guo QL. p300 exerts an epigenetic role in chronic neuropathic pain through its acetyltransferase activity in rats following chronic constriction injury (CCI). *Mol Pain* 2012; 8: 84.
 45. Huang Z, Peng S, Knoff J, Lee S, Yang B, Wu TC, Hung CF. Combination of proteasome and HDAC inhibitor enhances HPV16 E7-specific CD8+ T cell immune response and antitumor effects in a preclinical cervical cancer model. *J Biomed Sci* 2015; 22: 7.
 46. Kim EJ, Kim YH, Rook AH, Lerner A, Duvic M, Reddy S, Robak T, Becker JC, Samtsov A, McCulloch W, Waksman J, Whittaker S. Clinically significant responses achieved with romidepsin across disease compartments in patients with cutaneous T-cell lymphoma. *Leuk Lymphoma* 2015; 2015: 1-22. ■

