Basic Research for Pain

38

Yong Luo and Shiqian Shen

Key Points

- Stem cell therapy provides promise for treating discogenic pain.
- Targeting CGRP(R) with monoclonal antibodies represents a breakthrough in migraine prophylaxis. Other monoclonal antibodies under development may prove effective for spine pain.
- Innovative imaging modalities facilitate pain diagnosis and treatment.
- Gut microbiome is a new frontier in pain research, which offers unique opportunities in probing the complex relationship between dietary/environmental factors and pain.

Introduction

Pain is a pathophysiological state defined by the International Association for the Study of Pain as "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such" [1, 2]. Pain can be either acute or chronic based on its duration. Pain often becomes chronic when the duration is beyond 3 months for nonmalignant pain. With more than 100 million Americans suffering from chronic pain, the economic costs of pain in the United States are enormous. It is estimated that the annual cost of chronic pain is as high as $635 billion a year, which is more than the yearly costs for cancer, heart disease, and diabetes [3, 4]. Despite the high annual cost of chronic pain, in 2017 only $516 million was funded by NIH for pain research, which is way far less than the funds for cancer, heart disease, and diabetes research ($5980 million, $1370 million, and $1108 million, respectively). The limited funding in pain research is partially due to the lack of recognition of the importance of basic research on the advancement of pain treatment clinically. As it was recently emphasized by the American Academy of Pain Medicine, pain is the driving force for progress of pain treatment [5]. In this chapter, our goal is to review, summarize, and discuss the recent basic research findings that have advanced or will likely advance future pain treatments. We will focus on (1) stem cell therapy, (2) monoclonal antibody-based pharmacotherapy for chronic pain, (3) new imaging modality for the detection of pain signal and its response to treatment, and (4) gut microbiome modulation of neuropathic and inflammatory pain.

Stem Cell Therapy

Pain can be caused by degenerative diseases, such as herniated disc, osteoarthritis, and ligament injury, and by nerve damage, such as postherpetic neuropathy and diabetic neuropathy; therefore, the idea of using stem cells to regenerate the degenerated materials and even re-establish normal innervation becomes appealing to researchers. The majority of the stem cells used in research are mesenchymal stem cells (MSCs) derived from bone marrow. MSCs have the capacity of self-renewal while maintaining multipotency. They can be differentiated into osteoblasts and chondrocytes under neurons under appropriate induction conditions.

Discogenic pain has been a common but difficult to treat pain condition secondary to degeneration. Recently, stem cell therapy started to emerge as a new modality to treat discogenic pain. In a pilot study in 2011, ten patients with chronic pain due to lumbar disc degeneration were treated by intra-disc injection of autologous expanded bone marrow MSCs. Both safety and efficacy were demonstrated in this study. Nine out of ten patients experienced pain and disability reduction by 61.5% and 48%, respectively, at 3 months and continued to improve at 6 and 12 months [6, 7]. Although this was not a controlled randomized study, it still proved the safety of autologous MSC injections for discogenic pain. A comparison study in 2015

Y. Luo · S. Shen (✉)
Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA
e-mail: sshen2@mgh.harvard.edu

J. Mao (ed.), *Spine Pain Care*, https://doi.org/10.1007/978-3-030-27447-4_38

with 26 patients again demonstrated the safety and efficacy of autologous MSC injections for discogenic pain. In this study, patients were divided equally into two groups. One group received one level of intra-disc injection of autologous MSCs, and the other group received two levels of autologous MSC injections. Significant decrease in both pain and disability scores was similarly observed in both groups. No significant side effects were observed [8]. Nonetheless, the efficacy of MSCs injections for discogenic pain is still awaiting for data from large multicenter randomized controlled trials.

Monoclonal Antibody-Based Pharmacotherapy for Chronic Pain

Monoclonal antibodies represent major breakthroughs in modern medicine, particularly in the treatment of cancers with anti-PD1/PDL1 and anti-CTLA4 antibodies [9, 10]. Similarly, pain treatment using monoclonal antibodies has made significant progress recently, particularly in migraine prevention. In 2018, the US Food and Drug Administration approved two monoclonal antibodies targeting calcitonin gene-related peptide (CGRP): anti-CGRP receptor mAb (erenumab, Novartis, Amgen) and anti-CGRP mAb (fremanezumab, Teva; galcanezumab, Eli Lilly) for migraine prevention [11–14]. These antibodies exert their function by targeting the trigeminovascular unit and decreasing neurogenic inflammation. In double-blinded clinical trials, these antibodies reduce the days with headaches by about 40% versus about 20% with placebo treatment.

Other monoclonal antibodies, particularly those targeting inflammatory cytokines, such as TNF-a, IL-17, and IL-23, are originally designed and aimed to treat autoimmune diseases, such as Crohn's disease, rheumatoid arthritis, and psoriasis [15–18]. Pain is one of the major clinical presentations in these conditions. Clinical use of these antibodies for treating autoimmune conditions and associated pain symptoms has gained popularity. Humira, a fully humanized anti-TNFα monoclonal antibody used for rheumatoid arthritis and Crohn's disease, is one of the best-selling drugs globally, with $19.94 billion of revenues generated in 2018 for its manufacturer. Monoclonal antibodies not only treat joint pain/arthritis in the setting of autoimmune diseases but also induce arthritis pain in some cases. For example, in the aforementioned cancer immunotherapy (checkpoint therapy) with anti-PD1/PDL1 and anti-CTLA4 antibodies, immune-related inflammatory arthritis has been recognized as a side effect that affects many different joints with concurrent pain complaints [19].

There is currently no monoclonal antibody that is primarily used for chronic pain except for migraine. However, monoclonal antibodies against nerve growth factor (NGF) have gained significant considerations as new potential pain treatment modalities. NGF is a neurotrophic factor involving in neuron growth, differentiation, and survival [20]. Numerous researchers have repeatedly demonstrated that NGF level is elevated in chronic pain conditions such as diabetic neuropathy, cancer pain, and chronic pancreatitis, suggesting its important role in chronic pain signaling [21–23]. Upon tissue damage caused by noxious stimuli, inflammatory factors such as IL-1 and TNFα are released, which increases the production of NGF. NGF binds to trkA (tropomyosin receptor kinase A) at terminal A-delta and C nerve fibers. The interactions between NGF and trkA initiate a serial of downstream pain signaling pathways involving pain initiation, maintenance, and modulation [22]. Because of NGF's important role in initiation and maintenance of pain signaling, anti-NGF antibody has been developed and underwent clinical trials targeting the NGF signaling pathway as a potential promising treatment for chronic pain conditions. Tanezumab, a humanized IgG2 anti-NGF monoclonal antibody, has been demonstrated efficacy in treating arthritic pain in several clinical trials. In a clinical trial that involved 444 patients by Lane et al. in 2010, tanezumab up to 200 ug/kg improved pain from knee arthritis by 45–62% [24]. Improvement in stiffness and limitations in physical function were also reported over 16 weeks following treatment. The most common adverse effects reported are headache and paresthesia. In a similar randomized, double-blind, placebo-controlled clinical trial with 690 patients, tanezumab treatments at different doses of 2.5 mg, 5 mg, and 10 mg on day 1, 57, and 113 improved arthritic knee pain by 51–62% using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and numerical rating scale (NRS) [25]. Again, the most common reported side effects are headache and paresthesia. The efficacy of tanezumab in treating chronic low back pain was demonstrated in a randomized, double-blind, placebo-controlled trial involving 217 patients in 2011 by Katz et al. [26]. Treatment with 200 μg/kg of tanezumab for 6 weeks was associated with 52% improvement in pain intensity and greater improvement in Roland-Morris Disability Questionnaire and Brief Pain Inventory scores. Additional research and phase III clinical trials of tanezumab on various pain conditions are necessary to characterize the mechanisms of action, safety, and efficacy.

New Imaging Modality for the Detection of Pain Signal and Its Response to Treatment

Imaging studies are commonly performed to aid the diagnosis of pain and to guide clinical treatment. However, correlation between radiologic structural abnormalities and clinical symptoms in low back pain patients is poor. For example, in population study, it has been shown that about 40% of people under age of 30 years old display lumbar intervertebral disc degeneration on the MRI, with no clinical symptoms of back pain. Lumbar disc degeneration on MRI is seen in 90%

of individuals older than 50–55 years of age [27]. A recent study examined 200 subjects and found that combined MRI changes in lumbar spine do not correlate with pain intensity, depressive and anxiety syndromes, and quality of life in patients with low back pain [28]. Significant efforts have been devoted to improving the imaging techniques for better diagnosis and treatment.

The dynamic nature of the spine and its mobility across multiple segments is difficult to depict with any single imaging modality. To circumvent this limitation, dynamic MRI has been advocated [29]. Conventional MRI is usually performed in a supine position, at rest, which may not reveal the underlying pathology which is only evident when some extent of spine loading is present. MRI in upright standing position and flexed and extended position provides additional information that is not revealed by MRI in supine position. More recently, weight-bearing MRI particularly those with a side-bending task has been investigated. Pilot study indicates that intervertebral rotations and translations have good reliability when validated against participant-specific three-dimensional models [30]. Current dynamic MRI techniques need to be further developed to optimize its speed and diagnostic accuracy. Its eventual clinical use may improve assessment of in vivo spine stability and examination of outcomes of surgical and nonsurgical interventions applied to manage pathological spine motion.

Chronic pain involves complex brain processing pathways that have gained considerable research interests. Accumulating evidence using functional MRI has suggested altered corticostriatal processing is implicated in chronic pain [31]. In patients with fibromyalgia, there is reduced mPFC activity during gain anticipation, possibly related to lower estimated reward probabilities as well as dramatically heightened mPFC activity to no-loss (nonpunishment) outcomes. Moreover, fibromyalgia patients demonstrate slightly reduced activity during reward anticipation in other brain regions, which included the ventral tegmental area, anterior cingulate cortex, and anterior insular cortex [31]. Heightened anticipation and fear of movement-related pain have been linked to detrimental fear-avoidance behavior in chronic low back pain. Fear of pain demonstrates significant prognostic value regarding the development of persistent musculoskeletal pain and disability. There are significant fear constructs that are implicated in pain processing [32].

Spinal manipulative therapy has been proposed to work partly by exposing patients to nonharmful but forceful mobilization of the painful joint, thereby disrupting the relationship among pain anticipation, fear, and movement. Using functional MRI, patients with chronic low back pain have been found to demonstrate high blood oxygen level-dependent signal in brain circuitry that is implicated in salience, social cognition, and mentalizing. The engagement of this circuitry is reduced after spinal manipulative therapy [33]. Pain assessment with pain intensity score and facial expression have both been used clinically. Pain facial expressions are mainly related to the primary motor cortex and completely dissociated from the pattern of brain activity varying with pain intensity ratings. Stronger activity has been observed in patients with chronic back pain specifically during pain facial expressions in several non-motor brain regions such as the medial prefrontal cortex, precuneus, and medial temporal lobe. In contrast, no moderating effect of chronic pain was observed on brain activity associated with pain intensity ratings. Therefore, pain facial expressions and pain intensity ratings may reflect different aspects of pain processing and suggest that distinctive mechanisms are involved in different aspects of chronic pain [34].

Recent progress has been made to image neuroinflammation, considering there is ample evidence that chronic pain, including neuropathic chronic pain, has components of heightened immune activation [35–40]. Novel contrast agents or radioligands offer promising properties in identifying neuroinflammation with MRI or positron emission tomography-MRI (PET/MRI). A molecular biomarker, the sigma-1 receptor (S1R), has been shown to be implicated in neuroinflammation and nerve injury. [18F]FTC-146 (6-(3-[18F]fluoropropyl)-3-(2-(azepan-1-yl)ethyl)benzo[d] thiazol-2(3H)-one) is a radioligand that is selective for S1R and is able to locate the site of nerve injury in a rat model with PET/MRI [41]. Using similar PET/MRI technology, patients with chronic low back pain demonstrate brain glial activation in the thalamus and putative somatosensory representations of the lumbar spine and leg, revealed by radioligand (11)C-PBR28 that binds to brain translocator protein TSPO [42]. In human lumbar degenerative disc disease, several levels of degeneration are commonly present, and to diagnose the "culprit" level that is responsible for clinical symptoms could be challenging. A recent study employed ferumoxytol, a nanoparticle formulation of iron, to image the neuroinflammation around nerve roots that might be key for lumbar radiculitis [43]. Ferumoxytol is approved by the US Food and Drug Administration to treat iron-deficiency anemia. Nanoparticles are captured by the monocytes-macrophages, which are also critical components of the immune system. In a human subject with lumbar disc degeneration at several levels, nerve root inflammation was successfully identified with ferumoxytol-contrasted MRI at the level that was concordant with clinical pain symptoms.

Gut Microbiome Modulation of Neuropathic and Inflammatory Pain

Gut microbiota is the consortium of microorganisms in the gastrointestinal tract. Gut microbiota is essential to human health and is critical for the homeostasis of multiple key systems, including the immune system, the endocrine system, and the nervous system. In fact, gut microbiota plays a

major role in the bidirectional communication between the gut and the brain. Recently, evidence points to an intriguing association between gut microbiota and neuropsychiatric disorders such as schizophrenia, autistic disorders, anxiety disorders, and major depressive disorders. There is also a critical role for gut microbiota in the pathogenesis of many pain conditions.

Chemotherapy-induced peripheral neuropathy is present in about one third of patients undergoing therapy and is a major dose-limiting side effects of treatment. Limb and perioral area numbness, paresthesia, and pain are the cardinal symptoms of chemotherapy-induced peripheral neuropathy. With the rapidly increasing numbers of cancer patients and survivors, chemotherapy-induced pain has become a major factor negatively impacting quality of life in cancer patients. In a recent research study, using a mouse model of oxaliplatin-induced pain, it has been shown that gut microbiota eradication using a cocktail of wide spectrum of antibiotics prevents the development of chemotherapy-induced pain. Similarly, germ-free mice, which do not harbor endogenous gut microbiota, are protected from developing chemotherapy-induced pain. Gut microbiota restoration using fecal transplantation reverses the protection mediated by the germ-free status. From a mechanistic standpoint, chemotherapy triggers gut inflammation and epithelial barrier leakage, which promotes bacteria translocation, transient bacteremia, and shedding of bacterial products into the bloodstream, including lipopolysaccharide. Toll-like receptor 4, the receptor for lipopolysaccharide, mediates some of the impact of gut microbiota on the development of chemotherapy-induced pain. Besides neuropathic pain, germ-free mice demonstrate attenuated acute inflammatory pain as well.

One area that has received considerable consideration is visceral pain. Given the anatomical location of gut microbiota in the gastrointestinal tract, it is natural to relate it directly to many diseases in the digestive tract, such as inflammatory bowel disease, colon cancer, etc. Irritable bowel syndrome presents with episodes of constipation, diarrhea, and abdominal pain. In a Danish population study, antibiotics were found to be a risk factor for asymptomatic irritable bowel syndrome [44]. It is plausible that the gut microbiota changes secondary to antibiotics are associated with the development of irritable bowel syndrome. In diarrhea-dominant irritable bowel patients, the abundant phyla *Firmicutes* is significantly decreased, and *Bacteroidetes* is increased. Moreover, the alterations of predominant fermenting bacteria such as *Bacteroidales* and *Clostridiales* might be involved in the pathophysiology of diarrhea-dominant irritable bowel syndrome [45]. In an Australian study of patients with irritable bowel syndrome, depression was negatively associated with *Lachnospiraceae* abundance. Patients exceeding thresholds of distress, anxiety, depression, and stress perception showed significantly higher abundances of *Proteobacteria*. Patients with anxiety were characterized by elevated *Bacteroidaceae*. These microbial changes might underscore the psychological distress which is a key pathogenic factor in irritable bowel syndrome [46].

Therapeutics based on gut microbiota to treat irritable bowel syndrome so far have led to inconclusive results [47]. A multi-strain probiotic regimen for 8 weeks increased beneficial bacteria and decreased harmful bacteria in the microbial stool analysis. The small intestine bacteria overgrowth prevalence also decreased at the end of treatment. However, the average levels of fecal calprotectin showed a decreasing tendency, without reaching statistical significance [48]. In a recent meta-analysis, 53 RCTs of probiotics, involving 5545 patients, were analyzed. Particular combinations of probiotics, or specific species and strains, appeared to have beneficial effects on global irritable bowel syndrome symptoms and abdominal pain, but it remained difficult to draw definitive conclusions about their efficacy [47].

References

1. Nicholas M, Vlaeyen JWS, Rief W, Barke A, Aziz Q, Benoliel R, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. Pain. 2019;160(1):28–37.
2. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2019;160(1):19–27.
3. Groenewald CB, Essner BS, Wright D, Fesinmeyer MD, Palermo TM. The economic costs of chronic pain among a cohort of treatment-seeking adolescents in the United States. J Pain. 2014;15(9):925–33.
4. Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain. 2012;13(8):715–24.
5. Cheng J. State of the art, challenges, and opportunities for pain medicine. Pain Med. 2018;19:1109.
6. Noriega DC, Ardura F, Hernández-Ramajo R, Martín-Ferrero MÁ, Sánchez-Lite I, Toribio B, et al. Intervertebral disc repair by allogeneic mesenchymal bone marrow cells: a randomized controlled trial. Transplantation. 2017;101(8):1945–51.
7. Orozco L, Soler R, Morera C, Alberca M, Sánchez A, García-Sancho J. Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study. Transplantation. 2011;92(7):822–8.
8. Pettine KA, Murphy MB, Suzuki RK, Sand TT. Percutaneous injection of autologous bone marrow concentrate cells significantly reduces lumbar discogenic pain through 12 months. Stem Cells. 2015;33(1):146–56.
9. Keytruda UK's first early-access drug. Nat Biotechnol. 2015;33(5):437.
10. Trial watch: ipilimumab success in melanoma provides boost for cancer immunotherapy. Nat Rev Drug Discov. 2010;9(8):584.
11. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A controlled trial of erenumab for episodic migraine. N Engl J Med. 2017;377(22):2123–32.
12. Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017;16(6):425–34.

13. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med. 2017;377(22): 2113–22.
14. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial. Cephalalgia. 2018;38(8):1442–54.
15. Scheinfeld N. Adalimumab (HUMIRA): a review. J Drugs Dermatol. 2003;2(4):375–7.
16. Furue K, Ito T, Furue M. Differential efficacy of biologic treatments targeting the TNF-alpha/IL-23/IL-17 axis in psoriasis and psoriatic arthritis. Cytokine. 2018;111:182–8.
17. Wang EA, Suzuki E, Maverakis E, Adamopoulos IE. Targeting IL-17 in psoriatic arthritis. Eur J Rheumatol. 2017;4(4):272–7.
18. Alunno A, Carubbi F, Cafaro G, Pucci G, Battista F, Bartoloni E, et al. Targeting the IL-23/IL-17 axis for the treatment of psoriasis and psoriatic arthritis. Expert Opin Biol Ther. 2015;15(12):1727–37.
19. Naidoo J, Cappelli LC, Forde PM, Marrone KA, Lipson EJ, Hammers HJ, et al. Inflammatory arthritis: a newly recognized adverse event of immune checkpoint blockade. Oncologist. 2017;22(6):627–30.
20. Aloe L. Rita Levi-Montalcini: the discovery of nerve growth factor and modern neurobiology. Trends Cell Biol. 2004;14(7):395–9.
21. Watson JJ, Allen SJ, Dawbarn D. Targeting nerve growth factor in pain: what is the therapeutic potential? BioDrugs. 2008;22(6):349–59.
22. Denk F, Bennett DL, McMahon SB. Nerve growth factor and pain mechanisms. Annu Rev Neurosci. 2017;40:307–25.
23. Nencini S, Ringuet M, Kim DH, Chen YJ, Greenhill C, Ivanusic JJ. Mechanisms of nerve growth factor signaling in bone nociceptors and in an animal model of inflammatory bone pain. Mol Pain. 2017;13:1744806917697011.
24. Lane NE, Schnitzer TJ, Birbara CA, Mokhtarani M, Shelton DL, Smith MD, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. N Engl J Med. 2010;363(16):1521–31.
25. Brown MT, Murphy FT, Radin DM, Davignon I, Smith MD, West CR. Tanezumab reduces osteoarthritic knee pain: results of a randomized, double-blind, placebo-controlled phase III trial. J Pain. 2012;13(8):790–8.
26. Katz N, Borenstein DG, Birbara C, Bramson C, Nemeth MA, Smith MD, et al. Efficacy and safety of tanezumab in the treatment of chronic low back pain. Pain. 2011;152(10):2248–58.
27. Cheung KM, Karppinen J, Chan D, Ho DW, Song YQ, Sham P, et al. Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. Spine (Phila Pa 1976). 2009;34(9):934–40.
28. Babinska A, Wawrzynek W, Czech E, Skupiński J, Szczygieł J, Łabuz-Roszak B. No association between MRI changes in the lumbar spine and intensity of pain, quality of life, depressive and anxiety symptoms in patients with low back pain. Neurol Neurochir Pol. 2019;53(1):74–82.
29. Michelini G, Corridore A, Torlone S, Bruno F, Marsecano C, Capasso R, et al. Dynamic MRI in the evaluation of the spine: state of the art. Acta Biomed. 2018;89(1-S):89–101.
30. Mahato NK, Montuelle S, Clark B. Assessment of in vivo lumbar inter-vertebral motion: reliability of a novel dynamic weight-bearing magnetic resonance imaging technique using a side-bending task. Asian Spine J. 2019;13:377. [Epub ahead of print].
31. Martucci KT, Borg N, MacNiven KH, Knutson B, Mackey SC. Altered prefrontal correlates of monetary anticipation and outcome in chronic pain. Pain. 2018;159(8):1494–507.
32. Meier ML, Vrana A, Humphreys BK, Seifritz E, Stämpfli P, Schweinhardt P. Pain-related fear-dissociable neural sources of different fear constructs. eNeuro. 2019;5(6): pii: ENEURO.0107–18.2018.
33. Ellingsen DM, Napadow V, Protsenko E, Mawla I, Kowalski MH, Swensen D, et al. Brain mechanisms of anticipated painful movements and their modulation by manual therapy in chronic low back pain. J Pain. 2018;19(11):1352–65.
34. Vachon-Presseau E, Roy M, Woo CW, Kunz M, Martel MO, Sullivan MJ, et al. Multiple faces of pain: effects of chronic pain on the brain regulation of facial expression. Pain. 2016;157(8):1819–30.
35. Sommer C, Leinders M, Uceyler N. Inflammation in the pathophysiology of neuropathic pain. Pain. 2018;159(3):595–602.
36. Marrone MC, Morabito A, Giustizieri M, Chiurchiù V, Leuti A, Mattioli M, et al. TRPV1 channels are critical brain inflammation detectors and neuropathic pain biomarkers in mice. Nat Commun. 2017;8:15292.
37. Yamasaki R, Fujii T, Wang B, Masaki K, Kido MA, Yoshida M, et al. Allergic inflammation leads to neuropathic pain via glial cell activation. J Neurosci. 2016;36(47):11929–45.
38. Schomberg D, Ahmed M, Miranpuri G, Olson J, Resnick DK. Neuropathic pain: role of inflammation, immune response, and ion channel activity in central injury mechanisms. Ann Neurosci. 2012;19(3):125–32.
39. Liou JT, Liu FC, Mao CC, Lai YS, Day YJ. Inflammation confers dual effects on nociceptive processing in chronic neuropathic pain model. Anesthesiology. 2011;114(3):660–72.
40. Shen S, Lim G, You Z, Ding W, Huang P, Ran C, et al. Gut microbiota is critical for the induction of chemotherapy-induced pain. Nat Neurosci. 2017;20(9):1213–6.
41. Shen B, Behera D, James ML, Reyes ST, Andrews L, Cipriano PW, et al. Visualizing nerve injury in a neuropathic pain model with [(18)F]FTC-146 PET/MRI. Theranostics. 2017;7(11):2794–805.
42. Loggia ML, Chonde DB, Akeju O, Arabasz G, Catana C, Edwards RR, et al. Evidence for brain glial activation in chronic pain patients. Brain. 2015;138(Pt 3):604–15.
43. Shen S, Ding W, Ahmed S, Hu R, Opalacz A, Roth S, You Z, Wotjkiewicz GR, Lim G, Chen L, Mao J, Chen JW, Zhang Y. Ultrasmall superparamagnetic iron oxide imaging identifies tissue and nerve inflammation in pain conditions. Pain Med. 2018;19(4): 686–92.
44. Krogsgaard LR, Engsbro AL, Bytzer P. Antibiotics: a risk factor for irritable bowel syndrome in a population-based cohort. Scand J Gastroenterol. 2018;53(9):1027–30.
45. Zhuang X, Tian Z, Li L, Zeng Z, Chen M, Xiong L. Fecal microbiota alterations associated with diarrhea-predominant irritable bowel syndrome. Front Microbiol. 2018;9:1600.
46. Peter J, Fournier C, Durdevic M, Knoblich L, Keip B, Dejaco C, et al. A microbial signature of psychological distress in irritable bowel syndrome. Psychosom Med. 2018;80(8):698–709.
47. Ford AC, Harris LA, Lacy BE, Quigley EMM, Moayyedi P. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. Aliment Pharmacol Ther. 2018;48(10):1044–60.
48. Lee SH, Joo NS, Kim KM, Kim KN. The therapeutic effect of a multistrain probiotic on diarrhea-predominant irritable bowel syndrome: a pilot study. Gastroenterol Res Pract. 2018;2018:8791916.