



Current Challenges of Research into Fibromyalgia: From Clinical Studies to Animal Models

Chih-Hsien Hung^{1,2}, Chih-Cheng Chen^{1,3}

¹Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan

²Department of Neurology, Kaohsiung Medical University Hospital; Kaohsiung Medical University, Kaohsiung, Taiwan

³Taiwan Mouse Clinic- National Comprehensive Mouse Phenotyping and Drug Testing Center, Academia Sinica, Taipei 115, Taiwan

*Corresponding author: Chih-Cheng Chen, Taiwan Mouse Clinic- National Comprehensive Mouse Phenotyping and Drug Testing Center, Academia Sinica, Taipei 115, Taiwan, Tel: 886-2-2652-3917; Fax: 886-2-2782-9224; E-mail: chih@ibms.sinica.edu.tw

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A Brief Overview of Fibromyalgia

Fibromyalgia (FM) is a chronic pain syndrome characterized by widespread musculoskeletal pain [1]. The prevalence increases with age, ranging from 2 to 6 % of the population [2,3]. This syndrome predominantly affects female; the prevalence is six times more common in women than in men [4,5]. Patients with FM often describe their symptoms as a constant dull musculoskeletal ache, and sometimes muscle spasm or tightness [6]. The pain is diffuse over both sides of body, and may last for several months or even longer. The syndrome is commonly associated with several other symptoms, including fatigue, sleeping disturbance, cognitive impairment, and mood disorders [6,7]. Patients with FM usually complain about moderate to severe fatigue, even after sleeping for long period of time. Poor sleeping quality or insomnia is other common presentations. These patients can also suffer from cognitive disturbance. Patients may report difficulty in remembering and concentrating [7]. Depression and anxiety are also common in this group of patients (ranging from 30 to 50%) [8-10]. In addition, a variety of other pain symptoms are also reported in comorbidity with FM, such as headache and irritable bowel syndrome [8, 11].

The diagnosis of FM is mainly based on history and physical examination [12]. A history of chronic and widespread musculoskeletal pain for more than three months is essential for a diagnosis of FM. A traditional exam of tender point test is no more required in latest guideline [13,14]. The 2011 American College of Rheumatology (ACR) modified diagnostic criteria for FM provide a scale for measurement of the severity of symptoms that are characteristic of FM, with a sensitivity and specificity of 90.1 and 89.5 percent [14, 15]. Presentation of other common features helps to corroborate the diagnosis, including fatigue, sleeping disturbance, psychiatric disorders, and cognitive impairment. The ACR 2011 criteria also recognize the importance of these comorbid features that were not considered in the previous criteria. In contrast to other common pain syndromes (for example, rheumatoid arthritis and spondyloarthritis), laboratory and image testing are normal in patients with FM.

FM is often difficult to manage. Given the mechanism of FM remains unclear so far, the aim of current treatment is relieving the symptoms of FM rather than cure. Current treatments include non-pharmacologic and pharmacologic intervention, focusing on improving chronic diffuse pain, fatigue, sleeping disturbance, and cognitive dysfunction [1, 12]. Non-pharmacologic treatments include patient education, cognitive-behavior therapy, and relaxation techniques [16, 17]. Exercise is beneficial for improving pain, daily

function, and even sleeping quality [18]. Tai chi, an internal Chinese martial art, is proved to relieve the symptoms and to improve function [19]. Pharmacologic treatments also help to ease pain and improve life quality. The first line choices of treatment include tricyclic antidepressants, dual reuptake inhibitors, and anticonvulsants [12, 20]. To date, three drugs have been approved by the FDA for the treatment of pain in fibromyalgia: pregabalin, duloxetine, and milnacipran [1]. Although there are several agents available nowadays for relieving symptoms of FM, the results can be unsatisfying, or even frustrating. A 2012 system review and meta-analysis of antidepressants for treating FM found that only minority of patients experience substantial improvement with these drugs. The study also indicated that the adverse effect can be evident and intolerant during treatment [20].

Challenging Issues

A diagnosis of FM can be a clinical challenge for clinicians due to the lack of clinically useful marker. Unlike other pain syndromes, there is no diagnostic laboratory test or radiographic exam to help to diagnose FM so far, which makes the FM diagnosis mainly based on clinical symptoms. This diagnostic predicament often leads to delayed FM diagnoses. Recently, researchers worked on identifying measurable and reliable biomarkers that help to identify patients in susceptible individuals, with a view to facilitating diagnosis and treatment. Several candidate serum biomarkers have been put forward so far, including lysophosphocholines, S100B, and BDNF [21,22]. Their roles in the diagnostic process of FM remain to be further validated.

Is FM a form of myalgia or small-fiber neuropathy? Although FM is characterized by widespread musculoskeletal pain, recent studies in FM patients have revealed phenotypes of small-fiber neuropathy in most patients with evidences of reduced intradermal nerve-fiber density and hyperexcitability of silent C nociceptors [23,24]. How the small fiber neuropathy of skin is related to the development of myalgia is still not known and an interesting research topic. However, some FM patients did not have evidence of small-fiber neuropathy suggesting the heterogeneous nature of FM. More efforts on the clinical studies are needed to understand the biological meaning of small-fiber neuropathy in FM.

Another challenge in clinical practice is the unsatisfying responses with current treatments [20]. Current treatments for FM focus on symptom relieving, rather than cure [1,12]. Due to lack of knowledge about the pathogenesis, developing novel therapies can be difficult. Nowadays, several experimental animal models have been proposed to investigate FM, including repeated injections of acidic saline into gastrocnemius muscle [25], vagotomy [26], sound stress [27],

intermittent cold stress model [28], and more recently biogenic amine depletion [29]. These basic studies of pain biology help researchers to understand mechanisms of the FM pathogenesis. The results will help scientists to develop mechanism-based therapies, and eventually help patients to reach better therapeutic results.

Regarding pain research of basic science, intrinsic limitations of pain measurement exist in animal models, which constitute the major obstacles in these studies and thus make scientific challenge. Especially, recognizing diffuse bilateral ongoing pain in animal models is not an easy task. Although there is no difficulty in recognizing behavior change of unilateral spontaneous pain (e.g., licking, avoiding weight bearing, and autotomy) [30,31], assessing diffuse bilateral spontaneous pain is very difficult [32]. Several methods in attempt to measure pain degree are proved to be unreliable, including grooming pattern, exploratory and social behavior, or ultrasonic vocalization [33-35]. Therefore, studies of animal models of pain are restricted to measurement of evoked (or reflex) pain based on withdrawal response to a noxious and/or innocuous stimulation. However, as discussed above, FM mainly manifests widespread spontaneous myalgia rather than evoked pain. Reliable methods to measure spontaneous deep pain in rodents are needed. The mouse grimace scale, a novel method of facial expression analysis, is under development recently to assess the spontaneous pain in rodents and may be a possible solution [36].

Can we find new treatment modes from animal models? Although chronic widespread pain (e.g., hyperalgesia and/or allodynia) and some comorbidity (e.g., depression, autonomic disturbance) exist, these animal models lack some features of the human fibromyalgia “phenotypes” [37]. Nevertheless, fibromyalgia itself could be heterogeneous and studies of animal models have highlighted several key molecular targets involved in the development of the chronic widespread pain. Proton-sensing ion channels, such as acid-sensing ion channel 3 (ASIC3) and transient receptor potential channel V1 (TRPV1), are essential for priming the nociceptive circuitry and developing the chronic widespread pain; enhanced activity of Nav1.8 of nociceptors is required for the maintenance of the chronic pain [38,39]. Moreover, animal studies highlight a striking finding in substance P (SP)-mediated antinociceptive signaling existing in muscle nociceptors to prevent the nociceptor priming and the development of chronic pain [40,41]. In contrast to trigger neurogenic inflammation in skin, SP release from muscle afferent nerves elicits an inhibitory signal to inhibit ASIC3 activation in muscle nociceptors. The release of SP is evoked by a non-ASIC3, non-TRPV1 acid signaling in muscle afferents and then SP acts on its receptor NK1R to open M-type potassium channels via a G-protein-independent, tyrosine kinase dependent manner [42].

This substance P-mediated antinociception has profoundly changed our view of pain biology, because elevated level of substance P in CSF has been considered a biomarker of fibromyalgia for decades and blocking SP receptor (NK1R) signaling has being a favored strategy to develop analgesics targeting chronic pain including FM, although almost all clinical trials were failed [43,44]. The discovery of substance P-mediated antinociception highlights how poor we have known about the pain biology and how important the basic research is. Although it is still a long way to get a mechanism-based treatment for FM, we now at least have a new and promising direction to target chronic widespread muscle pain.

In conclusion, effective treatment of FM is still a challenge. Recent progress in serum biomarker search, diagnosis of C-fiber neuropathy in FM patients, and molecular targets in animal models of chronic

widespread pain are encouraging for a better understanding of the painful disease. Further research into the FM heterogeneity and neurobiological basis in animal models will facilitate progress in searching for effective treatment.

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