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Review:

Research progress of the role and mechanism of extracellular signal-regulated protein kinase 5 (ERK5) pathway in pathological pain*

Li-na YU[§1], Li-hong SUN[§2], Min WANG[2], Min YAN[†‡1,2]

([1]*Department of Anesthesiology, the Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310009, China*)

([2]*Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology, Xuzhou Medical University, Xuzhou 221000, China*)

[†]E-mail: zryanmin@zju.edu.cn

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Abstract: Extracellular signal-regulated protein kinase 5 (ERK5), also known as big mitogen-activated protein kinase 1 (MAPK1), is an important member of ERK family, which is a subfamily of the large MAPK family. ERK5 is expressed in many tissues, including the dorsal root ganglion (DRG) neurons and the spinal cord. In this review, we focus on elaborating ERK5-associated pathway in pathological pain, in which the ERK5/CREB (cyclic adenosine monophosphate (cAMP)-response element-binding protein) pathway plays a crucial role in the transduction of pain signal and contributes to pain hypersensitivity. ERK5 activation in the spinal dorsal horn occurs mainly in microglia. The activation of ERK5 can be mediated by *N*-methyl-D-aspartate (NMDA) receptors. We also elaborate the relationship between ERK5 activation and nerve growth factor-tyrosine kinase A (NGF-TrkA), and the connection between ERK5 activation and brain-derived neurotrophic factor (BDNF) in pathological pain in detail.

Key words: Extracellular signal-regulated protein kinase 5 (ERK5), Pain, Cyclic adenosine monophosphate (cAMP)-response element-binding protein (CREB), *N*-methyl-D-aspartate (NMDA), Nerve growth factor (NGF), Brain-derived neurotrophic factor (BDNF)

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1 Introduction

The mitogen-activated protein kinase (MAPK) cascade is a superfamily of intracellular signal transduction molecules, which includes extracellular signal-regulated protein kinase 1/2 (ERK1/2), p38 MAPK, c-jun *N*-terminal kinase (JNK), and ERK5 (Widmann *et al.*, 1999; Kyriakis and Avruch, 2001). MAPKs transduce a broad range of extracellular stimuli into intracellular responses and can regulate diverse physiological and pathological processes (Widmann *et al.*, 1999; Sweatt, 2001). Pathological pain is an expression of neuronal plasticity and is characterized by pain hypersensitivity. There are two important forms of pathological pain: inflammatory pain, which is initiated by tissue damage or inflammation, and neuropathic pain, which results from nerve injuries (Ji and Woolf, 2001). There are compelling reports indicating that the activation of MAPK in primary afferents and the spinal cord contributes to pain hypersensitivity and neuronal plasticity in pathological pain (Chang and Karin, 2001; Ji and Strichartz, 2004; Obata and Noguchi, 2004; Katsura *et al.*, 2007).

The ERK family participates in regulating nociceptive activities in primary sensory neurons after various kinds of pathologic stimuli, including peripheral nerve injuries and inflammation (Ji *et al.*, 1999). In contrast to ERK1/2 whose role has been studied extensively in the past (Rudolph *et al*., 2015), it is not until recent years that researchers have paid

‡ Corresponding author
§ The two authors contributed equally to this work
* Project supported by the Medical and Healthcare Project of Zhejiang Province (No. 2015119381), China
ORCID: Li-hong SUN, http://orcid.org/0000-0003-1726-059X

attention to the role of ERK5 pathway in regulating pain signals and have made great progress (Imbe *et al.*, 2011). ERK5 is specifically phosphorylated and activated by MAPK kinase 5 (MEK5). Several studies have reported that activation of ERK5 can regulate neuronal activity and thus modulate neuroplasticity, which is defined as the capacity of neurons to change their function, chemical profile, and structure (Ji and Woolf, 2001; Cao *et al.*, 2013). There are many reports indicating that ERK5 activation in the dorsal root ganglion (DRG) and the spinal cord takes part in mediating the transduction of pain signals, and contributes to hyperalgesia and allodynia after peripheral inflammation or nerve injuries (Mizushima *et al.*, 2007; Obata *et al.*, 2007; Xiao *et al.*, 2008). Given the crucial role of ERK5 in pain signal transduction, this review aims at summarizing the role of ERK5 pathway in pathological pain.

2 ERK5 pathway is involved in inflammatory pain and neuropathic pain

Inflammation induced by complete Freund's adjuvant (CFA) in rats could produce heat and cold hyperalgesia and induce the activation of ERK5 in DRG neurons and the spinal cord (Obata *et al.*, 2007; Xiao *et al.*, 2008). In the CFA-induced inflammatory pain model, the level of total ERK5 expression remained unaltered, but the level of phosphorylated ERK5 (p-ERK5; the activated state of ERK5 via phosphorylation) increased substantially. ERK5 activation caused by persistent peripheral inflammation was mainly in ipsilateral DRG and laminae I–II neurons of the superficial dorsal horn (Snider and McMahon, 1998). Katsura *et al.* (2007) found that in the acute inflammatory pain model induced by capsaicin injection in rats, there also occurred an acute increase in the level of p-ERK5. Besides, Mizushima *et al.* (2007) demonstrated that noxious heat and cold stimuli could lead to the activation of ERK5 in an intensity-dependent manner. Antisense knockdown of ERK5 could suppress the hyperalgesia caused by peripheral inflammation (Katsura *et al.*, 2007; Xiao *et al.*, 2008). Furthermore, the peripheral inflammation-induced c-fos expression in the DRG and the spinal cord could be significantly reduced by antisense knockdown of ERK5 (Xiao *et al.*, 2008). It is worth mentioning that c-fos protein is the product of the c-fos immediate early gene (IEG), and has been characterized as an indicator of neuronal activation in the central nervous system (CNS) (Coggeshall, 2005).

Neuropathic pain, which occurs after nerve injuries, produces chronic pain states characterized by hyperalgesia, allodynia, and spontaneous pain. It is known that neuropathic pain is a result of injury-induced peripheral and central neural plasticity (Woolf and Salter, 2000; Ji and Strichartz, 2004). Nerve injuries can induce the activation of ERK5 both in primary afferent neurons and the spinal cord in a neuropathic pain model induced by chronic constriction injury (CCI) or spared nerve injury (SNI) (Sun *et al.*, 2013). After partial nerve injuries, ERK5 activation regulates the expression of the transient receptor potential V1 (TRPV1) and the transient receptor potential A1 (TRPA1). Knockdown of ERK5 decreases the induction of TRPV1 and TRPA1 and inhibits the heat and cold hypersensitivity induced by SNI (Obata *et al.*, 2007). In brief, activation of ERK5 contributes to pain hypersensitivity, while antisense knockdown of ERK5, where the effects are present both in DRG and the spinal cord, can suppress the nerve injury-induced mechanical allodynia and thermal hyperalgesia (Jeong *et al*., 2014). Taken together, these findings suggest that the activation of ERK5 in primary sensory neurons and the spinal cord plays a crucial role in the pathogenesis of inflammatory pain and neuropathic pain.

3 ERK5/CREB pathway contributes to hypersensitivity in pathological pain

As an intracellular signal transduction molecule, activated ERK5 translocates to the nucleus, phosphorylates several nuclear factors, and adjusts the gene expression directly or indirectly (Cavanaugh, 2004). Many molecules are found to be downstream targets of the ERK5 pathway, including myocyte enhancer factor 2C (MEF2C), myocyte enhancer factor 2A (MEF2A), synapse-associated protein 1a (Sap1a), and cyclic adenosine monophosphate (cAMP)-response element-binding protein (CREB) (Kato *et al.*, 1997; Yang *et al.*, 1998; Kamakura *et al.*, 1999). Here we describe the ERK5/CREB pathway, which plays an important role in pain signal transduction.

After peripheral inflammation, p-ERK5 translocates to the nucleus and activates the transcription factor CREB through the activation of p90 ribosomal S6 kinase (RSK). The phosphorylated CREB (p-CREB; the activated state of CREB via phosphorylation) then binds to the cAMP-response element (CRE) in the promoter regions of the DNA and initiates the transcription of genes (Watson *et al.*, 2001). The CREB-binding site CRE has been identified in the promoter regions of some "pain genes," including c-fos, zif 268, cyclooxygenase-2 (COX-2), neurokinin-1 (NK-1), dynorphin, calcitonin gene-related peptide (CGRP), and brain-derived neurotrophic factor (BDNF) (Wisden *et al.*, 1990; Mannion *et al.*, 1999). Furthermore, the expression of CREB-dependent gene has been suggested to contribute to the central sensitization associated with persistent pain states (Liu *et al.*, 2003). Thus, it is reasonable to draw the conclusion that the activation of ERK5/CREB pathway in DRG and the spinal cord contributes to, at least partially, pain hypersensitivity and allodynia after peripheral inflammation.

Similarly, after nerve injuries, p-CREB level in the spinal cord also increases, the time course level of which is matched with the level of p-ERK5 and the degree of behavioral hyperalgesia. Antisense knockdown of ERK5 markedly inhibits the increase of p-CREB expression after nerve injuries (Zhang *et al.*, 2009). This indicates that CREB acts as one of the downstream targets of the ERK5 pathway in neuropathic pain. ERK5 takes part in regulating pain-related gene transcription via CREB phosphorylation and contributes to the nerve injury-induced long-term pain hypersensitivity (Ji and Woolf, 2001). Thus, the ERK5/CREB pathway also plays a substantial role in the pathogenesis of neuropathic pain. In conclusion, these studies demonstrate that the ERK5/CREB pathway contributes to hypersensitivity both in inflammatory and neuropathic pain (Fig. 1).

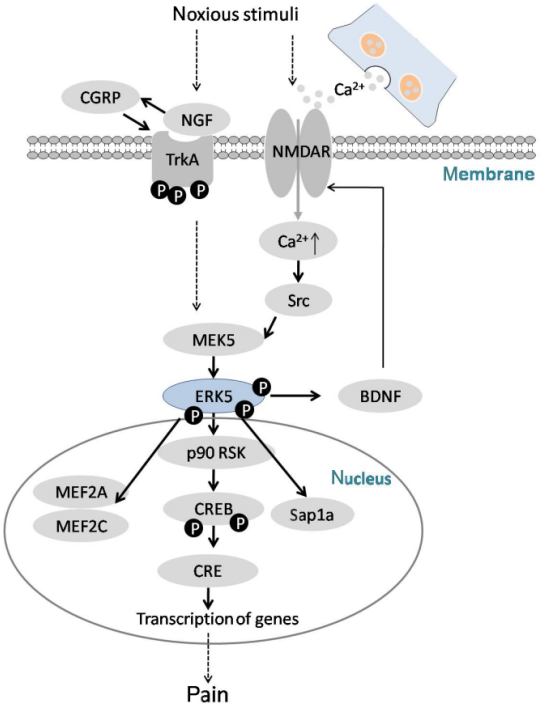

Fig. 1 Upstream and downstream mechanisms of the ERK5 signaling cascade in DRG neurons
Dashed lines indicate the need for further examination of possible signaling or the mechanism, which is complicated and abbreviated in this text. See text for details

4 ERK5 activation in the spinal dorsal horn occurs mainly in microglia

ERK5 activation in the spinal dorsal horn takes place mainly in microglia, rather than in neurons or astrocytes (Obata *et al.*, 2007). Microglia is a kind of glial cells in the CNS, and it is well known that the activation of microglia occurs after peripheral nerve injuries and contributes to the development of neuronal hyperalgesia and allodynia which underlies persistent pain conditions (Obata *et al.*, 2007). Microglia maintains a strong relationship with neurons and can change the activity of those neurons. The interaction between microglia and neurons plays important roles in the development of central sensitization (Ren and Dubner, 2016). Central sensitization is an activity-dependent functional plasticity, one pivotal feature of which is the increased excitability of nociceptive neurons in the spinal cord (Ji and Woolf, 2001). The specific mechanisms of nociceptive signal transduction between microglia and neurons are still not well established. Some studies have confirmed that the chemokine CX3CL1 and its receptor CX3CR1 play an important role in the interaction between microglia and neurons (Gao and Ji, 2010). In a recent study performed by our team, we demonstrated that CX3CR1 is required for ERK5 activation in the microglia after nerve injuries. The activation of ERK5 in the spinal cord could contribute to pain hypersensitivity induced by CX3CL1. CX3CL1/

CX3CR1 could mediate the nociceptive signaling between microglia and neurons through ERK5-mediated microglia activation (Sun *et al.*, 2013). In addition, activated microglia in the spinal cord contributes to the initiation of pathological pain responses and the development of neural plasticity after nerve injuries or peripheral inflammation via accelerating the production of proinflammatory cytokines, including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) (DeLeo and Yezierski, 2001; Watkins and Maier, 2003). Proinflammatory cytokines are known to induce behavioral hypersensitivity and play a crucial role in the maintenance of chronic pain states (Raghavendra *et al.*, 2003). Activation of some cellular events such as MAPK in the microglia could enhance the release of those proinflammatory mediators (Raghavendra *et al.*, 2003). Thus, it can be reasonably inferred that microglia and the activation of ERK5 in microglia in the spinal cord may be attractive targets for blocking neuronal nociceptive signal transmission (Sweitzer *et al.*, 2001).

5 ERK5 activation can be mediated by *N*-methyl-D-aspartate receptor

The activation of ERK5 can be mediated by the *N*-methyl-D-aspartate (NMDA) receptor and the subsequent associated intracellular signal transduction cascades (Wang *et al.*, 2004). NMDA receptor is a kind of ionotropic glutamate receptors, and one important role of the activated NMDA receptor is mediating calcium influx. NMDA receptor activation can trigger an increase of intracellular Ca^{2+} concentration and activate the ERK5 signal pathway. The activated ERK5 transmits the glutamate signals to the nucleus by phosphorylating nuclear transcription factors, and thus contributes to the development and maintenance of chronic pain (Zhang *et al.*, 2009). The calcium influx caused by NMDA receptor activation can induce Src kinase activation, which is an important activator of ERK5 (Wang *et al.*, 2004) (Fig. 1). In brief, NMDA receptors play important roles in the activation of ERK5 during the pathological process of chronic pain. Likewise, NMDA receptor and the activation of ERK5 mediated by NMDA receptor may also be potential targets for blocking nociceptive signal transmission.

6 Nerve growth factor has been implicated in the process of ERK5 activation

Nerve growth factor (NGF) is a member of the neurotrophin family and is involved in the regulation of the growth, maintenance, proliferation, and survival of certain target neurons. NGF is suggested to be an important mediator in the production of inflammatory pain (Lewin and Mendell, 1993; Sah *et al.*, 2003; Hefti *et al.*, 2006). NGF can be released from keratinocytes, fibroblasts, Schwann cells, and mast cells in the tissues after injury or inflammation (Wu *et al.*, 2007; Radtke *et al.*, 2010). The interaction between NGF and its receptor tyrosine kinase A (TrkA) has been implicated in the process of ERK5 activation (Watson *et al.*, 2001; Wang and Tournier, 2006). The CFA injection-induced ERK5 phosphorylation takes place mainly at the high-affinity receptor for NGF-TrkA containing neurons, and the activation of ERK5 plays a key role in NGF-induced sensory neuronal survival response (Watson *et al.*, 2001).

In DRG neurons, about half of the primary sensory neurons are peptidergic neurons marked by the calcitonin gene related peptide (CGRP) (Ju *et al.*, 1987; McCarthy and Lawson, 1990). CGRP is one of the most important nociceptive markers in inflammatory pain (Benemei *et al.*, 2009; Han *et al.*, 2010). Mice lacking CGRP or whose CGRP activity was inhibited pharmacologically do not develop hyperalgesia after inflammation (Smith *et al.*, 1992; Springer *et al.*, 2003). The CGRP-expressing neurons can present the active form of TrkA and then the activated TrkA is able to respond to NGF. Many studies have suggested that there is a close relationship between NGF and CGRP in sensory neurons (Schicho and Donnerer, 1999; Shadiack *et al.*, 2001; Yu *et al.*, 2012). Injection of NGF antiserum can decrease the levels of CGRP protein in the DRG of non-operative animals (Shadiack *et al.*, 2001). The level of CGRP mRNA in DRG is also absent in $TrkA^{-/-}$ mice (Patel *et al.*, 2000). These studies all support the close interplay between NGF-TrkA and CGRP. In the CGRP promoter, there is a cAMP-responsive element that is responsive to CREB (Lanigan and Russo, 1997; Freeland *et al.*, 2000). So, it is easy to understand why NGF can also regulate CREB activation in sensory neurons (Lonze and Ginty, 2002). NGF is released after the stimulation of nerve terminals and can

influence the neuronal function through binding to TrkA (Riccio *et al.*, 1997; Watson *et al.*, 1999; Campenot and MacInnis, 2004). While NGF binds to TrkA in neurons, several pathways are activated simultaneously, including the ERK5/CREB pathway, which leads to the enhancement of targeted gene expression (Perkinton *et al.*, 2002; Segal, 2003). It has been reported that NGF regulates CREB activation in sensory neurons and contributes to neuronal plasticity. This further verifies NGF's contribution to the ERK5/CREB pathway in pain signal transduction (Lonze and Ginty, 2002) (Fig. 1).

Meanwhile, in sensory neurons, ERK5 activation is essential in mediating the neurons' survival response to NGF (Watson *et al.*, 2001). NGF activates CGRP and CREB in primary sensory neurons in the DRG and regulates the activity of sensory neurons. This process can be mediated by the activation of ERK5 (Yu *et al.*, 2012). Inhibition of ERK5 activity could block the ability of NGF to increase CGRP expression in cultured DRG neurons (Park *et al.*, 2010).

Besides, it has also been reported that after CFA injection-induced inflammation, NGF is synthesized and released in the inflamed tissue, which leads to the increased expression of TRPV1 and TRPA1 through ERK5 activation (Obata *et al.*, 2007). Many studies have shown that TRPV1 and TRPA1 are respectively required for peripheral sensitization to noxious heat and cold stimuli (Caterina *et al.*, 2000). Therefore, the activation of ERK5 pathway is also essential to NGF-induced increase in the expression of TRP channels, and thus contributes to heat and cold hyperalgesia after peripheral inflammation.

Taken together, all these studies support the conclusion that, during inflammatory pain, NGF regulates sensory activity and influences the neuronal function via regulating CGRP expression, and plays an important role in the ERK5/CREB signal transduction process.

7 ERK5 activation regulates the expression of BDNF

In neuropathic pain, ERK5 activation can regulate the expression of BDNF, which is a crucial signaling molecule between microglia and neurons (Coull *et al.*, 2005; Katsura *et al.*, 2007). BDNF is a member of the neurotrophin family, which has been shown to play important roles in the development of pathologic pain (Sah *et al.*, 2003; Pezet and McMahon, 2006). In injured DRG neurons, especially in medium- and large-sized neurons, BDNFs are dramatically increased, the process of which can be regulated by ERK5 activation (Obata *et al.*, 2007). After nerve injuries, the BDNFs in primary afferents are transported to the central terminals in the spinal dorsal horn, where they regulate the excitability of the spinal neurons and play roles in neuropathic sensations (Michael *et al.*, 1997). It has been identified that the release of BDNF can be mediated by NGF via extracellular signal-regulated kinases (ERKs) (Matsuoka and Yang, 2012). In DRG neurons expressing TrkA, systemic application of NGF to rats results in an upregulation of the BDNF level, which plays a crucial role in mediating pathological pain signal transmission (Apfel *et al.*, 1996). Meanwhile, BDNF can enhance the excitability of the neurons in spinal dorsal horn through several mechanisms, including activation of certain NMDA receptors (Geng *et al.*, 2010). Thus, ERK5 activation regulates the expression of BDNFs and the BDNFs can modulate the neuron hyperexcitability during chronic neuropathic pain (Fig. 1).

8 Conclusions and perspectives

The study of molecular mechanisms in nociceptive signal transmission has always been popular in the field chronic pain research. In this review, we summarized the ERK5 pathway and described the role of ERK5 in pain signal transduction in pathological pain. Noxious stimuli can induce ERK5 activation in the DRG neurons and the spinal cord. The activation of the ERK5 pathway contributes to pain hypersensitivity and is involved in the formation of central sensitization in pathological pain. In supraspinal structures such as the descending pain modulation system, some MAPKs, including ERK1/2, p38, and JNK, take part in mediating neuropathic pain (Imbe *et al.*, 2011). At the level of the molecular structure, the amino-terminal half of ERK5 contains the kinase domain, which is similar to that of ERK1/2. Besides, PD98059 and U0126, which are inhibitors of

MEK1/2-ERK1/2, can also inhibit the activation of ERK5 (Mizushima *et al.*, 2007). It is possible that ERK5 and ERK1/2 regulate some homologous cellular signal transduction. Meanwhile, several studies have reported that the ERK5 pathway can modulate many pathological processes in the supraspinal structure. Qi *et al.* (2009) found that following psychophysical stress, the activity of ERK5 changes in the frontal cortex. In a recent research, Wang *et al.* (2015) have confirmed that the activation of ERK5 in the cerebrospinal fluid-contacting nucleus (CSF-CN) contributes to the development of neuropathic pain. Therefore, it is very likely that ERK5 activation may also be involved in the descending pain modulation system. More studies are needed to examine the role of the ERK5 pathway in the supraspinal structures in modulating neuropathic pain.

Better and deeper investigation of the ERK5 transduction pathway may provide further insights into the potential mechanisms underlying pathological pain and will help us exploit new therapeutic opportunities targeted specifically at inhibiting the pain signal transduction.

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Compliance with ethics guidelines

Li-na YU, Li-hong SUN, Min WANG, and Min YAN declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：ERK5信号通路在病理性疼痛中的作用及其机制的研究进展

概　要：细胞外信号调节蛋白激酶5（ERK5），也称大丝裂原活化蛋白激酶1，是ERK家族（MAPK大家族的一个亚家族）的一个重要成员。ERK5在背根神经节和脊髓中均有表达。本文着重阐述ERK5相关的信号通路在病理性疼痛中的作用：ERK5/CREB通路在疼痛信号的传递和痛觉过敏的形成中起重要作用；脊髓背角中ERK5的活化主要在小角质细胞；ERK5的活化可由NMDA受体介导。同时，我们细述了在病理性疼痛中，ERK5活化与NGF-TrkA和BDNF的关联。

关键词：细胞外信号调节蛋白激酶 5（ERK5）；疼痛；cAMP反应原件结合蛋白；*N*-甲基-D-天冬氨酸受体；神经生长因子；脑源性神经营养因子