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Review

Protein Kinases as Mediators for miRNA Modulation of Neuropathic Pain

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Abstract: Neuropathic pain is a chronic condition resulting from injury or dysfunction in the somatosensory nervous system, which leads to persistent pain and a significant impairment of quality of life. Research has highlighted the complex molecular mechanisms that underlie neuropathic pain and has begun to delineate the roles of microRNAs (miRNAs) in modulating pain pathways. miRNAs, which are small non-coding RNAs that regulate gene expression post-transcriptionally, have been shown to influence key cellular processes, including neuroinflammation, neuronal excitability, and synaptic plasticity. These processes contribute to the persistence of neuropathic pain, and miRNAs have emerged as critical regulators of pain behaviors by modulating signaling pathways that control pain sensitivity. miRNAs can influence neuropathic pain by targeting genes that encode protein kinases involved in pain signaling. This review focuses on miRNAs that have been demonstrated to modulate neuropathic pain behavior through their effects on protein kinases or their immediate upstream regulators. The relationship between miRNAs and neuropathic pain behaviors is characterized as either an upregulation or a downregulation of miRNA levels that leads to a reduction in neuropathic pain. In the case of miRNA upregulation resulting in an alleviation of neuropathic pain behaviors, protein kinases exhibit a positive correlation with neuropathic pain, whereas decreased protein kinase levels correlate with diminished neuropathic pain behaviors. The only exception is GRK2, which shows an inverse correlation with neuropathic pain. In the case of miRNA downregulation resulting in a reduction in neuropathic pain behaviors, protein kinases display mixed relationships to neuropathic pain, with some kinases exhibiting positive correlation, while others exhibit negative correlation. By exploring how protein kinases mediate miRNA modulation of neuropathic pain, valuable insight may be gained into the pathophysiology of neuropathic pain, offering potential therapeutic targets for developing more effective strategies for pain management.

Keywords: miRNAs; kinases; neuropathic pain

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1. Introduction

Neuropathic pain is a chronic, debilitating condition caused by injury or dysfunction of the somatosensory nervous system [1–5]. Unlike nociceptive pain, which stems from acute tissue damage and typically resolves with healing, neuropathic pain persists beyond the initial injury, often becoming long-term or even lifelong. Affecting an estimated 3% to 17% of the global population [6,7], neuropathic pain significantly diminishes quality of life and remains a major challenge within the field of pain management [8–11].

Despite decades of research, effective treatment of neuropathic pain remains a significant clinical challenge [11–15]. Current pharmaceutical approaches, including antiepileptic drugs, antidepressants, and opioids, often fall short, with nearly 50% of patients failing to achieve adequate pain relief [12–14,16,17]. This underscores the urgent need for novel therapeutic strategies. A major obstacle lies within the complex molecular and cellular mechanisms underlying neuropathic pain, which involve neuroinflammation, altered synaptic plasticity, and dysregulated signaling pathways [4,18,19]. A deeper understanding of these processes at the molecular level is essential for identifying new and more effective therapeutic targets.

MicroRNAs (miRNAs) are a class of short, non-coding RNA molecules that regulate gene expression post-transcriptionally by binding to target messenger RNAs (mRNAs), leading to their degradation or translational repression [20–23]. These molecules play essential roles in a variety of biological and pathological processes, including neuroinflammation, neuronal excitability, and synaptic plasticity—factors that contribute to the persistence of neuropathic pain [24,25]. Recent evidence suggests that miRNAs are key modulators of neuropathic pain behaviors, either exacerbating or alleviating pain states by targeting specific signaling pathways.

Among these pathways, protein kinases are critical cellular regulators that mediate diverse biological functions through the phosphorylation of proteins [26–28]. Many protein kinases have been implicated in neuropathic pain modulation, either promoting or suppressing pain signaling depending on their specific roles in various intracellular cascades [29,30]. Given the emerging evidence linking miRNA activity to modified protein kinase signaling in neuropathic pain models, this review focuses on miRNAs that have been demonstrated to modulate neuropathic pain behavior through direct or indirect effects on the mRNAs encoding protein kinases or their immediate upstream regulators. By elucidating these interactions, we aim to provide insight into the regulatory mechanisms of neuropathic pain and potential therapeutic targets. For a more comprehensive list of miRNAs implicated in neuropathic pain, readers are directed to the following review articles [31–37].

2. miRNA Modulation: Upregulation or Downregulation Can Alleviate Neuropathic Pain

A growing body of literature has shown that miRNAs can causally influence neuropathic pain behaviors. We identified two distinct motifs regarding the relationships that characterize the interconnection between changes in miRNA levels and the consequences on neuropathic pain states.

For the first motif, which is more abundantly reported in the literature, the upregulation of specific miRNAs results in the attenuation of neuropathic pain behaviors; in other words, the increased expression of these miRNAs leads to reduced pain. As summarized in Table 1 and illustrated in Figure 1, the miRNAs belonging to this relationship pattern predominantly target protein kinases that exhibit a positive correlation with neuropathic pain; specifically, in this model, when the levels of these protein kinases decrease, neuropathic pain behaviors also diminish. This suggests that these kinases play a pro-nociceptive role in neuropathic pain at the cellular level, and their suppression, whether by miRNAs or other means, may provide therapeutic benefits. However, there is one exception to this pattern of parallel change between the level of kinase activity and the severity of neuropathic pain, G-protein receptor kinase 2 (GRK2). This kinase displays a negative correlation with neuropathic pain [38], with GRK2 levels increasing with miRNA expression as neuropathic pain subsides.

Table 1. Upregulation of miRNA, via kinase mediation, alleviates neuropathic pain.

↑ miRNA ⇒ Kinase ⇒ ↓ Neuropathic Pain						
lncRNA	**miRNA**	**Intermediary**	**Protein Kinase**	**Neuropathic Pain**	**Model**	**Reference**
-	miR-183 ↑	-	MAP3K4 ↓	down ↓	Rat, CCI	[39]
-	miR-15a ↑	-	AKT3 ↓	down ↓	Rat, CCI	[40]
-	miR-150 ↑	-	AKT3 ↓	down ↓	Rat, CCI	[41]
-	miR-20b-5p ↑	-	AKT3 ↓	down ↓	Rat, CCI	[42]
-	miR-101 ↑	-	mTOR ↓	down ↓	Rat, CCI	[43]
-	miR-183 ↑	-	mTOR ↓	down ↓	Rat, CCI	[44]
-	miR-362-3p ↑	PAX2 ↓	MEK1/2 ↓	down ↓	Rat, SCI	[45]
-	miR-206 ↑	-	MEK ↓	down ↓	Rat, CCI DRG	[46]
-	miR-186-5p ↑	CXCL13 ↓ CXCR5 ↓	ERK ↓	down ↓	Mouse, SNL	[47]
-	miR-143 ↑	-	ERK1/2 ↓	down ↓	Rat, SNL-induced DRG	[48]
-	miR-26a-5p ↑	-	MAPK6 ↓	down ↓	Rat, CCI	[49]
-	miR-146a-5p ↑	-	IRAK1 ↓	down ↓	Rat, CCI	[50]
LINC00052 ↓	miR-448 ↑	-	JAK1 ↓	down ↓	Rat, SNL	[51]
-	miR-124 ↑	-	GRK2 ↑	down ↓	Mouse, de novo GRK2 knockout	[38]

Abbreviations of nerve injury models: CCI, chronic constriction injury; DRG, dorsal root ganglia; SCI, spinal cord injury; SNL, spinal nerve ligation. Upward arrows (↑) indicate upregulation; downward arrows (↓) indicate downregulation.

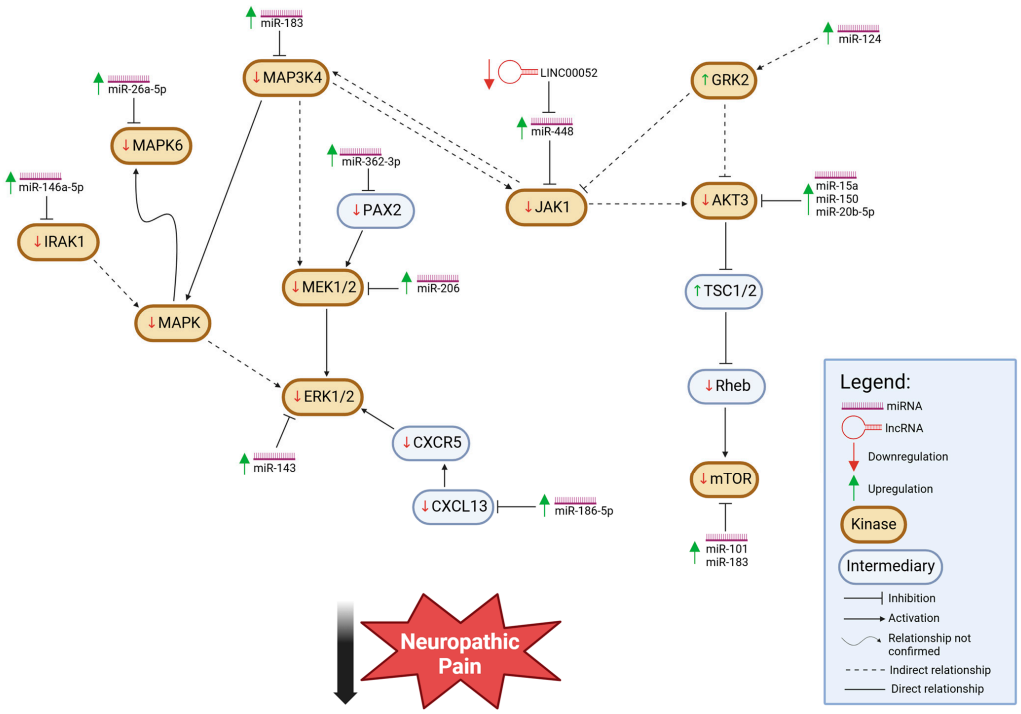


Figure 1. Upregulation of miRNA, via kinase mediation, alleviates neuropathic pain. The upregulation of miRNAs is indicated by an upward green arrow. Reduction in kinase activities or expression levels, which is the case for all kinases directly or indirectly impacted by miRNA, is marked by a downward red arrow, except for GRK2, which shows increased levels with miRNA upregulation with an upward green arrow. Additionally, TSC1/2, an intermediary protein, is also upregulated in this motif. The outcome of all indicated changes in miRNA or other factors' levels is the alleviation of neuropathic pain.

For the second motif, the downregulation of certain miRNAs results in a reduction in neuropathic pain behaviors. As summarized in Table 2 and illustrated in Figure 2, the kinases targeted by the miRNAs within this pattern display mixed relationships to neuropathic pain, with some kinases exhibiting a positive correlation in which kinase downregulation relieves pain, and other kinases exhibiting a negative correlation in which kinase downregulation exacerbates pain. This suggests a more complex regulatory landscape in which the miRNA-mediated modulation of protein kinases has varying effects depending on the specific molecular context.

Table 2. Downregulation of miRNA, via kinase mediation, alleviates neuropathic pain.

↓ miRNA ⇒ Kinase ⇒ ↓ Neuropathic Pain						
lncRNA	**miRNA**	**Intermediary**	**Protein Kinase**	**Neuropathic Pain**	**Model**	**Reference**
-	miR-155 ↓	SOCS1 ↑	p38 ↓	down ↓	Rat, CCI	[52]
-	miR-221 ↓	SOCS1 ↑	p38 ↓	down ↓	Rat, CCI	[53]
-	miR-133a-3p ↓	-	p38 ↓	down ↓	Rat (diabetic), sciatic nerve	[54]
-	miR-15a/16 ↓	-	p38 ↓	down ↓	Mouse, CCI	[55]
-	miR-21 ↓	TLR8 ↓	ERK ↓	down ↓	Mouse, DRG, Tlr8 knockout	[56]
-	miR-142-3p ↓	AC9 ↑	AMPK ↑	down ↓	Rat, CCI, SNI	[57]
lncRNA CCA11 ↑	miR-155 ↓	-	SGK3 ↑	down ↓	Rat, bilateral CCI	[58]
-	miR-155 ↓	-	SGK3 ↑	down ↓	SD rat, bilateral CCI	[59]
-	miR-15a/16 ↓	-	GRK2 ↑	down ↓	Mouse, CCI	[55]

Abbreviations of nerve injury models: CCI, chronic constriction injury; DRG, dorsal root ganglia; SD rat, Sprague Dawley rat; SNI, spared nerve injury. Upward arrows (↑) indicate upregulation; downward arrows (↓) indicate downregulation.

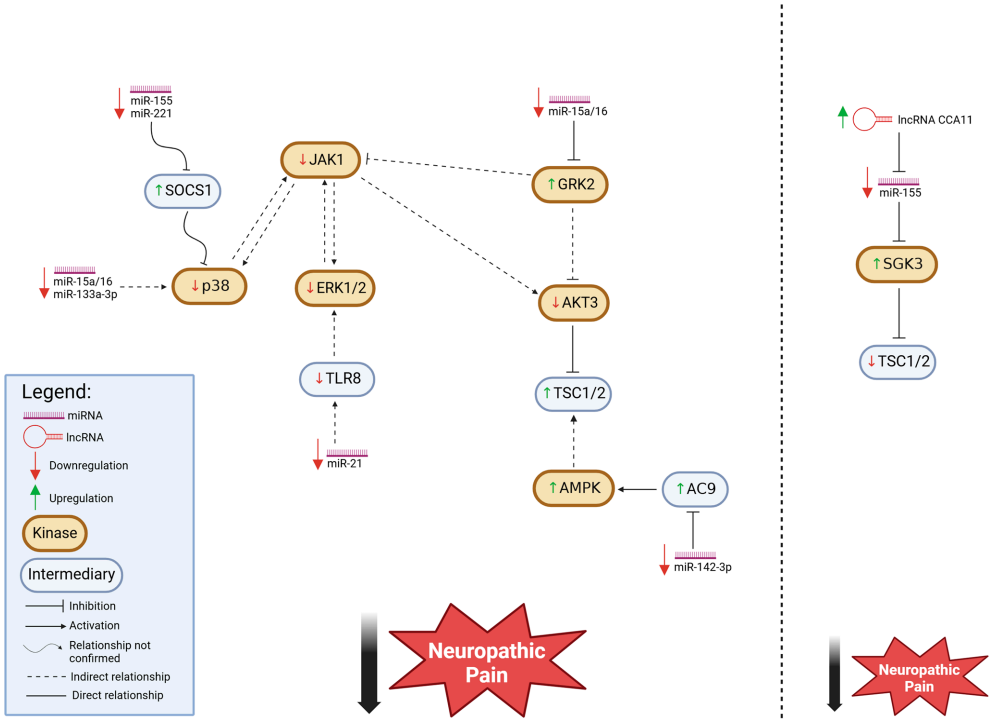


Figure 2. Downregulation of miRNA, via kinase mediation, alleviates neuropathic pain. Downregulation of miRNAs is indicated by a downward red arrow. Changes in the levels of kinases and/or other factors

can be either increased, as indicated by an upward green arrow, or decreased, as indicated by a downward red arrow. Note: the SGK3-mediated pathway is distinct from the indicated kinase network due to its opposing effect on TSC1/2 compared to AKT3, which is another upstream regulator of TSC1/2. Depending on the upstream regulator involved, TSC1/2 expression can be either upregulated or downregulated, correlating with pain attenuation. Ultimately, the combined effects of changes in miRNA levels and other regulatory factors contribute to the reduction in neuropathic pain.

Tables 1 and 2 list the miRNA–kinase–neuropathic pain cases, indicating the directionality of changes for miRNAs, kinases, and neuropathic pain behaviors. Table 3 lists the kinase names with their abbreviations discussed in this article, as well as alternative abbreviations often encountered in the literature. By categorizing these patterns of miRNA involvement in neuropathic pain, we can begin to discern relevant regulatory mechanisms and potential therapeutic targets. The following sections will explore specific miRNA-protein kinase interactions, highlighting the functional roles of protein kinases in neuropathic pain and implications for future research and clinical applications.

Table 3. Protein kinase names and abbreviations.

Protein Kinase Abbreviation	Alternative Abbreviations	Full Name
MAP3K4	MTK1; MEKK4; MAPKKK4; PRO0412; MKKK4	Mitogen-activated protein kinase kinase kinase 4
JNK	MAPK8; JNK1; PRKM8; SAPK1; JNK-46; JNK1A2; SAPK1c; JNK21B1/2	Jun N-terminal kinase
MKK4	MAP2K4; JNKK; MEK4; SEK1; SKK1; JNKK1; SERK1; MAPKK4; PRKMK4; SAPKK1	Mitogen-activated protein kinase kinase 4
MEK1/2	MAP2K1/2	Mitogen-activated protein kinase 1/2
ERK1/2	MAPK1/2	Extracellular signal-regulated kinase 1/2
JAK1	JTK3; AIIDE; JAK1A; JAK1B	Janus kinase 1
MAP2K	MKK	Mitogen-activated protein kinase kinase
AKT3	MPPH; PKBG; MPPH2; PRKBG; STK-2; PKB-GAMMA; RAC-gamma; RAC-PK-gamma	AKT Serine/Threonine kinase
mTOR	SKS; FRAP; FRAP1; FRAP2; RAFT1; RAPT1	Mechanistic target of rapamycin kinase
IRAK1	IRAK; pelle	Interleukin 1 receptor-associated kinase
MAPK6	ERK3; PRKM6; p97MAPK; HsT17250	Mitogen-activated protein kinase 6
GRK2	BARK1; ADRBK1; BETA-ARK1	G protein-coupled receptor kinase 2
AMPK	PRKAA1; AMPKa1; AMPK alpha 1	Adenosine monophosphate-activated protein kinase
SGK3	CISK; SGK2; SGKL	Serum/glucocorticoid-regulated kinase family member 3

3. Protein Kinase Involvement in miRNA Upregulation Leading to Alleviation of Neuropathic Pain

Multiple kinases, through direct or indirect interactions, can form a complex regulatory network (Figure 1). A general pattern within this network reveals that kinase activity

is co-regulated with the attenuation of neuropathic pain; specifically, key kinases are downregulated in parallel with reductions in pain behavior. This coordinated downregulation suggests a functional relationship between these kinases and pain modulation. Importantly, miRNAs play a crucial role in this regulatory framework, as their upregulation in these cases contributes to the suppression of specific kinases involved in pain signaling. By targeting and downregulating these kinases, upregulated miRNAs help reinforce the pathway leading to neuropathic pain relief. This intricate interplay between miRNA expression and kinase regulation highlights a potential avenue for therapeutic intervention in neuropathic pain management.

3.1. Mitogen-Activated Protein Kinase Kinase Kinase 4 (MAP3K4)

Mitogen-activated protein kinase kinase kinase 4 (MAP3K4) plays a crucial role in cellular signaling, particularly in the mitogen-activated protein kinase (MAPK) cascade [60–62]. In this cascade, it is upstream from many kinases such as MKK4/6/7, JNK, and p38 [60–62].

MAP3K4 activates the MAPK pathway by phosphorylating and activating MAP2Ks [60–62], specifically MKK4 and MKK7 [62], which are responsible for phosphorylating and activating downstream MAPKs such as JNK and p38 [63,64]; therefore, MAP3K4 serves as a key regulator of the MAPK signaling cascade.

MAP3K4 indirectly [60–62] influences MEK1/2 through cross-talk between the JNK/p38 MAPK pathways and the ERK pathway [60,65–68]. Additionally, MAP3K4 is an upstream kinase in the MAPK pathway, triggering the cascade, which eventually leads to MEK1/2 activation [62,69].

Cross-talk between JAK1 and MAP3K4 occurs through the activation of MAPK pathways [60,70]. JAK1-STAT signaling can influence the activation of MAPK cascades indirectly by promoting the expression of genes that regulate proteins involved in MAPK activation [71]. Specifically, MAP3K4 can activate JNK [62,72], which can contribute to the inflammatory response initiated by JAK1 activation [73–75]. This cross-talk between cytokine signaling and MAPK pathways defines the complex relationship between the two kinases.

In the CCI model of rats, increased miR-183 levels suppressed MAP3K4 activities, resulting in attenuated neuropathic pain [39].

3.2. AKT Serine/Threonine Kinase 3 (AKT3)

AKT serine/threonine kinase 3 (AKT3) is a key regulator in the phosphoinositide 3-kinase (PI3K)-AKT-mTOR pathway, influencing cell growth, survival, and metabolism, particularly in brain development and neuronal protection [76].

In the neuropathic pain model of CCI, increased levels of miR-15a [40], miR-150 [41], and miR-20b-5p [42] suppressed AKT3 kinase activities, leading to attenuated neuropathic pain.

3.3. Mechanistic Target of Rapamycin Kinase (mTOR)

The mechanistic target of rapamycin kinase (mTOR) mediates cellular responses to stressors such as DNA damage and nutrient deprivation [77]. mTOR is a component of two distinct complexes: mechanistic target of rapamycin complex 1 (mTORC1), which controls protein synthesis, cell growth, and proliferation [78], and mechanistic target of rapamycin complex 1 (mTORC2), which is a regulator of the actin cytoskeleton and promotes cell survival and cell cycle progression [78].

AKT3 promotes mTOR activation by inhibiting tuberous sclerosis complex subunit 1/2 (TSC1/2) through phosphorylation [79–82]. This, in turn, allows Ras homolog enriched in brain (Rheb) to remain active and stimulate mTOR signaling [83,84]; thus, the down-

regulation of AKT3 positively correlates with mTOR downregulation and neuropathic pain attenuation.

In the neuropathic pain model of CCI, increased levels of miR-101 [43] and miR-183 [44] suppressed mTOR expression, attenuating neuropathic pain.

3.4. Mitogen-Activated Protein Kinase 1/2 (MEK1/2)

Mitogen-activated protein kinase 1/2 (MEK1/2) is a dual-specificity kinase that functions as a critical component of the MAPK/ERK signaling pathway [85]. They act as intermediaries between MAP3Ks, such as MAP3K4, by phosphorylating and activating ERK1/2 [86], which in turn regulates cell proliferation, differentiation, and survival [87].

MAP3K4 is upstream of MEK1/2 in certain signaling cascades [88], and activates MEK1/2 through intermediates such as MAP2Ks [86], contributing to ERK1/2 activation.

MEK1/2 are the direct activators of ERK1/2 [85]. Upon activation by upstream kinases, MEK1/2 phosphorylates ERK1/2 on specific threonine and tyrosine residues, leading to ERK1/2 activation and subsequent cellular responses [89].

Paired-box gene 2 (PAX2) is a transcription factor that promotes the expression of upstream activators such as receptor tyrosine kinases (RTKs) [90,91], leading to the activation of Ras and then Raf, ultimately leading to the phosphorylation and activation of MEK1/2 [92].

In the SCI rat model, increased levels of miR-362-3p suppress PAX2, which in turn leads to the suppression of MEK1/2 and, therefore, reduced neuropathic pain levels [45]; similarly, in the model of CCI of DRG in rats, increased miR-206 suppresses MEK and neuropathic pain [46], though it is not indicated that PAX2 is involved in this mechanism, nor is the specific isoform of MEK specified.

3.5. Extracellular Signal-Regulated Kinase 1/2 (ERK1/2)

Extracellular signal-regulated kinase (ERK1/2) is located downstream from MEK in the MAPK cascade and is a key enzyme in the ERK signaling pathway [88]. MEK1/2 phosphorylates ERK1/2 on threonine (T) and tyrosine (Y) residues within the threonine-glutamic acid-tyrosine (TEY) motif [93], activating ERK1/2.

Upon activation, toll-like receptor 8 (TLR8) recruits myeloid differentiation primary response 88 (MyD88) [94] which facilitates the activation of another protein kinase, IRAK1 [94–96], associates with the tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) [97], aiding in the activation of MAPK signaling. This, in turn, leads to the activation of MEK1/2, which then phosphorylates and activates ERK1/2.

C-X-C motif chemokine ligand 13 (CXCL13) is a chemokine that binds to the C-X-C motif chemokine receptor 5 (CXCR5) [98], which is a G-protein-coupled receptor (GPCR). Upon CXCL13 activation, CXCR5 activates G-protein signaling, leading to MEK1/2 activation [99], which leads to ERK1/2 phosphorylation and activation [95].

In the neuropathic pain model of SNL-induced DRG of rats, increased levels of miR-143 [48] suppressed ERK1/2 activity, leading to attenuated neuropathic pain; similarly, in the neuropathic pain model of SNL in mice, increased miR-186-5p [47] suppressed CXCL13 and subsequently suppressed CXCR5 and ERK, leading to attenuated neuropathic pain. In this specific model, though, it is not specified which isoform of ERK is suppressed, but rather, the general type of kinase, ERK, is identified.

3.6. Mitogen-Activated Protein Kinase 6 (MAPK6)

Mitogen-activated protein kinase 6 (MAPK6) is a non-canonical MAPK, meaning it has unique activation mechanisms and does not follow the traditional rapidly accelerated fibrosarcoma (RAF)-MEK-ERK cascade [100–102]. Unlike ERK1/2's activation through the TEY motif, MAPK6's corresponding motif is SEG [100,103–105]. Not much is known

about the role of MAPK6, but it does engage in regulatory relationships within the broad MAPK signaling network [106,107]. MAPK6 is activated through protein phosphorylation cascades and acts as an integration point for multiple biochemical signals [104,107].

In the neuropathic pain model of CCI, the upregulation of miR-26a-5p suppressed MAPK6 expression, resulting in attenuated neuropathic pain [49].

3.7. Interleukin 1 Receptor-Associated Kinase (IRAK1)

Interleukin 1 receptor-associated kinase (IRAK1) plays an important role in the regulation of the expression of inflammatory genes. Upon activation by their respective ligands, toll-like receptors (TLRs) and interleukin-1 (IL-1) recruit MyD88 [97], leading to the phosphorylation and activation of IRAK1 [96,108]. Once activated, IRAK1 phosphorylates and activates TRAF6, which then activates several kinases in the MAPK family, including ERK1/2, p38, and JNK [94].

In the neuropathic pain model of CCI, increased expression of miR-146a-5p suppressed IRAK1 signaling, leading to attenuated neuropathic pain [50].

3.8. Janus Kinase 1 (JAK1)

Janus kinase 1 (JAK1) is a protein that helps transmit signals for cytokines and growth factors [109], making it a key part of immune function. JAK1 is activated by cytokines, stimulating phosphoinositide 3-kinase (PI3K), which in turn activates AKT3 [109].

In the neuropathic pain model of SNL in rats, decreased levels of the lncRNA (long non-coding RNA) LINC00052 (long intergenic non-coding RNA 00052) have been found to increase levels of miR-448 [51], leading to decreased JAK1 levels and attenuated neuropathic pain.

3.9. G Protein-Coupled Receptor Kinase 2 (GRK2)

G protein-coupled receptor kinase 2 (GRK2) plays a key role in GPCR signaling [110,111], indirectly inhibiting JAK1 by phosphorylating upstream GPCRs [112–114], which disrupts the JAK signaling pathway and thereby reducing the downstream signaling cascade associated with JAK1 activity [112,115].

GRK2 negatively regulates AKT3 signaling through interactions with phosphatases such as protein phosphatase 2A (PP2A), leading to AKT3 dephosphorylation and, therefore, inactivation [110,111].

In the neuropathic pain model of de novo GRK2 knockout mice, increased levels of miR-124 [38] increased GRK2 expression, leading to attenuated neuropathic pain.

4. Protein Kinase Involvement in miRNA Downregulation Leading to Alleviation of Neuropathic Pain

Figure 2 illustrates the protein kinases involved in the second motif, along with their direct and indirect interaction partners. This kinase network presents a more intricate regulatory landscape in the context of neuropathic pain behaviors. Unlike the uniform co-regulation observed in other networks, kinases in these cases show a more nuanced interplay, where some kinases exhibit a positive correlation with neuropathic pain, meaning their upregulation is associated with increased pain behaviors, while others display a negative correlation in which their downregulation aligns with pain attenuation. These opposing regulatory pathways suggest that different subsets of kinases may contribute to distinct mechanisms underlying pain modulation, potentially reflecting the balance between pro-inflammatory and anti-inflammatory signaling pathways. Understanding these complex interactions may provide deeper insight into the molecular underpinnings of neuropathic pain and inform the development of more targeted therapeutic strategies.

4.1. Mitogen-Activated Protein Kinase (MAPK): p38

Mitogen-activated protein kinase (MAPK) is a protein kinase family that controls how cells respond to stimuli [104]. p38 is part of the MAPK family and regulates many important cellular processes [116] such as inflammation, cell growth, apoptosis, and tissue homeostasis [117]. Four p38 isoforms have been identified (p38α, p38β, p38γ, and p38δ) [117], though it is not indicated which isoform specifically is involved in the neuropathic pain network.

JAK1 and MAPK pathways interact in a complex but coordinated manner. JAK1, through cytokine receptor activation [118,119], can indirectly activate MAPK signaling [120,121]; additionally, MAPK signaling can modulate JAK1 activity [122,123], creating feedback loops that fine-tune cellular functions.

Suppressor of cytokine signaling 1 (SOCS1) inhibits MAPK signaling by indirectly blocking the activation of the upstream kinases, primarily by targeting and inhibiting the JAK family of kinases, which are crucial for the phosphorylation cascade leading to MAPK activation [124].

In the CCI model of rats, decreased levels of both miR-155 [52] and miR-221 [53] led to increased levels of SOCS1. This decreased p38 expression levels, attenuating neuropathic pain.

In the diabetes mellitus (DM) sciatic nerve of model rats, decreased levels of miR-133-3p [54] suppressed p38, attenuating neuropathic pain; additionally, in the CCI model of mice, decreased levels of miR-15a/16 [55] also suppressed p38, attenuating neuropathic pain.

4.2. Extracellular Signal-Regulated Kinase (ERK)

Extracellular signal-regulated kinase (ERK) is located downstream from MEK in the MAPK cascade and is a key enzyme within the ERK signaling pathway [88].

In the DRG Tlr8 knockout mouse model, decreased expression of miR-21 [56] downregulated Tlr8 and, consequently, led to decreased levels of ERK as well as attenuated neuropathic pain.

4.3. Adenosine Monophosphate-Activated Protein Kinase (AMPK)

Adenosine monophosphate-activated protein kinase (AMPK) is a protein kinase that plays a crucial role in regulating energy metabolism [125]. AMPK and AKT3 both work on TSC1/2 with opposing effects. AMPK activates TSC1/2, which leads to mTOR inhibition [126,127], while AKT3 inhibits TSC1/2, which leads to mTOR activation [128,129]. This balance between AMPK and AKT3 through TSC1/2 ensures regulated cellular responses.

In the CCI SNI model of rats, decreased levels of miR-142-3p led to an increase in AC9 levels, which in turn led to a decrease in cyclic AMP (cAMP) [57]. This decrease in cAMP increased AMPK expression, attenuating neuropathic pain.

4.4. Serum/Glucocorticoid Regulated Kinase Family Member 3 (SGK3)

Serum/glucocorticoid regulated kinase family member 3 (SGK3) phosphorylates several target proteins and has a role in neutral amino acid transport and activation of potassium and chloride channels [130,131]. SGK3 phosphorylates TSC, inhibiting TSC1/2 [132,133]. This inhibition leads to the activation of Rheb [134,135], which stimulates mTOR [133,134].

In the neuropathic pain models of bilateral CCI, upregulation of lncRNA CCA11 [58] suppressed miR-155 [59], upregulating SGK3 and attenuating neuropathic pain.

4.5. G Protein-Coupled Receptor Kinase 2 (GRK2)

G protein-coupled receptor kinase 2 (GRK2) plays a key role in GPCR signaling [110,111]. GRK2 negatively regulates AKT3 signaling through interactions with phosphatases such as protein phosphatase 2A (PP2A) [136–138], leading to AKT3 dephosphorylation and inactivation.

In the CCI model of mice, decreased levels of miR-15a/16 [55] led to increased GRK2 expression, attenuating neuropathic pain.

5. Concluding Remarks

In this review, we summarize key findings from the literature demonstrating causal relationships between miRNA regulation and neuropathic pain behaviors, with a specific focus on protein kinases as mediators of these effects. Two relationship patterns characterize miRNA modulation of neuropathic pain: (1) upregulation of miRNA attenuates neuropathic pain, largely through the suppression of pro-nociceptive protein kinases, and (2) downregulation of miRNA leads to pain attenuation, either by relieving the receptive regulation of anti-neuropathic signaling pathways, or by directly promoting their activation. These relationship patterns highlight the complex regulatory networks underlying the mechanisms for neuropathic pain, where protein kinases serve as critical molecular mediators in the cellular signaling cascades.

Given the high prevalence of neuropathic pain and a lack of effective therapies [6,7,9–17], there is an urgent need to develop novel treatment strategies that target the underlying molecular mechanisms of pain pathophysiology. Our discussion underscores the potential of miRNA-based approaches in this context, as miRNAs serve as upstream regulators and are capable of modulating multiple pain-related pathways simultaneously. The role of protein kinases as mediators of miRNA also points to the potential of targeting intracellular signaling molecules as a pain management strategy, offering the opportunity to identify kinase-specific interventions that may work independently or synergistically with miRNA-targeted therapies.

The therapeutic potential of miRNA modulation is increasingly being recognized [139–141]; specifically, both miRNA mimics and miRNA inhibitors can be used to manipulate miRNA levels, thus achieving the in vivo effect of either miRNA upregulation or miRNA downregulation [142–144]. In the context of neuropathic pain, the evidence summarized in this review suggests that both miRNA activation and inhibition could have therapeutic value, depending on the specific miRNA and its downstream targets. For miRNAs whose upregulation can lead to alleviation of neuropathic pain (Table 1, Figure 1), desirable therapeutic outcomes may be achieved with miRNA mimics, i.e., synthetic double-stranded RNA molecules that mimic the function of these endogenous miRNAs; similarly, for miRNAs whose downregulation can attenuate neuropathic pain (Table 2, Figure 2), favorable clinical results may be attained with miRNA inhibitors, i.e., single-stranded RNAs that are complementary to endogenous miRNAs, thus achieving the effect of gene silencing by specifically inhibiting these endogenous miRNAs. The ability to selectively regulate miRNA activity using miRNA modulators may open exciting avenues for the development of precision medicine approaches to neuropathic pain management.

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