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REVIEW

Emerging roles of microRNAs in morphine tolerance

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Abstract: Morphine is commonly used in clinical management to alleviate moderate-to-severe pain. However, prolonged and repeated use of morphine leads to tolerance. Morphine tolerance is a challenging clinical problem that limits its clinical application in pain treatment. The mechanisms underlying morphine tolerance are still not completely understood. MicroRNAs (miRNAs) are small noncoding RNAs containing 18~22 nucleotides that modulate gene expression in a post-transcriptional manner, and their dysregulation causes various diseases. miRNAs bind to the 3′-UTR (untranslated region) of target gene mRNA, inhibiting or destabilizing translation of the transcripts. Morphine causes differential miRNA upregulation or downregulation. This review will present evidence for the contribution of miRNAs to tolerance of the antinociception effect of opioids.

Keywords: microRNA, morphine tolerance, MOR, β-arrestin 2, CaMKII/NMDAR

Introduction to morphine tolerance

Morphine is used extensively in clinical practice for the treatment of acute and chronic pain as well as cancer-related pain.[1] Long-term morphine treatment is usually accompanied by morphine tolerance.[2] Morphine tolerance is characterized by a progressively decreasing pain control response, requiring increasing morphine dosage to achieve adequate analgesia after long-term application.[3] Morphine tolerance is the major reason for pain treatment failure, and the molecular mechanisms of morphine tolerance are complicated.

Opioid receptors and morphine tolerance

Opioid tolerance reflects changes in how systems affected by the opioid respond such as changes in receptor density or desensitization of receptors.[4] The opioid receptor belongs to the G protein-coupled receptor (GPCR) family and primarily mediates the analgesic function of morphine. Morphine targets mu opioid receptor (MOR) through adenylyl cyclase (AC) and extracellular signal-regulated kinase (ERK) pathways as well as intracellular calcium storage and cell membrane ion channels to form antinociceptive tolerance.[5] Endocytosis of MOR through corresponding kinases, including protein kinase C (PKC), protein kinase A (PKA), and GPCR kinases (GRKs) to promote serine or threonine phosphorylation on MOR, facilitates the development of morphine tolerance (Figure 1).[6] A previous study reported that delta opioid receptor (DOR) is a key receptor in morphine antinociceptive tolerance. MOR analgesic tolerance is reduced by blockade of DORs that interact with MORs.[7,8] Recent studies show that the MOR/DOR interaction in

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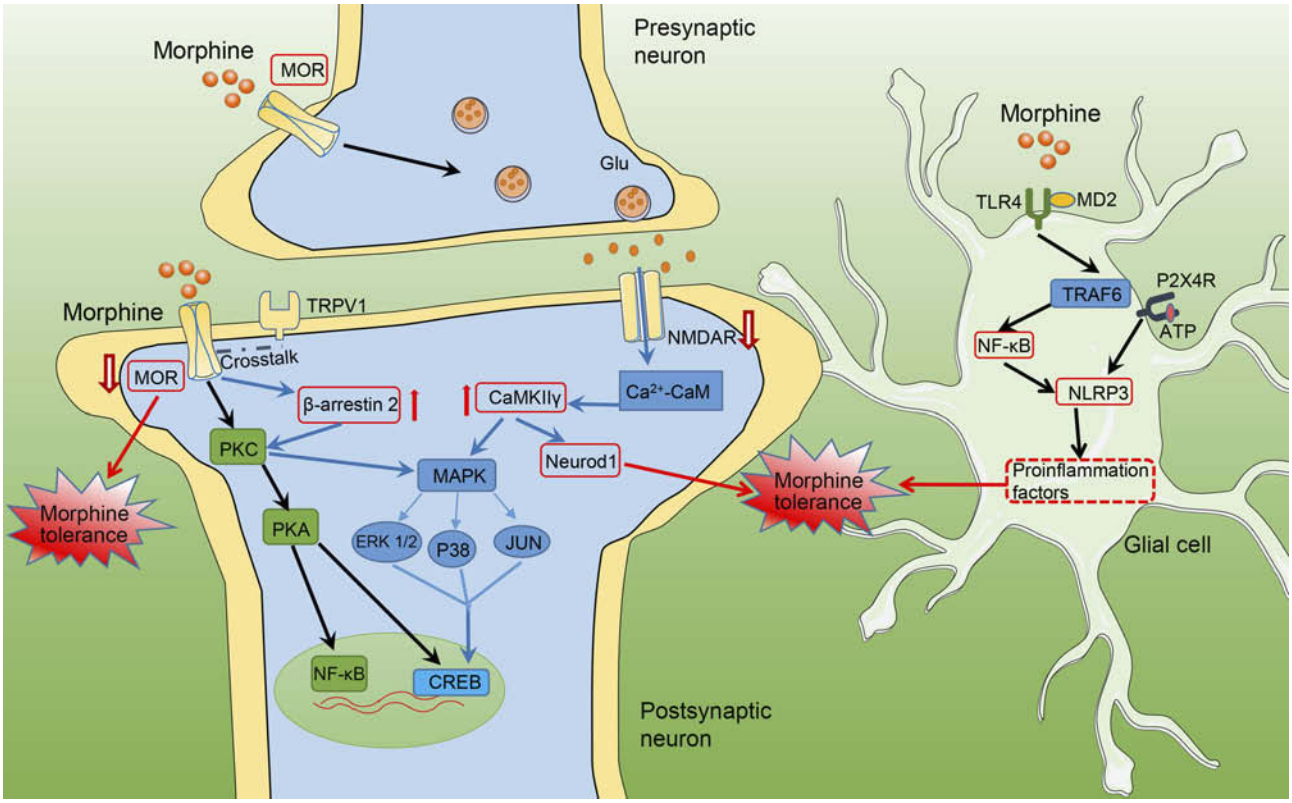

Figure 1 Schematic showing mechanisms underlying morphine tolerance. Schematic model showing how MOR/β-arrestin 2 and NMDAR/CaMK II γ-dependent signaling in neuron plays a crucial role in the promotion of morphine tolerance. Morphine induces activation of glial cells and upregulates proinflammatory cytokines via the TLR4/NF-κB pathway to facilitate morphine tolerance.

Abbreviations: MAPK, mitogen-activated protein kinase; ERK1/2, extracellular signal-regulated kinase 1/2; NeuroD 1, neurogenic differentiation factor 1; TRAF6, tumor necrosis factor receptor-associated factor 6; P2X4R, purinergic P2X4 receptors; ATP, adenosine 5'-diphosphate; NLRP3, NACHT, LRR and PYD domains-containing protein 3 inflammasome.

nociceptive afferent neurons in the dorsal root ganglion may contribute to morphine analgesic tolerance.[9] Cyclin-dependent kinase 5 (Cdk5) phosphorylated DOR at Thr-161 accelerated the development of morphine tolerance.[8] Besides, one mechanism for the role of DOR in modulating analgesia is through MOR–DOR heterodimerization.[10] The DOR antagonist can increase MOR binding and signaling by occupancy of DOR and enhance morphine-mediated analgesia.[10,11] Furthermore, morphine tolerance can be blockaded by genetic interruption of DOR system.[12] In addition, co-administration of a κ-receptor antagonist with morphine suppressed the development of antinociceptive tolerance to morphine.[13]

Synaptic connections and morphine tolerance

Recently, most cellular studies on morphine tolerance have focused on synaptic mechanisms. N-methyl-D-aspartic acid receptor (NMDAR), platelet-derived growth factor receptor β (PDGFR-β),[14] and substance *P* precursor proteins (tachykinin precursors) in the synapse were reported indirectly participated in morphine tolerance.[8,15] The presynaptic glutamate receptor, which is co-expressed with the transient receptor potential vanilloid 1 (TRPV-1), promotes glutamate release and produces long-term potentiation (LTP) to facilitate morphine tolerance.[16] Studies have demonstrated that chronic morphine treatment leads to a reduction in postsynaptic K+ conductance and voltage-gated calcium channels in the periaqueductal gray (PAG).[17] Besides, transcription factors, such as cAMP-response element binding (CREB)[18] and nuclear factor-κB (NF-κB),[19] are also regulated by morphine and participate in synaptic plasticity and the pathology of morphine tolerance.

Inflammatory factors and morphine tolerance

A large number of researchers have found that long-term morphine application results in neuroinflammatory responses, especially those mediated by toll-like receptor-4 (TLR4), in the brain and spinal cord, which are a very important cause of morphine tolerance.[20] TLR4 is

a key innate immune receptor, and morphine bound to myeloid differentiation factor 2 (MD-2) activates TLR4 signaling facilitating morphine tolerance.[21] Recently, increasing evidence indicates that morphine tolerance is accompanied by increased glial cell activation.[22] The number of inflammation-associated astrocytes and microglia was significantly increased by morphine in the spinal cord of rats; moreover, these increased cell numbers were accompanied by morphological changes.[23] Pentoxifylline inhibits astrocyte activation and releases neuroinflammatory factors, such as tumor necrosis factor alpha (TNF-α), IL–1β, and IL–6), effectively reversing the development of morphine tolerance.[24] Morphine activates microglial cells, upregulates microglia marker (CD-11b or Iba1) expression, acts on TLR4 and activates proinflammatory signaling to facilitate morphine tolerance.[25] In addition, P2X4 and P2X7,[26,27] ATP receptors, were upregulated in microglia of the spinal cord by morphine, and its antagonists prevented the development of morphine tolerance (Figure 1).

The mechanisms underlying morphine tolerance are not completely understood, and effective prevention and treatment measures are lacking. In recent years, some studies have stated that many of the mechanisms that have been implicated in opioid tolerance appear to be regulated by miRNA.[28] This review discusses how abnormally expressed miRNAs promote morphine tolerance by targeting its downstream genes.

MicroRNA (miRNA) synthesis and function

miRNAs are a group of noncoding, single-stranded small RNAs approximately 18～22 nucleotides (nt) in length. When pri-miRNAs are synthesized in the cell nucleus, dicer enzymes process the pre-miRNAs into mature miRNAs, which are rapidly transferred to the cytoplasm. miRNAs guide Argonaute (AGO) proteins and recruit miRNA-induced silencing complex (miRISC) to mRNA targets.[29] Negative miRNA regulation functions include direct degradation of target gene mRNA and modulation of target gene mRNA stability to indirectly inhibit target gene translation.[30] When multiple 3′-UTR-binding sites are present, the negative regulatory function of target genes is more obvious.[31] miRNAs have also been reported to bind to mRNA-coding regions. However, the inhibitory effect of binding to the coding regions is lower than of binding to the 3′-UTRs.[32]

Recent studies have clearly demonstrated that miRNAs are essential and critical players in mammalian development and closely associated with human genetic diseases, nervous system development, and the development and progression of certain major diseases.[33–35] In opioid analgesic efficiency research, we found that miRNAs play an indispensable role in morphine tolerance, drug addiction, and opioid receptor expression.[36]

miRNAs participate in morphine tolerance

With the gradual increase in the number of miRNA and morphine tolerance studies, accumulating results have demonstrated that morphine-induced antinociceptive tolerance is accompanied by upregulation or downregulation of many miRNAs in vivo and in vitro and that the differentially expressed miRNAs are important regulators of morphine tolerance. A growing number of studies have reported miRNA mechanisms in morphine tolerance (Table 1).

miRNAs regulate opioid receptor expression to accelerate morphine tolerance

let-7 is one of the earliest discovered miRNAs after lin-4. let-7 is a highly conserved miRNA. Let-7 family are encoded by 13 genomic loci in the human body[37] and mainly participates in stem cell differentiation, nerve and muscle tissue development, and cell proliferation and differentiation.[38] Under morphine stimulation, let-7 expression is upregulated. Validation with luciferase assays showed that the let-7 sequence has many binding sites on the 3′-UTR of the MOR gene. Morphine upregulates let-7 and downregulates MOR protein expression in SH-SY5Y cells.[39] Downregulation of let-7 in the mouse brain partially reversed morphine tolerance.[40] Further studies showed that let-7 does not directly reduce MOR mRNA degradation; instead, it reduces the binding between ribosomes and mRNAs through a *P*-body to influence MOR translation and decrease MOR expression.[41] These results suggest that the "star molecule" let-7 plays an important role in MOR and participates in morphine tolerance.[39] Long-term morphine treatment increased miR23b expression in a dose- and time-dependent manner and repressed target MOR1 mRNA with polysomes through the MOR1 3′-UTR.[42] After chronic treatment of mice with μ-opioid agonists (morphine or fentanyl), miR-339-3p was increased in the hippocampus and inhibited MOR 3′-UTR activity by binding to its target sequence and promoting mRNA decay.[43] miR-107 and miR-103 were increased in Be(2)C cells and mouse striatum,

Table 1 miRNAs and morphine tolerance

Name	Change	Drug studied	Tissue	Function
miR-16	Decreased	Morphine	CEM ×174 cell	Binds to the MOR-1 mRNA 3'-UTR and suppress OPRM1 gene expression.[74]
miR-103/miR-107	Increased	Morphine/ fentanyl	Mouse (prefrontal cortex)/human embryonic kidney 293(HEK293 cells)/ Be(2)C cells	Downregulates polyribosome-associated MOR-1A in both Be(2)C cells and the striatum of a morphine-tolerant mice.[44]
miR-339	Increased	Morphine	Mouse hippocampus/mouse neuroblastoma neuro2A(N2A) cell	Inhibits the production of MOR protein by destabilizing MOR mRNA.[43]
miR-let-7 family	Increased	Morphine	Mouse brain/HEK293 cells	Mediates movement of MOR mRNA into *P*-bodies, leading to translational repression.[39]
miR-23b	Increased	Morphine	Human neuronal cell lines (NMB)/ HEK293 cells	Inhibits lysome-mRNA association with MOR (mouse neuronal N2A cells).[75]
miR-365	Decreased	Morphine	Spinal cord (rat)	Involved in morphine tolerance development and maintenance through regulation of β-arrestin 2.[51]
miR-219-5p	Decreased	Morphine	Spinal cord (rat)	Alleviates morphine tolerance by inhibiting the CaMKIIγ/NMDA receptor pathway.[55]
miR-190	Decreased	Morphine/ fentanyl	Hippocampus (mouse)	A key post-transcriptional repressor of neurogenic differentiation factor NeuroD.[76]
miR-338	Decreased	Morphine	Spinal cord (rat)	Regulated by miR-338, CXCR4 was significantly increased, and play an important role in morphine tolerance.[77]
miR-223-3p	Increased	Morphine	Spinal cord (rat)	Upregulates the expression of NLRP3 to facilitate morphine analgesic tolerance.[64]
miR-375	Increased	Morphine	Dorsal root ganglia (DRG:mouse)	Ameliorates morphine tolerance by downregulating JAK2/STAT3 expression.[78]

mainly functioned as repressive elements on MOR1, and participated in morphine tolerance by repressing the expression of MOR.[44] Consequently, morphine regulates MOR expression through a number of miRNAs in cell lines and in animals to aggravate morphine tolerance (Figure 2).

miRNAs regulate β-arrestin 2 to participate in morphine tolerance

miR-365 is present in many types of cancer cells including colorectal cancer,[45] lung cancer,[46] and cholangiocarcinoma cell.[47] In gastrointestinal cancer, miR-365 inhibits cell cycle progression through inhibition of cyclin D1 (CCND1) to inhibit cancer development.[45] miR-365 was decreased in malignant glioma cells and functioned in phosphoinositide-3-kinase regulatory subunit 3 (PIK3R3) to participate in glioma progression, and overexpression of miR-365 inhibited glioma proliferation and invasion. miR-365 was upregulated in the ischemic brain, inhibited the target gene PAX6 (a neurogenic fate determinant) expression, and exacerbated ischemic brain injury.[48]

Arrestins are inhibitory proteins, and β-arrestin 2 is a -subtype[49] that can activate GPCRs to mediate internalization and desensitization of MOR. Upregulated β-arrestin 2 functions on MOR to attenuate the analgesic effects of opioid drugs through AC, ERK pathways, intracellular calcium storage, and cell membrane ion channels. β-arrestin2-knockout mice have been reported to represent an animal model in which the morphine-induced desensitization of MOR has been significantly impaired and display an enhanced and prolonged response to morphine in pain perception.[50] Our study revealed that miR-365 was significantly decreased, accompanied by high expression of β-arrestin 2, in the spinal cord of morphine group rats compared with saline group rats. Luciferase assays showed that miRNA-365 has many binding sites with the 3′-UTR of the target gene β-arrestin 2 (Figure 2).[51] Our research data suggest that morphine tolerance occurs via the miR-365/β-arrestin 2 pathway. In addition, miR-365 targets β-arrestin2 by inhibiting ERK/CREB activation, thus reducing IL-1 and TNF-α content, and lowering morphine analgesic tolerance.[52] Therefore, miR-365 might become a potential target for prevention and treatment of morphine tolerance (Figure 2).

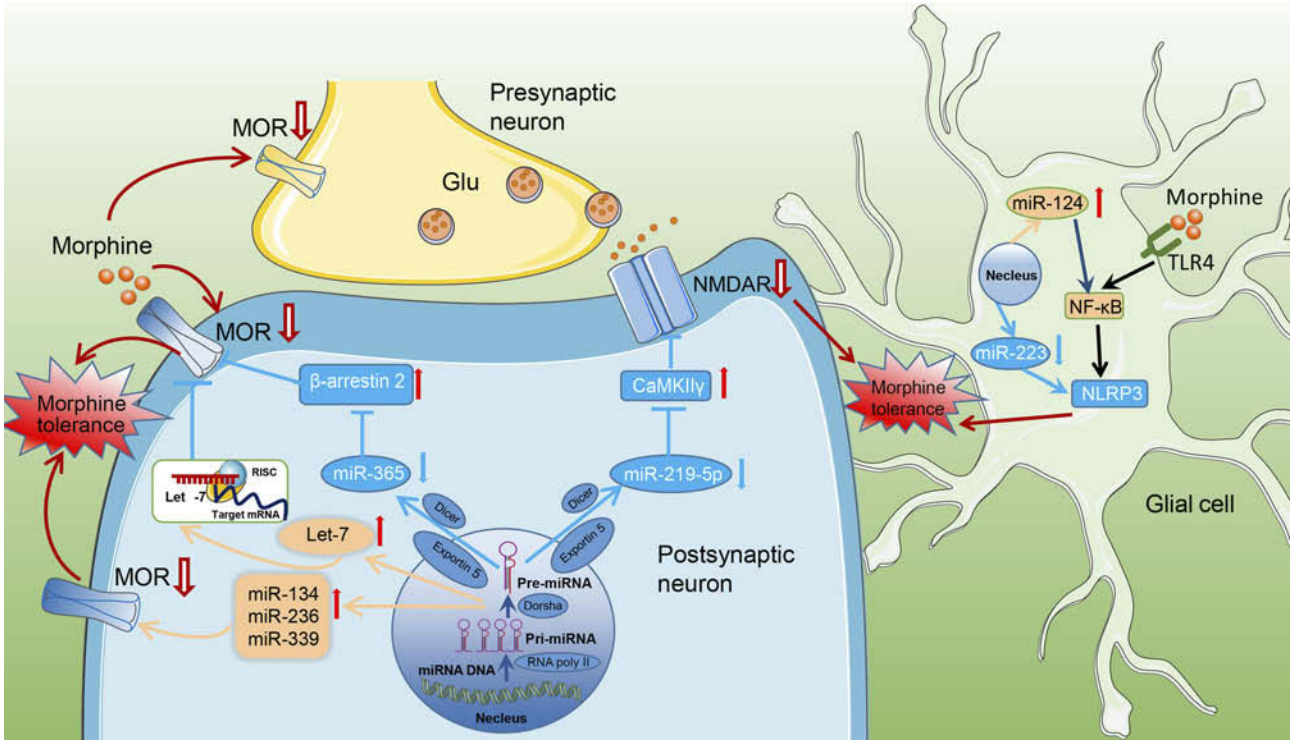

Figure 2 Schematic diagram showing the mechanism of morphine tolerance regulation by miRNAs. Morphine induces many miRNAs. Pri-miRNAs are synthesized in the nucleus and transferred to the cytoplasm, Dicer makes pre-miRNA into mature miRNA. Differentially expressed miRNAs regulate neuroplasticity-related target protein expression and thereby participate in the development of morphine tolerance. miR-365 was significantly downregulated after morphine administration, along with its target gene β-arrestin 2, and acted indirectly on MOR to participate in morphine tolerance. In addition, morphine induced low miR-219-5p expression in the spinal cord and further upregulates CaMKIIγ to promote morphine tolerance. MOR is the primary opioid receptor and the target of miR-134/miR-339/miR-236, which are involved in morphine tolerance. Mature let-7 is exported from the nucleus into the cytosol and incorporated into RISC, a protein composed of translational machinery that recruits target mRNA to *P*-bodies and effectively reduces polysome-bound mRNA, resulting in translation repression. In glial cells, morphine administration altered the expression of miR-124 or miR-223, along with their target gene, which participated in morphine tolerance.
Abbreviations: RISC, RNA-induced silencing complex; miR, microRNA.

miRNAs aggravate morphine tolerance through CaMKII/NMDAR

Calmodulin-dependent protein kinase II (CaMKII) is a serine/threonine protein kinase composed of α, β, γ, and δ subunits. CaMKII is extensively distributed in the central and peripheral nervous systems to regulate synaptic transmission and neuronal functions. Immunofluorescence experiments have demonstrated that MOR and CaMKIIγ are co-expressed and are mainly present in neural pathways that conduct pain. Previous research showed that morphine increased the expression of CaMKII in the dorsal root ganglia (DRG) directly influencing the expression of calcition gene-related peptide (CGRP) required for the development of tolerance to morphine-induced analgesia.[53] CaMKII downregulation inhibited both CREB activation induced by morphine and phosphorylation of opioid receptor and attenuated the development of morphine tolerance.[54] The expression of miR-219-5p was downregulated in the spinal cords of morphine tolerance rats and acted on the downstream target gene CaMKIIγ.[55] CaMKII activates CREB to promote NR1 synthesis. NMDAR activation causes calcium influx to increase calcium concentrations in the cytoplasm and recruit CaMKII to increase the Ca/CaM*KII* complex concentration and mediate the conduction of neuronal activity.[56]

NMDA participates in morphine tolerance development and neuronal plasticity within the central nervous system. NMDAR is one of the receptors that transmit excitatory neuronal signals. NMDAR primarily mediates calcium influx and transduction of downstream signaling to induce cellular internal cascade amplification and causes internalization of MOR.[57] NR1 is a subunit of endogenous NMDA receptors.[58] In the mouse brain chronic morphine treatment alters the expression level of NR1, which plays an important role in morphine tolerance.[59] Animal studies have shown that the mRNA levels of NR1 in the striatum are significantly upregulated in morphine tolerance models to accelerate morphine tolerance development. Our group showed that morphine

induces low miR-219-5p expression in the spinal cord to further upregulate the expression of target proteins, CaMKIIγ, and NR1 (Figure 2). These results suggest that morphine tolerance development is associated with the miR-219-5p/CaMKIIγ pathway.[55]

miRNAs alleviate morphine tolerance by controlling the expression of inflammatory factors

Chronic morphine exposure often results in increased expression of various proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, in vitro and in vivo and elevates lipopolysaccharide (LPS)-induced immune response.[60] Inhibition of the function of glial cells, including astrocytes and microglia, can attenuate the development of morphine analgesic tolerance.[61] The ventrolateral periaqueductal gray glial contributes to morphine tolerance by activating the innate immune receptor TLR4.[62] TLR4 signaling increased the expression of the NLRP3 inflammasome in microglia through NF-κB within a period of morphine-induced sensitization.[63] miR-223 negatively regulated NLRP3 inflammasome expression to relieve morphine analgesic tolerance.[64] Furthermore, TLR4-mediated NF-κB activation in the spinal cord is involved in the development and maintenance of morphine tolerance.[65] Morphine-induced upregulation of miR-124, which directly inhibits its downstream targets NF-κB and TRAF6, plays a critical role in morphine-mediated microglia immunity suppression (Figure 2).[66]

Studies in miRNA clinical trials

A lot of studies involving miRNA treatments have been conducted over the years, and a small number of miRNA composites have moved into clinical application. The locked nucleic acid (LNA) drug miravirsen[67,68] and a GalNAc-conjugated antimiR against miR-122, both designed to treat hepatitis C virus (HCV) infection by suppressing the function of miR-122, have undergone Phase Ⅰ trials in HCV-infected patients.[69] A miR-29 mimic for patients with scleroderma and an LNA-based antimiR-155 for patients with cutaneous T-cell lymphoma are in Phase Ⅰ clinical trials.[70] A growing number of studies have shown that miRNAs are involved in morphine tolerance, but potential miRNA therapeutic rarely move into clinical development. One of the challenges is that clinical drugs mainly target drug enrichment sites through target proteins, and miRNAs have diverse downstream action sites and do not have specific target proteins. Second, miRNAs are exogenous small RNAs and thus, for further clinical application, it is very important to increase miRNA lipophilicity or use specific technologies to allow miRNA to rapidly enter cells through cell membranes and exert regulatory functions. Third, potential immune-related adverse reactions and jaundice should be taken into consideration.

Conclusions

The human genome generates approximately 1,500 miRNAs. Biomedically oriented miRNA studies have generated a large amount of miRNAs information including pathway, disease, organs, and target analysis. This information can be searched on the website of miEAA miRase, miRWalk, and miRTarbase.[71] Several binding bases are required between a miRNA and its target gene mRNA, and thus the association between miRNAs and target genes is a network-like relationship. One miRNA can act on many target genes to negatively regulate target protein expression and thus can participate in many pathophysiological processes in human diseases. Recently, many studies have revealed molecular mechanisms of miRNAs and target genes in morphine tolerance, differentiation, and cancer, but the biological effects of miRNAs have not been completely determined.[72] Additional miRNAs, such as miR-873a-5p, will likely be found to further elucidate the mechanisms underlying the development and progression of morphine tolerance.

Increasing research has revealed that miRNAs participate in morphine tolerance development, and interference with certain miRNAs has been shown to inhibit morphine tolerance development in rodents. let-7 and miR-365, involved in the MOR and β-arrestin2 pathway, may have therapeutic potential that may be explored in future clinical trials. Researchers have reported that there are two application routes, intravenous injection and subcutaneous injection, for miRNA treatment and that miRNAs would form the basis of a new treatment approach.[73] Additionally, more studies need to be carried out to examine the mechanisms by which miRNAs participate in morphine tolerance.

Currently, there is a huge gap between preclinical and clinical studies regarding the role of miRNAs in opioid tolerance and the potential implications in human subjects. Therefore, with further in-depth miRNA-related translational studies, miRNAs may become targets for drug development for the prevention and treatment of morphine tolerance.

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Disclosure

The authors declare that they have no competing interests associated with this work.

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