MicroRNAs as regulators of drug abuse and immunity

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Abstract

MicroRNAs (miRNAs) are 20-22 nucleotide non-coding RNAs that participate in gene regulation. They bind to 3’-untranslated regions of their mRNA targets, inhibiting the transcripts’ translation and/or destabilizing them. Chronic drug abuse induces changes of miRNAs expression in the brain, which is thought to contribute to addictive behaviors. Lots of miRNAs have been identified to play critical roles in the development of drug addiction. Moreover, miRNAs have been shown to play critical roles in a broad array of biologic processes, including regulation of the cell cycle, oncogenic transformation, immune cell regeneration and differentiation, and psychiatry disorders. We hypothesized that chronic drug abuse leads to aberrant expression of several miRNAs, and then aberrant miRNAs influence the innate and adaptive immunity, especially differentiation and function of T cells and B cells, through down-regulated miRNAs’ target gene expression. Characterization of miRNA actions is important and has high potential effect for the management of drug addiction and immunity diseases. miRNAs are potential biomarkers, and the modulation of their expression can be used for therapeutic purposes.

Key words: innate immunity, microRNA, immunity, drug abuse, adaptive immunity.

Introduction

In the year 2011 there were approximately 14.0 million drug users between the ages of 15 and 64 years, 1.6 million drug abusers with HIV and 0.2 million drug-related deaths [1]. It is important to note that most of the drug-related deaths were in young people and could have been prevented. Drug abuse is a chronic brain disease with severe social and economic consequences that are associated with significant mortality and morbidity [2]. Abuse substances, such as opiates, cocaine, marijuana, alcohol, and nicotine, all have been reported to impair the immune system and enhance or suppress immune response cell function [3-7]. Additionally, an increasing number of studies have focused on the associations between drug abuse and the immune system. More and more studies have focused on non-coding microRNAs (miRNAs) at the molecular level.

miRNAs are 20-22 nucleotide non-coding RNAs that regulate gene expression by binding to the 3’-untranslated regions (3’-UTRs) of their mRNA targets. Because of this mechanism, miRNAs silence or prevent the translation of their target genes. Previous studies have shown that miRNAs are master regulators of genes and their networks. Aberrant miRNA expression has been closely linked to various diseases, including psychiatric disorders, neuronal development, and immune-related disorders [8-11].

Our goals in this review were to summarize the research results of aberrant expression of miRNAs after chronic drug abuse and cite specific examples of how miRNAs affect the innate and adaptive immune systems. We concentrated on the intermediate effects of specific miRNAs involved in chronic drug abuse and immune system diseases.

Chronic drug abuse changes the expression of microRNAs

Chronic drug abuse up-regulates or down-regulates the expression of related genes, that contribute to drug addiction behaviours such as craving and seeking. As described in previous studies, a large number of genes, such as brain-derived neurotrophic factor (BDNF), cAMP response element binding protein (CREB), and methyl CpG binding protein 2 (MeCP2), have been shown to play critical roles in the development of drug addiction. More importantly, many of these genes require a complex network to exert their regulatory functions on drug abuse. If we were able to identify the master regulator of this network, we could provide insights into safe and effective therapies to treat drug addiction. Unfortunately, we do not completely understand this regulatory network and the master regulator remains unknown.
Table 1. miRNAs in drug abuse and immunity

| Drug       | microRNA | Regulation | Reference                                                                 | Immunity         | Reference                                                                 |
|------------|----------|------------|---------------------------------------------------------------------------|------------------|---------------------------------------------------------------------------|
| Cocaine    | miR-212  | Up         | Hollander et al. 2010 [13]; Im et al. 2010 [14]; Xu et al. 2013 [15]      | Innate immunity  | Wanet et al. 2012 [62]; Nahid et al. 2013 [63]                              |
|            | miR-132  | Up         | Nudelman et al. 2010 [16]                                                 | Innate immunity  | Wanet et al. 2012 [62]; Nahid et al. 2013 [63]                              |
|            | miR-181a | Up         | Chandrasekar et al. 2009 [18]; Chandrasekar et al. 2011 [19];             |                  |                                                                            |
|            |          |            | López-Bellido et al. 2012 [20]                                            |                  |                                                                            |
|            | miR-124  | Down       | Chandrasekar et al. 2009 [18]; Chandrasekar et al. 2011 [19]              |                  |                                                                            |
|            | let-7d   | Down       | Chandrasekar et al. 2009 [18]; Chandrasekar et al. 2011 [19]              |                  |                                                                            |
|            | miR-133b | Down       | Chen et al. 2013 [22]; Barreto-Valer et al. 2012 [23]                      |                  |                                                                            |
|            | miR-134  | Up         | Chen et al. 2013 [22]                                                     |                  |                                                                            |
|            | miR-22   | Up         | Chen et al. 2013 [22]                                                     |                  |                                                                            |
| Nicotine   | miR-21   | Up         | Huang and Li 2009 [25]; Zhang et al. 2014 [26]                            | Innate immunity  | Sheedy et al. 2010 [65]                                                   |
|            |          |            | Maccani et al. 2010 [27]; Shan et al. 2009 [28]; Wang et al. 2014 [29]   | Innate immunity  | Chen 2011 [64]                                                            |
|            | miR-335  | Up         | Huang and Li 2009 [25]                                                    |                  |                                                                            |
|            | miR-146a | Down       | Maccani et al. 2010 [27]; Shan et al. 2009 [28]; Wang et al. 2014 [29]   | Innate immunity  | Taganov et al. 2006 [46]; Hou et al. 2009 [47]; Chassin et al. 2010 [48]; |
|            |          |            |                                                                            | Adaptive immunity| Pauley et al. 2011 [49]; Rebane et al. 2014 [50]; Schulte et al. 2013 [51]; |
|            |          |            |                                                                            |                  | Curtale et al. 2010 [77]; Lu et al. 2010 [78]; Rusca and Monticelli 2011 [79] |
|            | miR-133  | Down       | Shan et al. 2009 [28]; Wang et al. 2014 [29]                              |                  |                                                                            |
| Opiate     | let-7    | Up         | Wu et al. 2009 [31]                                                       |                  |                                                                            |
|            | miR-23b  | Up         | He et al. 2010 [32]                                                       |                  |                                                                            |
|            | miR-190  | Up         | Zheng et al. 2010 [33]                                                    |                  |                                                                            |
|            | miR-133b | Down       | Zheng et al. 2010 [33]                                                    |                  |                                                                            |
| Amphetamine| miR-29a  | Up         | Lippi 2011                                                                |                  |                                                                            |
|            | miR-29b  | Up         | Lippi 2011                                                                |                  |                                                                            |
|            | miR-182  | Up         | Lippi 2011                                                                |                  |                                                                            |
|            | miR-183  | Up         | Lippi 2011                                                                |                  |                                                                            |
|            | miR-181a | Up         | Saba et al. 2012 [21]                                                     | Adaptive immunity| Ebert et al. 2009 [66]; Li et al. 2007 [67]; Li et al. 2012 [68]          |
| Alcohol    | miR-9    | Up         | Tatro et al. 2013 [34]                                                    |                  |                                                                            |
|            | miR-21   | Down       | Sathyan et al. 2007 [35]                                                  |                  |                                                                            |
|            | miR-335  | Down       | Sathyan et al. 2007 [35]                                                  |                  |                                                                            |
|            | miR-9    | Down       | Sathyan et al. 2007 [35]                                                  |                  |                                                                            |
|            | miR-153  | Down       | Sathyan et al. 2007 [35]                                                  |                  |                                                                            |
Interestingly, previous studies have shown that miRNAs are master gene regulators and play critical roles in the regulation of the cell cycle, immune cell regeneration and differentiation, cancer, and psychiatry disorders. Consistent with these diverse roles, recent studies have detected many roles for miRNAs in chronic drug abuse.

**Cocaine**

Cocaine is a central nervous system stimulant that exerts widespread effects in the striatum [12]. Three studies have demonstrated that chronic cocaine administration increases the expression of miR-212 in the dorsal striatum in rats [13-15]. Further results indicated that exogenous miR-212 in the striatum decreases addicted rat cocaine intake behaviours. Finally, Kenny’s group demonstrated that miR-212 controls drug intake by activating the CREB gene. Therefore, miR-212 maybe a protective factor for compulsive cocaine intake. The same study also illustrated that there is a homeostatic negative balance between miR-212 and MeCP2. More importantly, the interactive balance between miR-212 and MeCP2 coincided with cocaine sensitization reward effects [14]. Interestingly, chronic cocaine use also increased miR-132 expression in the striatum of rats [16]. miR-212 and miR-132 have overlapping seed regions, and a homeostatic relationship between miR-132 and MeCP2 was observed in brain cortical neurons [17]. It is possible that miR-132 is also a protective factor for compulsive cocaine intake.

Chronic cocaine exposure also increases miR-181a expression [18-20]. Aberrant expression of miR-181a, which binds to the 3’-UTR of the GluA2 subunit of the AMPA receptor (GRIA2), influences the function of the GABA system [21]. Chandrasekar and Dreyer et al. showed that chronic cocaine abuse decreases miR-124 and let-7d levels. miR-124 and let-7d down-regulate the expression of BDNF and the dopamine receptor 3 (DRD3) gene, respectively. When these miRNAs are over expressed in the NAc of rats, an intensive conditioned place preference (CPP)

### Table 1. miRNAs in drug abuse and immunity

| Drug        | microRNA | Regulation | Reference                  | Immunity   | Reference                      |
|-------------|----------|------------|----------------------------|------------|--------------------------------|
|             | miR-382  | Down       | Wang et al. 2009 [36]       |            |                                |
|             | miR-124a | Down       | Bahi and Dreyer 2013 [37]   |            |                                |
|             | miR-29b  | Down       | Qi et al. 2014 [38]         |            |                                |
|             | miR-124  | Down       | Mizuo et al. 2012 [39]      |            |                                |
|             | miR-9    | Up         | Pietrzykowski et al. 2008 [40]|            |                                |
|             | miR-124  | Up         | Dong et al. 2014 [42]       |            |                                |
|             | miR-206  | Up         | Tapocik et al. 2013 [41]    |            |                                |
|             | miR-181a | Up         | Asquith et al. 2014 [44]    |            |                                |
|             | miR-221  | Up         | Asquith et al. 2014 [44]    | Innate     | Lu et al. 2011 [59]            |
|             | miR-155  | Up         | Asquith et al. 2014 [44]    | Innate     | Schulte et al. 2013 [51];      |
|             |          |            |                            | immunity   | Curtis et al. 2015 [52];       |
|             |          |            |                            |            | Cui et al. 2012 [53];          |
|             |          |            |                            |            | Ghorpade et al. 2012 [54];     |
|             |          |            |                            |            | Koch et al. 2012 [55];         |
|             |          |            |                            |            | Cardoso et al. 2012 [56];      |
|             |          |            |                            |            | Wang et al. 2010 [57];         |
|             |          |            |                            |            | Richmond et al. 2015 [58];     |
|             |          |            |                            |            | Lu et al. 2011 [59];           |
|             |          |            |                            |            | Zhou et al. 2010 [60];         |
|             |          |            |                            |            | Martinez-Nunez et al. 2009 [61];|
|             |          |            |                            |            | Vigorito et al. 2013 [69];     |
|             |          |            |                            |            | Blüml et al. 2010 [71];        |
|             |          |            |                            |            | O’Connell et al. 2010 [72];    |
|             |          |            |                            |            | Rodriguez et al. 2007 [73];    |
|             |          |            |                            |            | Thai et al. 2007 [74];         |
|             |          |            |                            |            | Cardoso et al. 2012 [75];      |
|             |          |            |                            |            | Lu et al. 2009 [78];           |
|             |          |            |                            |            | Zhang et al. 2012 [84];        |
|             |          |            |                            |            | Chen et al. 2014 [85];         |
|             |          |            |                            |            | Sandhu et al. 2012 [86];       |
|             |          |            |                            |            | Dorsett et al. 2008 [87]       |
for cocaine was observed [18, 19]. One Chinese study indicated that repeated cocaine exposure and subsequent abstinence change the expression of various miRNAs, including miR-133b, miR-134, and miR-22 [22]. Another study demonstrated that chronic cocaine use led to abnormal miR-133b expression [23].

Nicotine

To date, there have been few clinical studies published that have focused on the relationship between miRNA regulation and nicotine abuse [24]. Most studies suggest that chronic nicotine abuse up-regulates the expression of miR-21, which is a critical master regulator of the immune system. By culturing rodent neuronal cells, Huang and Li found that miR-21 was over-expressed in oesophageal tissue samples after smoking and that miR-21 up-regulation by nicotine was also detected in cell lines [25]. Zhang et al. found that miR-21 was significantly up-regulated in oesophageal tissue samples after smoking and that cigarette smoking may affect downstream signalling by changing the expression of miRNAs.

A particularly intriguing example of this was demonstrated by Sathyan et al. from a study by Sathyan et al. [35]. Using cell culture experiments, Sathyan et al. identified the following miRNAs as being alcohol-sensitive: (1) miR-21, (2) miR-335, (3) miR-9, and (4) miR-153. Alcohol significantly suppressed the expression of these four miRNAs. Wang also showed that chronic alcohol consumption decreased miR-9 expression, which is markedly increased in the cells exposed to MA compared to the controls. Later, they found that miR-9 binds to the calcium-activated channel subfamily M alpha member 1 (KCNMA1) and negatively regulates its expression. Their results suggest that elevated miR-9 expression, which is induced by MA, leads to the suppression of KCNMA1. As previous studies have reported, KCNMA1 may affect neurotransmitter release in dopaminergic neurons.

Amphetamines

Researchers found consistent up-regulation of the miR-29a/b and miR-182/183 clusters in most brain regions when mice were exposed to 5 mg/kg amphetamine for 5 days. Additionally, miR-181a is strongly enriched in the nucleus accumbens, suggesting that miR-181a might regulate the expression of synaptic proteins at this specific site [21]. There is only one study that focuses on miRNA expression in methamphetamine (MA) abusers [34]. By screening MA abuser and control frontal cortex autopsy tissues, the authors found that miR-9 expression was significantly increased in MA abusers. To verify this result, SH-SY5Y cells were exposed to MA. Based on the q-PCR results, it is worth noting that miR-9 expression was remarkably increased in the cells exposed to MA compared to the controls. Later, they found that miR-9 binds to the calcium-activated channel subfamily M alpha member 1 (KCNMA1) and negatively regulates its expression. Their results suggest that elevated miR-9 expression, which is induced by MA, leads to the suppression of KCNMA1. As previous studies have reported, KCNMA1 may affect neurotransmitter release in dopaminergic neurons.

Alcohol

In addition to cocaine and other psychomotor stimulants, chronic alcohol abuse has also been shown to regulate miRNA expression. A particularly intriguing example for the role of miRNAs in chronic alcohol abuse comes from a study by Sathyan et al. [35]. Using cell culture experiments, Sathyan et al. identified the following miRNAs as being alcohol-sensitive: (1) miR-21, (2) miR-335, (3) miR-9, and (4) miR-153. Alcohol significantly suppressed the expression of these four miRNAs. Wang also showed that chronic alcohol consumption decreased miR-382 expression in the accumbens of rats [36]. They showed that miR-382 negatively regulates dopamine D1 receptor expression, which plays an important role in the reward system. Another study showed that chronic alcohol intake decreased miR-124a expression in the dorsolateral striatum of rats and that the over expression of miR-124a decreased alcohol-induced CPP and reduced alcohol consumption behaviours in rats [37]. Using a neuronal model, chronic alcohol exposure suppressed miR-29b expression and
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Promoted neuronal apoptosis. When miR-29b was over expressed in the neuronal model, it protected the neurons against apoptosis [38]. When abstinence was examined in alcohol-addicted rodents and cells, withdrawal caused dynamic molecular and cellular changes. Mizuo et al. found that the miR-124 levels were reduced in the limbic forebrain following alcohol withdrawal [39].

In contrast to the studies mentioned above, chronic alcohol use has also been shown to elevate the levels of specific miRNAs, including miR-9, miR-124, miR-181a, and miR-155. Pietrzykowski et al. exposed rats to chronic intermittent amounts of alcohol and observed an increase in miR-9 expression. Up-regulation of miR-9 led to the degradation of BK splice variants [40]. Similarly, Tapocik et al. and Dong et al. have shown that escalating levels of alcohol intake can increase the expression of miR-206 and miR-124, respectively [41, 42]. It should be noted that miR-206 negatively regulates the expression of brain-derived neurotrophic factor (BDNF), which is deemed to play a vital role in the motivational effects of alcohol and other addictive drugs [43]. Asquith revealed that chronic alcohol dependence up-regulated miR-181a and miR-221 in the peripheral blood mononuclear cell (PBMC) and miR-155 in the colon of rats [44].

In addition to identifying changes in the miRNA levels after alcohol treatment in animal models and cell lines, Lefkow analysed post-mortem brains from 14 alcoholics and 13 matched healthy controls. Approximately 35 miRNAs were markedly up-regulated in the alcoholics compared to the controls [45]. Notably, miR-146a, which is associated with immunity disorders, was up-regulated in the frontal cortex of alcoholics [46].

Altogether, the examined studies illustrate that miRNA-mediated gene regulation plays a critical role in the complicated interactions involved in chronic exposure to addictive drugs. We hypothesize that chronic drug abuse leads to the aberrant expression of several miRNAs. These aberrantly expressed miRNAs influence innate and adaptive immunity, specifically the differentiation and function of T and B cells, by down-regulating the expression of the miRNA target genes.

miRNAs in immunity

The human body has two main defence systems against foreign invaders, the innate and adaptive immune systems. The innate immune system, also known as the non-specific immune system, is a natural immune defence system, which was formed during the development and evolution of the body, that has nonspecific defence functions immediately after birth. The following are types of innate immune cells: (1) phagocytes, (2) dendritic cells (DCs), (3) NK cells, (4) NKT cells. In contrast, the adaptive immune system, also called the acquired immune system, is developed through asymptomatic infection or artificial inoculation and prepares the body to fight infection. T and B lymphocytes are essential to the adaptive immune system.

Generally, miRNAs can affect immune system function in two ways. miRNAs can control differentiation of innate and adaptive immune responses in the mammalian immune system. In the bone marrow and thymus, miRNAs are involved in cell function and differentiation, specifically for T and B lymphocytes.

miRNAs in innate immunity

The innate immune system is characterized by rapid responses to pathogens. Emerging data have identified the important contribution of miRNAs to the development and function of innate immune cells. Among the miRNAs that influence the innate immune system, miR-146a, miR-155, and miR-132 have been the most intensively studied.

miR-146a is located on chromosomes 5 and extensively expressed in the hematopoietic system. Tanganov first reported that miR-146a might be involved in the innate immune response [46]. miR-146a is an NF-kB-dependent miRNA that targets the NF-kB pathway, which is the central pathway in innate immunity. Studies reported that miR-146a directly targets and represses several downstream signalling molecules, including IL-1 receptor associated kinase 1 (IRAK1), IL-1 receptor associated kinase 2 (IRAK2), and TNF receptor-associated factor 6 (TRAF6) [47]. Both of these genes encode key adaptors molecules downstream of Toll-like and cytokine receptors. Chassin demonstrated that miR-146a repressed IRAK1, and induced intestinal epithelial innate immune tolerance which will be protected neonates from bacteria-induced epithelial damage [48]. Based on the results of Sjögren’s syndrome patients and mouse model, Pauley revealed miR-146a had a role in increasing phagocytic activity and suppress inflammatory cytokine production in human mononcytic THP-1 cells [49]. With tissue culture and in vivo experiments, Rebane demonstrated that miR-146a-mediated repression in allergic skin inflammation occurs partially through direct targeting IRAK1 [50].

miR-155 is another key miRNA that plays a role in the innate immune system [51, 52]. miR-155 has been shown to greatly influence macrophage and DC functions [53,54]. In macrophages, a number of stimuli, such as chronic alcohol abuse, enhance miR-155 expression via NF-kB; miR-155 is involved in macrophage polarization and the regulation of apoptosis [55]. From Wang’s research, the expression of miR-155 was markedly up-regulated in macrophages infected with vesicular stomatitis virus. In subsequent studies, scientists demonstrated that miR-155 positively regulates the host antiviral innate immune response through its target suppressor of cytokine signalling 1 (SOCS1) [56, 57]. When mouse macrophages were exposed to lipopolysaccharide (LPS), the expression of miR-
miRNAs in adaptive immunity

The adaptive immune system mainly consists of T and B lymphocytes. miRNAs are emerging as critical regulators in the development and function of the adaptive immunity system. The contribution of specific miRNAs, such as miR-181a, miR-155, and miR-146, to the adaptive immune response is remarkable during the differentiation and functional processing of T and B lymphocytes.

miR-181a is widely expressed during the T cell differentiation process. This miRNA specifically modulates T cell antigen receptor (TCR) response [66]. Li and colleagues indicated that enhanced expression of miR-181a augmented the sensitivity to peptide antigens in mature T cells, and vice versa [67]. When inhibited miR-181a level reduced sensitivity, and then impairs both positive and negative selection of T cells. Interestingly, in immature T cells, higher miR-181a level means greater T cell sensitivity. Based on the results, we concluded that miR-181a acts as a regulator of T cell antigen sensitivity. Similar to this research results, another group found that decline in miR-181a expression impaired T cell receptor sensitivity, respectively [68].

Another miRNA, miR-155, is also widely expressed in immune cells [69]. There are reports that miR-155 is involved in disparate facets of the adaptive immune system [70]. In a study of miR-155 deficiency mice, the generation of pathogenic autoreactive T cells was greatly reduced compared with controls [71]. In the hematopoietic system, miR-155 promotes the development of manifold T cells, such as the T helper 17 (Th17) cell and Th1 cell subsets [72]. In addition, according to studies by Rodriguez et al. and Thai et al., miR-155 is essential for Th2 differentiation [73, 74]. The above results support miR-155 as having a critical role in the inflammatory response pathway. Notably, miR-155 is also associated with regulatory T (Treg) cell function. Indeed, miR-155 sustains Treg cell proliferation and homeostasis and down-regulates suppressor of cytokine signalling 1 (SOCS1) [56, 75, 76]. Therefore, miR-155 appears to regulate T cell (and B cell, see below) differentiation and function.

Additional Treg function to regulate microRNA is provided by miR-146a. miR-146a is low in naive human T cells, but is enhanced expression in human memory T cells [77]. Results from miR-146a-deficient mice showed an increase in the percentage of INFγ-producing T-cell subset with absence of miR-146a [78]. More importantly, Lu’s group reported that miR-146a is critical for Treg suppressor functions among the miRNAs prevalently expressed in Treg cells. miR-146a targets signal transducer and activator transcription 1 (Stat1) in Treg cells. Abrerrant expression of this miRNA enhances Stat1 expression and activation. Abrerrant expression of miR-146a also breaks down immunological tolerance, which has been shown to manifest as fatal IFNγ-dependent immune-mediated lesions [46, 79].

A number of miRNAs, including miR-181, miR-150, and miR-34a, have been reported to control B lymphocyte differentiation, from pre-B to mature-B, and the function of mature B lymphocytes. miR-150 expression is enhanced in the lymph nodes and spleen during T and B cell maturation [80]. Zhou et al. illustrated that abnormal miR-150 expression in hematopoietic stem cells deeply impaired the formation of mature B cells [81]. Chen et al. found that miR-181 was expressed in mouse marrow and that abnormal miR-181 expression led to an increased fraction of B lymphocytes in adult mice [82]. Recently, miR-34a has been shown to regulate B cell development in murine bone marrow [83]. A study by Rao showed that miR-34a
blocked the transition from pro-B cell to pre-B cell and reduced the maturation rate of B cells by targeting Foxp1. miR-155 regulates the activation and function of B cells [84]. Chronic lymphocytic leukemia (CLL) cells with enhanced miR-155 expression silenced Src homology 2 domains containing inositol polyphosphate phosphatase 1 (SHIP-1) protein, which activated in response to B-cell receptor (BCR) ligation [85]. Conversely, transfection of miR-155 inhibitor to CLL cells had the opposite effects. Based on ectopic miR-155 expression transgenic mouse model, Sandhu indicated that miR-155 can targets histone deacetylase 4 (HDAC4) and impairs transcriptional activity of B-cell lymphoma 6 (BCL6) [86]. miR-155 has been shown to target the transcription factors PU.1 and AID, which are regulators of Ig diversification [87]. Another study demonstrated that miR-181b directly targeted AID [88]. In other words, miR-155 and miR-181b regulate the activation of B cells by specifically targeting the transcription factor AID. In summary, the above-mentioned studies show that specific miRNAs are critical for the development of a function of B cells. These miRNAs bind to key target genes that are mainly involved in transcriptional regulation and cell death pathways.

Conclusions

There is an elevated incidence of immune diseases in drug abusers. The role of miRNA in the immune system and drug abuse represents a rapidly developing area of research. The function of most miRNAs in relation to drug abuse and immune diseases is still not clearly understood. Most of the studies detected abnormal miRNA expression in chronic drug abuse and aberrant miRNA expression that affected the immune system. Unfortunately, the molecular mechanisms regarding how drug abuse changes miRNA expression levels and leads to immune system diseases is poorly understood. We aim to develop additional studies to understand the specific mechanisms. When we clearly understand the mechanisms, miRNAs can be used as potential non-invasive biomarkers with therapeutic aims to treat the immunity diseases of drug abusers.

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