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# The role of miRNAs in cytokine signaling

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## 1. ABSTRACT

This review explores the relationship between cytokines and microRNAs (miRNAs). In particular, the regulation of miRNAs by pro-inflammatory cytokines, anti-inflammatory cytokines, interferons and transforming growth factor beta are examined, highlighting how miRNAs can mediate some of the known functions of these cytokines, as well as identifying novel gene targets, mechanisms and cross-talk between pathways.

## 2. INTRODUCTION

Cytokines play an important physiological role in the cell, communicating pathogen invasion, facilitating pathogen clearance and wound healing, or simply modulating homeostasis of the cell. Much effort has been placed into understanding the individual effects of cytokines, through analysis of transcription factor activation and subsequent gene induction, with the aim of manipulating these findings into therapeutics for both inflammatory disorders and cancer. Accumulating evidence suggests that cytokines can also regulate microRNAs (miRNAs), revealing some exciting and novel aspects of cytokine signaling that have previously remained uncharacterized.

The discovery of miRNAs has opened a new field of molecular biology. Briefly, mature miRNAs are small ~22 nucleotide RNA sequences. They are initially transcribed as primary transcripts from the introns of protein-coding genes or the exons of non-coding genes by the RNA polymerase II or RNA polymerase III (1). These transcripts are sequentially processed into shorter precursor transcripts in the nucleus by the enzyme Drosha and further processed into their mature form by the enzyme Dicer in the cytoplasm (1). Formation of an RNA-induced silencing complex (RISC) composed of Dicer and other RNA-binding proteins such as argonaute, ensures that the mature miRNA is successfully guided to the 3' untranslated region (UTR) of protein-coding target mRNA sequences (1). Partial or exact complementary base-pairing of the miRNA results in respective degradation or translational inhibition of the target protein-coding mRNA (2). miRNAs therefore act as fine-tuners or modulators of gene expression. To date, over 900 human miRNAs are thought to exist where each miRNA is predicted to target up to 200 mRNA sequences (3). Specificity of miRNA targets appears to be dependent on the co-expression of miRNAs and their mRNA target transcripts in specific cell types and tissues, but also dependent on the basal expression of miRNAs or

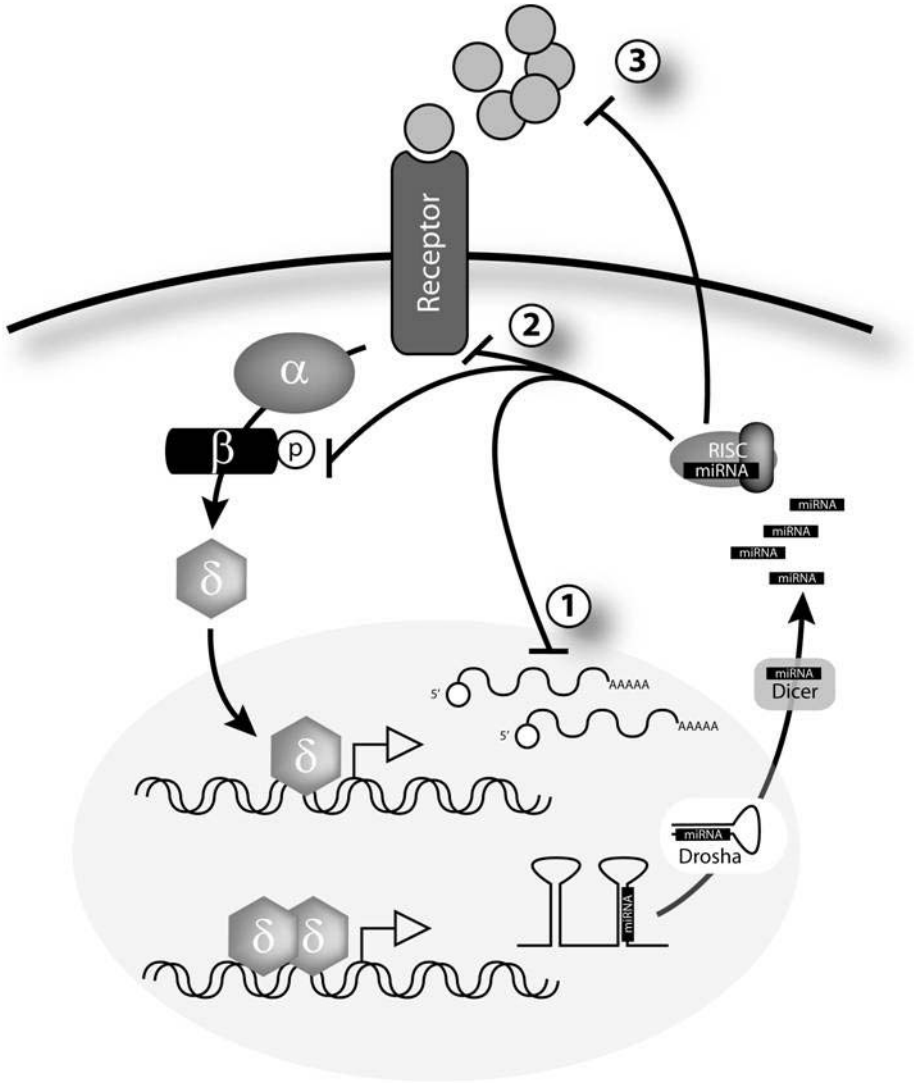


**Figure 1.** Cytokine binding to cytokine receptors initiates signaling cascades that lead to the transcription of target genes and miRNAs. miRNA primary transcripts are processed by Drosha and Dicer to form mature miRNAs that associate with the RISC complex where they are guided to the 3'UTR of target mRNA sequences, resulting in degradation, translational inhibition and/or destabilization. The predicted functional outcome of cytokine-induced miRNAs is depicted where miRNAs can modulate 1) known and novel target genes, 2) cytokine signaling components and receptors, 3) cytokine expression.

transient induction in response to cellular processes (4). Their importance is further highlighted by amounting evidence demonstrating a role for miRNAs in disease progression (5). For these reasons, much effort has been placed on understanding how miRNAs are regulated and function within the cell.

In this review, the regulation of miRNAs by pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF), the anti-inflammatory cytokine IL-10, anti-viral cytokines such as interferons (IFN) and the regulatory cytokine transforming growth factor beta (TGF-beta) are examined. In particular, these cytokines regulate the transcriptional induction of miRNAs that appear to play key roles in eliciting cytokine function. The reciprocal effect is also highlighted where miRNAs can modulate cytokine signalling (Figure 1). In addition, miRNAs have provided a new link between inflammation and cancer. The observation that viruses can also encode miRNAs to modulate cytokine expression further highlights the importance of miRNAs in cytokine signalling.

## 3. CYTOKINE REGULATION OF miRNA

### 3.1. Interleukin-1

The innate immune response is one of the host's first lines of defense against invading pathogens. Pattern recognition receptors, expressed on immune surveillance cells, can recognize specific pathogenic moieties, resulting in the initiation of signaling cascades and the induction of cytokines that are required to fight the infection. One of the first cytokines to be secreted is IL-1, which acts on

**Table 1.** miRNAs regulated by cytokines, their targets and biological response

| Cytokine | miRNA | Target | Biological response of miRNA/target gene | Ref |
|---|---|---|---|---|
| IL-1 | miR-146 | IRAK1,TRAF6 | Inhibit IL-1 response | 8-10 |
| | miR-155 | TAB2 | Inhibit IL-1 response | 11, 12 |
| | miR-9 | NF-kappaB | Inhibit IL-1 response | 13, 14 |
| TNF | miR-146 | Not known | Not known | 8 |
| | miR-155 | FADD, TNF* | Inhibit apoptosis, TNF stabilization | 15, 18 |
| | miR-16, miR-221 | TNF | TNF destabilization | 23, 25 |
| | miR-369-3 | TNF | TNF stabilization | 26 |
| IL-6 | miR-21 | Bim*, Casp-3* | Cell-mediated survival | 31-33 |
| | Let-7 family | NF2, IL-6 | Cell-mediated survival, modulation of IL-6 | 32, 38 |
| | miR-370 | Tpl-2 | Cell-mediated survival | 39 |
| | miR-148a, miR-152 | DMT-1 | Cell-mediated survival | 40 |
| | miR-17/92 | SOCS1, BMPR2 | Modulation of IL-6 and TGF-beta signaling | 41, 42 |
| IL-10 | miR-155 | SHIP1 | Anti-inflammatory response | 46 |
| | miR-106a, miR-466l | IL-10 | IL-10 stabilization | 50, 51 |
| IFN-alpha/beta | miR-122 | HCV | Reduce HCV replication | 55, 56 |
| | miR-21 | Not known | Suppression of cell growth | 57 |
| IFN-gamma | miR-513, miR-221 | B7-H1, ICAM-1 | Inflammatory regulation | 58 |
| TGF-beta | miR-155 | RhoA | Induces EMT | 65 |
| | miR-21 | TGF-beta RII | Induces EMT, modulation of TGF-beta | 66, 74 |
| | miR-23 | Smad3 | Induces EMT, modulation of TGF-beta | 68, 72 |
| | miR-181 | TIMP3 | Induces EMT | 69 |
| | miR-200 family | ZEB1, SIP1 | Modulation of TGF-beta signaling | 70 |
| | miR-216a, miR-217 | PTEN | Modulation of TGF-beta signaling | 71 |
| | miR-106b cluster | E2F1 | Inhibition of TGF-beta induced genes | 75 |

Direct and indirect* targets are listed if known, as well as the biological response mediated by the miRNA or its target gene.

surrounding endothelial cells and fibroblasts, causing them to release cytokines, chemokines, adhesion molecules and matrix metalloproteinases, which provide a stimulus for mononuclear infiltration to the area (6).

IL-1 signaling through the IL-1 receptor involves recruitment of adaptor molecules and IRAK kinases, which phosphorylate and dissociate to interact with TRAF6. TRAF6 leads to activation of the TAB2 complex, which through a series of events leads to activation of NF-kappaB and MAPK signaling cascades, which are required for the induction of IL-1-responsive genes. However, it is of equal importance that IL-1 signaling is switched off, as IL-1 exacerbation has been associated with numerous diseases such as sepsis, gout, rheumatoid arthritis and Alzheimer's disease (7). This is achieved through IL-1 receptor antagonist binding or induction of the cytoplasmic protein A20 (7). However, it is becoming increasingly clear that IL-1 induction of miRNA may also play a role in switching off the IL-1-mediated inflammatory response (Table 1).

The first example of miRNA induction by IL-1 was demonstrated in the human monocytic leukemia cell line THP1 when miR-146a and miR-146b were induced by IL-1beta in an NF-kappaB-dependent manner (8). The induction of miR-146a was shown to target and repress two upstream components of IL-1 signaling, IRAK1 and TRAF6, thereby creating a negative feed-back loop by acting to switch off or 'fine-tune' the pro-inflammatory response. This was corroborated by later studies, which showed that over-expression of miR-146 could reduce the expression of IL-1-induced inflammatory cytokines in both epithelial and primary fibroblasts cells (9, 10). Although this effect did not appear to be controled by the targeted regulation of IRAK1 and TRAF6 in epithelial cells, IRAK1 was shown to be down-regulated in fibroblasts, concluding that the negative regulation of IRAK1 and TRAF6 by miR-146 may be cell-type dependent (9, 10).

Induction of miR-155 and miR-9 has also been shown to modulate IL-1 signaling (11-13). For example, in an mRNA microarray screen where miR-155 was inhibited in dendritic cells, several components of the IL-1 signaling pathway were up-regulated, including IL-1 itself, caspase-1, Pellino and TAB2, the latter being experimentally confirmed as a direct target for miR-155 (11). Furthermore, enforced expression of miR-155 in rheumatoid arthritis synovial fibroblasts could block the production of IL-1-induced matrix metalloproteinase 3 (12). Induction of miR-9 in human polymorphonuclear neutrophils and monocytes was shown to target the p50 subunit of NF-kappaB (13) and over-expression of miR-9 in human primary chondrocytes could decrease IL-1-induced TNF-alpha and matrix metalloprotease 13 secretion (14). Taken together, it appears that the IL-1 induction of miRNAs plays an important role in its negative regulation and highlights how manipulation of miRNAs could present new avenues for the therapy of IL-1-associated diseases.

It must be pointed out that Toll-like receptors (TLR), a family of receptors related to the IL-1 superfamily can also induce miR-146a, miR-155 and miR-9, where they appear to have a similar regulatory function (8, 13, 15). However, the induction and function of TLR-mediated miRNA induction is well reviewed elsewhere and will not be covered here (16).

### 3.2. Tumor necrosis factor

TNF is another early response pro-inflammatory cytokine and is one of the principal mediators of the inflammatory response. This occurs via recruitment of adaptor molecules and TRAF2 activation, leading to NF-kappaB and MAPK activation resulting in cytokine production and induction of adhesion and inflammatory molecules. Elevated TNF is associated with many inflammatory disorders similar to those associated with IL-1, such as rheumatoid arthritis, inflammatory bowel disease and psoriasis. TNF can also induce apoptosis through recruitment of the adaptor molecule FADD and subsequent caspase activation (17). TNF can induce a sub-set of miRNAs and current evidence suggests that miRNAs play a role in mediating TNF mRNA stabilization (Table 1).

Similar to IL-1, TNF can induce miR-146 and miR-155 (8, 12, 15, 18). A role for TNF-induced miR-146 has yet to be elucidated, however miR-155 has been shown to target FADD, suggesting a negative feed-back mechanism for TNF-induced apoptosis (18). miR-155 appears to play a role in TNF stabilization, which was first demonstrated when miR-155-deficient B cells failed to produce TNF (19), followed later by *in vitro* studies demonstrating a role for miR-155 in TNF stabilization in HEK293 cells (18). Although an exact mechanism has yet to be elucidated, RNA-binding proteins may be playing a role (discussed next). In this last study, TNF was shown to contain a binding site for miR-125b in its 3'UTR. Given that miR-125b was down-regulated in response to TNF (18), this data highlights mechanisms whereby TNF can positively influence its own expression through induction of miR-155 and down-regulation of miR-125b.

Accumulating evidence suggests that miRNA may act in concert with other RNA-binding proteins to mediate the stability of mRNA. Recruitment of RNA-binding proteins such as tristetraprolin (TTP) and fragile-X-mental-retardation-related protein 1 (FXR1) to an adenosine/uridine-rich region (ARE) located within the 3'UTR of TNF, results in TNF mRNA destabilization or stabilization, respectively (20-22). For example, it was demonstrated that miR-16, a miRNA complementary to the ARE sequence, requires association with TTP in order to mediate TNF destabilization (23). Interestingly, miR-16 was labeled as a master regulator of miRNA-induced instability, where 217 of its predicted 801 targets contain ARE sequences within their 3'UTR (24). Similarly, induction of miR-221 in LPS-tolerized cells, was found to associate with TTP, resulting in TNF destabilization (25). The reverse effect was observed in serum-starved cells, where induction of miR-369-3, which bound directly to the TNF-ARE, could mediate TNF stabilization and translational activation (26). This effect was dependent on the recruitment of FXR1, which had already been shown to play a role in TNF stabilization (22) and suggests a similar mechanism may be at play for miR-155. Collectively this data highlights a fine-tuned interplay between miRNA and RNA-binding proteins, highlighting a novel and interesting aspect to miRNA biology as well as suggesting that other mRNA sequences with ARE may be regulated by a similar mechanism.

### 3.3. Interleukin-6

IL-6, also induced early in the innate immune response, plays a prominent role in regulating survival, differentiation and growth of infiltrating monocytes, as well as directing and influencing T and B cell function. Thus IL-6 appears to direct the transition from innate to acquired immunity. IL-6 initiates two arms of signaling, activation of JAK-STAT pathways as well as activation of MAPK and Akt cascades (27). Elevated IL-6 and/or dysregulation of IL-6 signaling components such as STAT3 have been associated with inflammatory disorders such as systemic lupus erythematosus and rheumatoid arthritis, as well as the progression of cancers including multiple myeloma, breast, prostate and cholangiocarcinoma (28-30). Recent evidence suggests a role for miRNAs in IL-6-mediated cell survival and IL-6 signaling modulation (Table 1).

miR-21 up-regulation was first identified in malignant myeloma, hepatocellular and cholinangiocyte cells that over-express IL-6 (31, 32). Further studies verified that in response to IL-6, STAT3 was recruited to the miR-21 promoter causing induction of the miR-21 primary transcript (31). Interestingly, over-expression of miR-21 in the absence of IL-6 could elicit some of the survival effects characterized by IL-6 (33). For example, injection of miR-21 into mouse embryonic blastocysts resulted in an indirect up-regulation of anti-apoptotic Bim and down-regulation of pro-apoptotic Caspase-3, two well known IL-6-induced genes (33). In addition, over-expression of miR-21 has been associated with cancers similar to those associated with elevated IL-6 signaling (34). It is possible that two tumor suppressors that are direct targets for miR-21, programmed cell death protein-4 and tension homologue deleted on chromosome 10, may be responsible for some of the IL-6-miR-21-associated cancers (34).

Up-regulation of let-7 miRNA family members were also identified in malignant cholinangiocytes stably over-expressing IL-6 (32). Further analysis experimentally validated neurofibromatosis 2 (NF2), a tumor suppressor and known modulator of STAT3 as a target for the let-7a family member (32). Over-expression of the let-7a precursor resulted in a decrease in NF2 protein expression and a concomitant increase in STAT3 phosphorylation, highlighting how excessive let-7a expression may contribute to IL-6 survival signals through persistent activation of STAT3 (32). On the contrary, low let-7 levels have been demonstrated in other cancer models such as lung, Burkitt lymphoma and breast cancer (35-38). In the latter, it was demonstrated that persistent NF-kappaB activation, a characteristic of immortalized MCF-10 breast cells, resulted in induction of the miRNA processor Lin28, a potent inhibitor of all let-7 family members. As IL-6 itself has been shown to be a specific target for let-7a (38), the repression of let-7a by Lin28 results in increased IL-6 expression contributing to the cellular transformation of MCF-10 cells. Furthermore, over-expression of combined let-7 members could block the cellular transformation of MCF-10 cells (38). The regulation of let-7a may therefore be cell-type specific or dependent on components from other signaling pathways besides IL-6.

Down-regulation of miR-370, miR-148a and miR-152 also appear to play a role in IL-6-mediated survival. Down-regulation of miR-370 was shown to result in an increase in the target Tpl-2, an upstream kinase for p38 MAPK, thus contributing to the progression of genes involved in pro-survival (39, 40), whereas overexpression of miR-148a and miR-152 precursors could decrease proliferation of various cholaniocarcinoma cell lines (40).

IL-6 may also modulate its own signaling pathway via induction of the miR-17/92 cluster. SOCS1, a known negative suppressor of the IL-6 pathway, was identified as a target for miR-17/92 (41). Inhibition of miR-17/92 rescued SOCS1 expression and decreased constitutive STAT3 phosphorylation in multiple myeloma cell lines (41). Interestingly, 13 out of 15 multiple myeloma cell lines that showed high miR-17/92 expression also had an absence of SOCS1 protein expression, allowing IL-6-mediated survival signals to continue (41). BMPR2, a receptor that belongs to the TGF-beta family, was also identified as a target for miR-17/92 and implicates a novel role for IL-6 in the regulation of TGF-beta signaling (42). Taken together, this data illustrates how miRNAs can contribute to IL-6-mediated cell survival and provides novel insights into the mechanism through which constitutive IL-6 and STAT3 expression contribute to cancer. It also demonstrates how manipulation of miRNA expression through over-expression or repression is sufficient to elicit a response independent of the original signal emphasising an important function in miRNA biology.

### 3.4. Interleukin-10

IL-10 is an anti-inflammatory cytokine that is crucial for dampening the inflammatory response after pathogen invasion. One particular mechanism of action is to down-regulate pro-inflammatory genes such as those encoding IL-1, TNF and IL-6. This is accomplished when IL-10 signals through the JAK1-STAT3 pathway, resulting in the induction of STAT3-responsive genes, the as-yet unknown products of which are responsible for the inhibition of these pro-inflammatory genes (43). The clinical use of IL-10 in inflammatory disorders such as Crohn's disease, rheumatoid arthritis and psorisias has been investigated, with unsuccessful outcomes (44). This is most likely due to that fact that IL-10 is a particularly pluripotent cytokine, which plays a role in regulating T cell subsets as well as positively regulating B cell function (45). Therefore, a role for IL-10 in miRNA regulation may aid some of the unanswered questions in the IL-10 field (Table 1).

We have recently shown a role for IL-10 in miRNA regulation and demonstrated that IL-10 inhibited the induction of miR-155 downstream of TLR4 stimulation in primary macrophages (46). This is particularly relevant considering miR-155 appears to play a pro-inflammatory role in macrophages, where its induction stabilizes TNF and results in the suppression of targets SHIP1 and SOCS1, two negative regulators of cytokine signaling pathways (18-19, 46-50). Furthermore, the IL-10-mediated inhibition of miR-155 led to an increase in SHIP1 expression, supporting the role of IL-10 as an anti-inflammatory mediator, as well as identifying a novel gene target for IL-10 (46). Further work will be required to investigate whether IL-10 can have a similar effect on miR-155 in other cell types and other miR-155 targets.

miRNAs can also regulate IL-10 stabilization, where over-expression of miR-106a, an miRNA with a binding site within the 3'UTR of IL-10, led to a repression of IL-10 expression (51). Conversely, induction of miR-466l was shown to competitively bind to the ARE located in the 3'UTR of IL-10, blocking TTP binding and protecting IL-10 from destabilization (52).

### 3.5. Interferons

Interferons (IFN) are cytokines that play a key role in host defense against viral invasion. To date, there are three sub-groups of IFN (type I, II and III) that signal by binding to their respective IFN receptors, resulting in association of JAK kinases and subsequent phosphorylation, dimerization and translocation of STAT transcription factors to the nucleus where they initiate transcription of specific IFN-stimulated genes. Type I IFN such as IFN-alpha and IFN-beta, secreted by dendritic cells and macrophages, stimulate induction of genes required for the anti-viral response, whereas IFN-gamma, a type II IFN, is the signature cytokine secreted by CD4+ Th1 cells and natural killer cells, and aids in the anti-viral response as well as promoting Th1 differentiation and macrophage antigen presentation. Although less is known about the type III IFNs, type I IFNs are therapeutically used for the treatment of viral infection, in particular hepatitis C virus (HCV) infection (53).

IFN regulation of miRNA may play a role in its anti-viral and therapeutic potential against HCV infection (Table 1). For example, miR-122, an miRNA highly expressed in the liver, was shown to facilitate HCV replication in liver cells and suggests that inhibition of miR-122 may be useful as a therapeutic tool (54). This finding was later tested *in vivo*, where inhibition of miR-122 in the liver of chimpanzees resulted in a long-lasting suppression of HCV (55). In one study using Huh7 liver cells, IFN-beta was shown to down-regulate miR-122 as well as up-regulating others, suggesting that miRNA modulation by IFN-beta may contribute to its anti-viral effect (56). However, pegylated IFN-alpha, used for the treatment of HCV infection, failed to reduce miR-122 in liver biopsies taken from treated patients and implicates a differential role for IFN-alpha and IFN-beta in miR-122 regulation (57). In addition, they failed to show a correlation between miR-122 and viral load in chronic HCV liver biopsies which questions the role of miR-122 in HCV replication (57). IFN-beta has also been found to reduce the transcriptional induction of miR-21 in a STAT3-dependent manner, suppressing the growth of glioma cells (58). This highlights a novel mechanism of negative regulation for miR-21, an miRNA implicated in inflammation and cancer (34).

In an effort to identify miRNAs induced by IFN-gamma, an miRNA array was performed on immortalized

human cholangiocytes. The majority of the miRNAs identified were down-regulated rather than induced (59). Of particular interest were miR-513 and miR-221, which target molecule B7-H1 and ICAM-1, proteins that play important roles in regulating inflammation in the liver (59). Up-regulation of these proteins could contribute to liver-associated inflammatory disorders and would be particularly relevant in the case of HIV disease progression, which is often associated with elevated B7-H1 expression (59). Regulation of IFN-gamma may be mediated by miR-155 where the IFN-gamma receptor was identified as its target in differentiating Th1 cells (60). Further work will be required to fully appreciate the role of IFN in miRNA regulation which will aid our knowledge of IFN signaling, functioning and therapeutic potential. It is interesting that bioinformatic analysis of the 3'UTR of STAT signaling components shows that they are heavily targeted by miRNAs, highlighting potential mechanisms for miRNAs in the regulation of IFN signaling (24).

### 3.6. Transforming growth factor beta

TGF-beta is a regulatory cytokine that controls cellular processes such as proliferation and differentiation, as well as playing a role in homeostatis and immunity. TGF-beta can induce Smad and non-Smad signaling pathways, such as MAPK and Akt cascades. In most instances, TGF-beta signaling will promote an anti-proliferative response by inducing cell-cycle check-point genes, as well as genes that can promote apoptosis. For this reason, TGF-beta has also been referred to as a tumor suppressor and many types of cancer have mutations in components of the TGF-beta pathway (61). However, increasingly TGF-beta has been shown to act as a tumor promoter and in fact, many types of cancers such as breast, prostate and colorectal are hallmarked by high levels of TGF-beta expression (62-64). In addition, TGF-beta is one of the major inducers of epithelial-mesenchymal transition (EMT), a critical step in the conversion of primary tumors to metastastic tumors (65). There is a strong indication that some functional aspects of TGF-beta are mediated by miRNAs (Table 1).

For example, TGF-beta induction of miR-155, miR-21, miR-23a and miR-181a, plus down-regulation of miR-200, have all been shown to play a role in TGF-beta - induced EMT. miR-155 and miR-21 were both up-regulated in a TGF-beta-induced model of EMT in murine mammory gland epithelial cells (66). Over-expression of miR-155 alone doubled the progression of TGF-beta-induced EMT, due to the repression of the miR-155 target RhoA, inhibiting its ability to maintain tight junction formation (66). This correlates with findings that miR-155 and miR-21 have both been found elevated in breast cancer tissues (66-68). Similarily, over-expression of TGF-beta-induced miRNA, miR-23a and miR-181b, could increase proliferation, survival and migration of hepatocellular carcinoma cells, another characteristic of EMT (69, 70). Furthermore, depletion of miR-181b could inhibit tumor formation of hepatocellular carcinoma cells when introduced into nude mice (70). Down-regulation of miR-200 family members were identified in a TGF-beta-induced EMT model in kidney epithelial cells and their over-expression was sufficient to prevent a TGF-beta-induced mesenchymal morphology (71), again highlighting the therapeutic potential of miRNA manipulation.

Modulation of TGF-beta signaling can also be mediated by miRNA. For example, TGF-beta induction of miR-216a and miR-217 were shown to target PTEN, an inhibitor of Akt activation, resulting in the propagation of the Akt signal and increased survival of glomerular mesangial cells (72). Bioinfomatic analysis also suggests that Smad signaling components are regulated by miRNA (24). Indeed, Smad3 was shown to be a direct target of the miR-23b cluster and miR-140 (73, 74). The TGF-beta receptor II was shown to be a direct target of miR-21 in adipose tissue-derived mesenchymal cells (75). In addition, many miRNAs can repress downstream TGF-beta effector genes. For example, the miR-106b cluster could inhibit E2F1 activity, resulting in reduced expression of TGF-beta genes such as p21, an inhibitor of the cell cycle as well as Bim, a pro-apoptotic gene, providing potential mechanisms as to why up-regulation of miR-106b-25 and inactivation of the TGF-beta signaling pathway are found in gastric cancer (76).

Another interesting aspect of TGF-beta signaling is the recent report that Smad proteins play a role in the actual biogenesis of miRNAs rather than the transcriptional induction. Smad1, Smad3 and Smad5 were shown to interact with the RNA helicase p68, a critical subunit of the Drosha microprocessor complex (77). siRNA targeted against p68 abolished TGF-beta induction of mature miR-21 transcripts. This mechanism is specific for miRNAs induced by TGF-beta and is synonymous with the NF-kappaB induction of Lin28, a microprocessing factor that down-regulates expression of let-7 family members (38). It highlights the hidden complexity of miRNA induction and regulation of targets by cytokines and suggests that similar mechanisms may exist for other cytokine signaling components.

## 4. IMPLICATIONS IN DISEASE

An accepted concept of thought is that inflammation and the progression of cancer are intimately linked. Infection and chronic inflammation contribute to about 1 in 4 of all cancer cases. For example, individuals with inflammatory bowel diseases are pre-disposed to colon cancers, chronic HCV infection predisposes to liver cancer and Epstein Barr virus (EBV) infection can cause B cell lymphomas, whereas chronic infection with the gram-negative bacteria *Helicobacter pylori* is the world's leading cause of gastric cancer. Therefore, the induction of miRNAs by cytokines and the observation that miRNAs are over-expressed in both inflammatory disorders and cancers highlights that miRNAs are an important link mediating these two diseases. This is particulary evident for IL-6 and TGF-beta, which have both been shown to induce miRNAs that play a prominent role in cell-mediated survival and cell transformation.

Perhaps more remarkable, is the discovery that viruses, in particular the herpesvirus family, can express

viral miRNA (v-miRNA) that repress cellular targets involved in the host's immune response, enhancing their survival and replication in the cell (78). EBV was the first virus shown to express v-miRNA, where predicted cellular targets include cell cycle regulators, cytokines and chemokines, as well as signaling components specific to B cell function (79). For example, EBV-miR-BART2 and EBV-miR-BHRF1 have been shown to target the T cell chemokine attractant CXCL-11 in diffuse large B cell lymphomas, thus aiding in immune suppression required for EBV progression (80). Interestingly, EBV has also been shown to potently induce miR-155 and miR-146a (81, 82), miRNAs that play key roles in regulating the host immune response (16). Furthermore, miR-155 is found to be over-expressed in the majority of B cell lymphomas (83-85). Interestingly, Kaposi's sarcoma-associated herpesvirus (KSHV) encodes a viral homologue of miR-155, suggesting that KSHV-miR-K12-11 may also contribute to disease progression in B cells (86). More recently, two other v-miRNA encoded by KSHV, miR-K12-3 and miR-K12-7, were shown to target C/ebp-beta, a transcription factor that regulates IL-6 and IL-10 expression (87). Collectively, these findings re-iterate the importance of miRNAs in cytokine function and modulation, where dysregulation or adaptation by viruses can lead to disease progression.

## 5. PERSPECTIVES

Cytokine regulation of miRNA has highlighted how miRNAs can play a role in mediating some of the known effects of cytokines, as well as identifying novel gene targets, mechanisms and cross-talk between pathways. For example, the study of miRNAs has unveiled a new role for Smads in miRNA processing; induction of miRNA by IFN-beta has highlighted novel mechanisms into its therapeutic potential; inhibition of miR-155 by IL-10 depicts a novel mechanism of regulation for the anti-inflammatory cytokine; the discovery of virally encoded miRNAs has opened a new field for viral therapeutics as well as deciphering novel methods used by viruses to negatively regulate the immune response. Of particular interest is how manipulation of miRNA expression through over-expression or repression is often sufficient to elicit a cytokine response independent of the original signal, a phenonomen that will greatly impact their use as therapeutic agents for cytokine effects.

In addition to providing relationships between miRNAs and the remaining cytokines that exist, future studies should make use of the novel cytokine targets that are identified through the study of miRNAs. Further, it will be necessary to understand how an individual miRNA can impact on global cytokine networks. Such studies clearly call for the generation of transgenic mice overexpressing or lacking individual miRNAs. Another interesting aspect to take into consideration is the need to fully understand the turnover of miRNA molecules in the cell. The half-life of miRNAs is thought to be more than 24 hours and recent progress suggests that there are many sophisticated mechanisms underlying miRNA persistence (2, 88). Cytokine mRNA sequences are significantly short-lived in comparison. Therefore are cytokine-induced miRNAs a method by which cytokines can prolong their response and if so, how do these miRNAs get switched off? In essence, we are only beginning to understand the relationship between miRNA and cytokines, where it is evident that much more remains to be explored.

## 6. ACKNOWLEDGMENTS

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**Abbreviations:** miRNAs: microRNAs, RISC: RNA-induced silencing complex, UTR: 3' untranslated region, IL: interleukin, TNF: tumor necrosis factor, IFN: interferons, TGF-beta: transforming growth factor beta, TLR: Toll-like receptors, TTP: tristetraprolin, FXR1: fragile-X-mental-retardation-related protein 1, ARE: adenosine/uridine-rich region, NF2: neurofibromatosis 2, HCV: hepatitis C virus, EMT: epithelial-mesenchymal transition, EBV: Epstein Barr virus, v-miRNA: viral miRNA

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