The Interplay among miRNAs, Major Cytokines, and Cancer-Related Inflammation

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Inflammation is closely related with the progression of cancer and is an indispensable component that orchestrates the tumor microenvironment. Studies suggest that different mediator and cellular effectors, including cytokines (interleukins, tumor necrosis factor-α [TNF-α], transforming growth factor-β [TGF-β], and granulocyte macrophage colony-stimulating factor [GM-CSF]), chemokines, as well as some transcription factors (nuclear factor-κB [NF-κB], signal transducer and activator of transcription 3 [STAT3], hypoxia-inducible factor-1α [HIF1α]), play a crucial role during cancer-related inflammation (CRI). MicroRNAs (miRNAs) are the key components of cellular physiology. They play notable roles during post-transcriptional gene regulation and, thus, might have a potential role in controlling the inflammatory cascade during cancer progression. Taking into consideration the role identified for miRNAs in relation to inflammatory cytokines, we have tried to review their participation in neoplastic progression. Additionally, the involvement of miRNAs with some important transcription factors (NF-κB, STAT3, HIF1α) and proteins (cyclooxygenase-2 [COX-2], inducible nitric oxide synthase [iNOS]) closely associated with inflammation during cancer has also been discussed. A clear insight into the responsibility of miRNAs in cytokine signaling and inflammation related to CRI could project them as new therapeutic molecules, which could lead to improved treatment of CRI in the near future.

Cancer is a public health issue of serious concern, as it represents the major cause of deaths throughout the world. GLOBOCAN 2018 estimated approximately 8.1 million new cancer cases globally.1 Among the various types of cancer, lung, prostate, breast, stomach, liver, pancreatic, and colon cancers are the leading cause of deaths throughout the globe.7 However, studies have shown that chronic inflammation and related infections influence the cause of various types of cancer and are the underlying reason for 15%–20% of deaths from cancer.8,9

Cancer was linked to inflammation for the first time in the 19th century when, in 1863, Rudolf Virchow hypothesized the functional relationship of chronic inflammation to the development of cancer.3 It has been observed that the cause of inflammation may range from microbial infections to exposure to chemicals and allergens to various pathological conditions. Inflammation is a double-edged sword, having a very delicate balance between the development of an anti- or pro-tumorigenic environment. A well-regulated acute inflammation is considered as anti-tumorigenic, whereas unregulated chronic inflammation develops a pro-tumorigenic environment.4,5 It was observed that chronic infection with inflammation develops into ~25% of all cancer cases throughout the world.6,7 Takahashi et al.8 showed that the presence of high carcinogenic substances is a source of tumor initiation due to their ability to cause chronic inflammation. Tobacco smoke is one such example of a potent tumor promoter with the capability of activating chronic inflammation. These observations have led to the idea that different cancers might develop from inflammation and continual irritation.9 Evidence based on various findings, ranging from molecular studies to epidemiological research, has documented the relationship between cancer and inflammation.

It has been suggested that cancer-related inflammation (CRI) is one of the most important physiological parameters in the diagnosis of malignancy. It is well documented that CRI is triggered by several factors, including chemokines and cytokines (Figure 1).10 Different inflammatory cytokines are dysregulated during cancer that might act as a biomarker for detecting cancer. However, comprehensive studies are requisite to recognize the level of inflammatory cytokines before considering them as biomarkers.

MicroRNAs (miRNA) are single-stranded non-coding RNAs that are also called ncRNAs, containing a small number of nucleotides, usually 21–23 nt. The miRNA controls target gene expression, particularly via the cleavage procedure or by modulation of target proteins at the translational level.11–13 Additionally, it has been observed that miRNAs are involved in gene silencing at the co-translational stage (enrolling protein decay factors such as exosomes) and even at the pre-translational stage (during chromatin remodeling).14 The first

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miRNA that was discovered is called lin-4, which was found to control the developmental timing in Caenorhabditis elegans (nematodes) by targeting the mRNA of a key developmental protein called lin-14.15,16 Thereafter, an additional miRNA (let-7) was also found to be a contributing factor in the development of C. elegans.17 It was observed that these small miRNAs are not only present in C. elegans but also exist in murine and human cells. The sequences of these miRNAs were found to be highly conserved.18 Studies have revealed that miRNAs encompass approximately 1% of the total human genome, and the miRNA family are the driving forces for the establishment of the inflammation associated skin conditions leading to cancer development.35 In the extrinsic pathway, inflammatory leukocytes and soluble mediators are the driving forces for the establishment of the inflammatory microenvironment. The inflammatory mediators are the key controllers at the junction of intrinsic and extrinsic pathways.

Various types of inflammatory cells are known to be the essential components of the tumor microenvironment participating in CRI. The tumor microenvironment consists of a number of different inflammatory cell types, including cancer-associated fibroblasts (CAFs), stromal cells, tumor-associated macrophages (TAMs), infiltrating immune cells, pericytes, and endothelial cells comprising the tumor vasculature.36 Tumor cells communicate with these inflammatory cells, via secreting cytokines and growth factors, to stimulate tumor growth and develop resistance against chemotherapy.

It has been demonstrated that several endogenous and exogenous inflammatory mediators/factors contribute to CRI via crosstalk.
between the inflammatory cells and tumor cells (Figure 2). It is well known that chemokines, cytokines, and several transcription factors act as inflammatory mediators and are important in the development of the inflammatory microenvironment, leading to increased risk of cancer development. Thus, cytokines are among the key machineries of CRI. The cytokines include interleukins (ILs), especially IL-1, IL-6, IL-17, and IL-23, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, growth factors, and colony-stimulating factors, which are either membrane-bound or are secreted molecules. These molecules have functional roles in proliferation, activation, and differentiation of cancer and immune cells. Chemokines are the major family of cytokines that are important in the development of CRI. Based on the relative position of their first two cysteine residues, chemokines can be categorized into four groups (CC, CXC, XC, and CX3C). Among these, the chemokines CCL2 and CXCL8 have a significant role in CRI. However, in addition to cytokines and chemokines, several other key endogenous factors, such as transcription factors, are also associated in the development of CRI, e.g., nuclear factor-κB (NF-κB), hypoxia-inducible factor-1α (HIF1α) and signal transducer and activator of transcription 3 (STAT3). Hence, intervention in the communication between cells and molecules within the tumor microenvironment can be an effective strategic approach for the development of effective therapies against cancer.

The Role of Extracellular miRNAs in Establishing Tumor Microenvironment

During inflammation, the expression pattern of miRNAs is found altered, suggesting that miRNAs might offer a link between inflammation and cancer. Moreover, it has been noted that some miRNAs have a prominent role in the regulation of innate immunity. Upregulated or downregulated miRNAs can lead to the development of immune tolerance, potential autoimmunity, a hyper-inflammatory phenotype, and cancer commencement and progression. Inflammatory mediators, chemokines, cytokines, and different proteins can regulate miRNA expression, which may contribute to the regulation of multiple genes and the gene regulatory networks associated with inflammation and oncogenesis. Indeed, miRNAs have also been found crucial for the development, differentiation, function, as well as survival of different cell types such as T and B lymphocytes, macrophages, dendritic cells, and other immune cells.

Several miRNAs are released from cells and have a functional role to establish the tumor microenvironment. These extracellular miRNAs can perform their function not only on cancer cells but also on the endothelial cells, immune cells, and fibroblasts present in the tumor microenvironment. It has been noted that extracellular miRNAs have an influence on tumor progression through bidirectional communication such as stromal-to-tumor and tumor-to-stromal communication. The route by which miRNAs are released in the extracellular environment is multifarious, including exosomes. Some miRNAs mediate the functioning of the extracellular vesicle in the tumor microenvironment. For example, miR-1 is known to mediate extracellular vesicle function, which is downregulated in glioblastoma multiforme (GBM).

Extracellular miRNAs can enter tumor cells, immune cells, or stromal cells present within the tumor microenvironment, where they can reprogram the cell transcriptome, resulting in alterations in the growth of tumor and metastasis by affecting cell growth, cell differentiation, migration, and angiogenesis. Some of the miRNAs involved in migration and metastasis are miR-200, miR-10b, and miR-21. miRNAs involved in angiogenesis are miR-16, miR-21, and miR-494. In addition, some exosomal miRNA are known to modulate the tumor immune response. For example, IL-4-stimulated macrophages have been found to secrete exosomes containing oncogenic miRNAs (miR-223), which helps in the invasiveness of breast cancer cells. It has also been demonstrated that when exosomal miR-21 attaches with Toll-like receptor 7/8 (TLR7/8) on macrophages, it helps to promote the secretion of IL-6, leading to enhancement of the pro-inflammatory response. As reported, certain miRNAs either get upregulated (e.g., Let-7g, miR-26b, miR-101, miR-141, miR-200b, miR-200c, miR-205, and miR-342-3p) or downregulated (e.g., miR-31-3p, miR-221-5p, and miR-221-3p) in CAFs. However, further
investigations are needed to bring deep insight into the particular involvement of these extracellular miRNAs in the tumor microenvironment.

**Role of miRNAs in CRI and Cytokine Signaling**

As discussed earlier, cytokines are key players of inflammation that might contribute in acute and chronic inflammation. Cancer progression is being controlled by immune cells, which are regulated by the cytokines in the tumor microenvironment. Evidence has revealed that miRNAs regulate the genes associated with secretion of different cytokines, suggesting that cytokine-mediated CRI is well regulated (Figure 3). Some of the inflammatory cytokines and associated miRNAs responsible for the pathogenesis of CRI are summarized below.

**TNF-α**

TNF-α, a potent cytokine, acts as an inflammatory mediator that is secreted by diverse types of cells such as macrophages, T and B cells, fibroblasts, and monocytes. TNF-α was primarily identified as an endotoxin-induced serum factor in the 1970s. Thereafter, the TNF-α gene was cloned in a cell line and the protein was characterized after purification. The characterized protein was then made commercially available. It has been suggested that TNF-α is an important mediator of inflammation and apoptosis. Based on the cell type, TNF-α interacts with either TNF-receptor 1 (TNFR1) or TNFR2 and can stimulate different cell processes such as necrosis, apoptosis, immune cell activation, differentiation, angiogenesis, and cell migration. These cellular activities are of great significance in tumor immune surveillance. When TNF-α binds to TNFR1, it can activate survival of the NF-κB pathway by sequential recruitment of TRADD and RIP. On the contrary, TNFR1 may also activate the caspase-dependent apoptotic pathway by stimulating the formation of the TRADD-Fas-associated death domain (FADD)-pro-caspase-8 complex. Therefore, being associated with critical cellular behavior, TNF-α can be held responsible for both pro- and anti-tumoral effects.

miR-145 is assumed to be a tumor suppressor and it is downregulated in multiple cancers. Zheng et al. showed that miR-145 is downregulated in triple-negative breast cancer (TNBC) tissue and the MDA-MB-231 cell line, while miR-145 is overexpressed in MDA-MB-231 cells treated with TNF-α, resulting in induced cell death and apoptosis. The co-immunoprecipitation assay showed that miR-145 facilitates the formation of the RIP1-FADD-caspase-8 apoptotic complex induced by TNF-α, leading to a caspase-8-mediated apoptotic signaling pathway. They further demonstrated that cellular inhibitor of apoptosis protein-1 (cIAP1), an apoptotic inhibitor, is a target for miR-145. cIAP ubiquitinates RIP1 and prevents apoptosis via TAK1 and NF-κB, Thus, miR-145-mediated downregulation of cIAP1 promotes deubiquitination of RIP1 and formation of a complex with caspase-8 and FADD, suggesting that miR-145 might regulate TNF-α-induced apoptosis in TNBC.

B cell chronic lymphocytic leukemia (CLL) is a well-known leukemia type, being prevalent in different parts of the world, particularly in the Western world. Higher levels of TNF-α have been observed in CLL patients. Some miRNAs have the ability to regulate the TNF/TNF gene superfamily in CLL. Srivastava et al. performed in silico target prediction and elucidated that miR-15a, miR-29a, and miR-181a directly target and deregulate members of TNF ligands (i.e., TNF, TNFR1, and LTβR [lymphotoxin β receptor]), a member of the TNFR superfamily (i.e., TNFRSF1A), and adaptor molecules (i.e., TNFR-associated factors [TRAFs] 3–6). These members of the TNF/TNFR superfamily and adaptor molecules are known to activate the NF-κB survival pathway. Therefore, miRNA-mediated targeting of the TNF/TNFR superfamily might be a possible therapy against leukemia.

TNF-α is also associated with colorectal cancer (CRC) progression. It has been shown that the level of TNF-α is elevated in CRC patients with lymph node metastasis. One of the critical molecular steps
during metastasis that facilitates epithelial cells to metastasize to distant sites is the epithelial-to-mesenchymal transition (EMT). Growing evidence suggests that miRNAs might regulate the genes related to EMT. Upregulation of miR-19a in CRC tissue and a relationship between the elevated level of miR-19a expression and lymph node metastasis in CRC cell lines were observed by Huang et al.\(^6\) The study also showed that miR-19a expression is increased by TNF-α, while in turn it represses TNF-α formation by a negative feedback loop; however, the exact mechanism is still not clear. This study also found that an increased level of miR-19a is associated with a decreased level of epithelial marker (E-cadherin) and an increased level of mesenchymal markers (N-cadherin, fibronectin, and vimentin) in CRC cells, suggesting induction of EMT.

Zhang et al.\(^6\) observed that TNF-α stimulates the nuclear translocation of NF-κB followed by the induction of miR-130a expression and downregulation of TNF-α. However, more mechanistic insight needs to be explored. They suggested a negative feedback loop of NF-κB/miR-130a/TNF-α in cervical cancer cells that might be responsible for the low level of TNF-α, resulting in carcinogenesis by avoiding apoptosis. Another miRNA, miR-21, also serves as a regulator of apoptosis along with cancer cell proliferation and is being suggested as a potential marker for detecting metastasis.\(^6\) Inhibition of phosphatase and tensin homology (PTEN) expression could be a plausible mechanism regulated by overexpressed miR-21 that affects cervical cancer cell migration and proliferation.\(^6\)

Although it has been shown that miR-21-mediated upregulation of TNF-α has a positive effect on HeLa cervical cancer cell proliferation, it exerts no effect on cell apoptosis.\(^6\) According to Zheng et al.,\(^6\) overexpression of TNF-α increases expression of miR-765, which reduces cancer cell migration, probably by directly repressing EMP3 translation and consequent upregulation of p66Shc. However, note that in Zheng et al.’s work a high dose of TNF-α (100 ng/mL) was used, which demonstrated an inhibitory effect on migration of the OSCC line instead of a stimulatory effect.\(^6\) Therefore, as TNF-α is a double-edged sword, understanding the crosstalk between various miRNAs and TNF-α and their roles in inducing different signaling pathways in cancer biology might assist in developing promising cancer therapeutic agents.

**IL-1**

IL-1 was first discovered at the beginning of the 1940s, and since then it has become one of the significant pro-inflammatory cytokines in medical science. The IL-1 family includes eleven members. Among them, seven members are ligands with agonist activity, i.e., IL-1 (β), IL-33, IL-18 and IL-36 (α, β, γ). Another three members (IL-1Ra, IL-38, and IL-36Ra) are receptor antagonists. Only IL-37 is an anti-inflammatory cytokine.\(^6\) As reported, the pro-inflammatory cytokine IL-1 has two important forms, i.e., IL-1α and IL-1β.\(^6\) The genes of these two cytokines are located on chromosome 2 and are in close vicinity, sharing ~27% aa sequence homology.\(^6\) In comparison to TNF-α, the inflammatory signaling mechanisms of IL-1α and IL-1β are much more complex. It has been noticed that these signaling mechanisms are mediated through cell-surface receptors.\(^3\) IL-1 was found to modulate the expression of genes that are known to mediate inflammation and cancer.\(^6\) In light of the current therapeutic approaches, a correlation between inflammation and tumorigenesis has also been exploited.

An elevated expression level of NF-κB (Rel A), IL-1β, and miR-181a in colon cancer was noted by Hai Ping et al.\(^7\) in colon cancer. It was observed that IL-1β induced the expression of miR-181a via the NF-κB signaling pathway, and miR-181a was able to promote cell proliferation by repressing PTEN, which is an important tumor suppressor and is frequently mutated in various cancers.

In another study, IL-1β upregulated the expression of miR-425, mediated by NF-κB signaling, in gastric cancer cells. Overexpressed miR-425 promoted the growth of gastric cancer cells by negatively regulating PTEN.\(^7\) The expression of another miRNA, miR-155, was induced by IL-1β in melanoma cells, where miR-155 mediated the downregulation of MITF-M (microphthalmia-associated transcription factor).\(^7\) MITF-M, a key transcription factor, is expressed solely in melanocytes and has the ability to regulate several genes responsible for differentiation, survival, and proliferation.

It was observed that silica particle-induced IL-1β secretion downregulated miR-101 and subsequently increased the expression of enhancers for zeste homolog 2 (EZH2), conferring metastasis and cancer cell proliferation in the Xuan Wei lung cancer cell line. Conversely, miR-101 suppresses translation of EZH2, attenuating cell growth and migration.\(^7\) Similarly, in another study, Wang et al.\(^7\) observed that the level of IL-1β is highly increased in patients with non-small-cell lung cancer (NSCLC). IL-1β repressed the expression of miR101 and caused an upregulation of the miR-101 target gene, Lin28B, a suppressor of the tumor-suppressive let-7 family of miRNAs. The IL-1β/miR-101/Lin28B pathway is dependent on cyclooxygenase-2 (COX-2) activity and promoted proliferation and migration of NSCLC cells. In conclusion, this pathway links inflammation signaling to cancer cell proliferation and migration in NSCLC and thus may in part explain inflammation-promoted tumorigenesis.

**IL-6**

IL-6 is a pleiotropic inflammatory cytokine produced by T helper cells, synovial fibroblasts, monocytes, and macrophages.\(^2\) IL-6 has various effects on the cells of the immune system and is essential for the regulation of a variety of immune functions such as immunoglobulin G (IgG) production and plasma cell differentiation.\(^2\) An elevated IL-6 level has been observed in the serum of patients with cancer inflammation,\(^7\) suggesting that overproduction of this protein cascade leads to an inflammatory condition. Besides inflammation, IL-6 is also involved in cancer progression.\(^7,8\)

Dong et al\(^8\) described the role of IL-6 and miR-21 on programmed cell death 4 (PDCD4) gene expression in the prostate cancer cell lines PC-3 and LNCaP. PDCD4 is a suppressor of tumor progression. Prostate cancer is among the prevalent cancers in the US. According to
their study, miR-21 can reduce the expression of PDCD4 by expressing IL-6 in prostate cancer cells.80 PDCD4 binds with translation initiation factors, such as eIF4G and eIF4A, to inhibit the process of translation, resulting in the inhibition of pro-oncogenic factors.

In another study, Xiang et al.81 observed that IL-6 activates STAT3. Constitutive activation of STAT3 in cancer promotes cell proliferation, survival, invasion, and angiogenesis. The study reported that in normal tissues, STAT3 can transcriptionally upregulate miR-146b, which further suppresses the activation of NF-κB by translational repression of the NF-κB activators, i.e., TRAF6 and IL-1R-associated kinase (IRAK1). Consequently, IL-6, an NF-κB target gene, is downregulated, preventing autocrine stimulation of STAT3 in a feedback loop. However, in cancer cells, the tumor-suppressive function is lost by promoter methylation of the miR-146b gene, which may result in persistent inflammation, prolonged NF-κB-IL-6-STAT3 activation, and subsequent tumor progression.82,83

Furthermore, it has been shown that miR-26 might control tumorigenicity and inflammation by downregulating the secretion of IL-6 and NF-κB signaling.83 Chen et al.84 observed that instead of directly targeting IL-6, miR-26 reduces IL-6 transcription triggered by TNF-α through silencing NF-κB signaling related factors high mobility group AT-hook 1 (HMGAI) and mucosa-associated lymphoid tissue lymphoma translocation gene 1 (MALT1) in adenocarcinomic alveolar basal epithelial A549 cells. In contrast, Jones et al.84 observed that miR-26 directly targets IL-6 3' UTR and silences IL-6 expression in A549 cells. This raises the possibility that miRNAs might act as a cytokine silencer, either by acting indirectly on signaling pathways or by directly acting on cytokine transcripts.

It has been observed that the upregulation of IL-6 results in a decrease of miR-26a expression in hepatocellular carcinoma (HCC) cells.85 In addition, miR-26a was found to repress the tumor growth and metastasis of human HCC in the nude mice model, and the tumor suppressor effect of overexpressed miR-26a is parallel to that of genetic inhibition of IL-6.86 It was suggested that miR-26a targets IL-6 and inhibits IL-6/STAT3 signaling. It is plausible that suppression of STAT might inhibit the transcription of anti-apoptotic genes, such as Bcl-2, Mcl-1, cyclin D1, and matrix metalloproteinase 2 (MMP2). Therefore, miR-26a possibly blocks the G1/S transition and promotes apoptosis in HCC cells. However, the molecular machinery by which miR-26a inhibits HCC remains unclear.86

**IL-17**

A pro-inflammatory cytokine, IL-17, is also secreted by a diversity of cells, including activated T helper cells, natural killer (NK) cells, macrophages, dendritic cells, γδ-T cells, and lymphoid tissue inducers.87,88 As IL-17 regulates the activities of the NF-κB and MAPK pathway proteins,89 it has been related to the progression of various inflammatory diseases, such as autoimmune disease.90,91 An association between IL-17 and cancer-associated inflammation has also been observed.91,92 Cao et al.93 suggested a negative correlation between miR-181a-5p and IL-17 in NSCLC and found that IL-17 upregulates vascular cell adhesion molecule 1 (VCAM-1) and downregulates miR-181a-5p via the NF-κB pathway. Furthermore, IL-17-induced VCAM-1 expression was diminished by the transfection of miR-181a-5p mimic. The suppression of VCAM-1 is possibly due to the direct binding of miR-181a-5p to 3' UTR of VCAM-1. Here, miR-181 functions as a tumor suppressor by reducing tumor cell proliferation and migration.94 VCAM-1 is associated with pathophysiological conditions, such as autoimmune diseases, infection tumor progression, and metastasis. Therefore, miR-181a-5p-mediated targeting of VCAM-1 could be a therapeutic approach against NSCLC progression under the influence of IL-17.

In another study, it was found that the expression levels of IL-17 and miR-221 were increased in papillary thyroid carcinoma (PTC).95 It was found that IL-17 and miR-221 were positively correlated to TNM (tumor, node, metastasis) staging, capsular invasion, and lymph node metastasis. Multiple myeloma (MM) is a type of cancer-related to plasma cells and is a type of white blood cell (WBC) cancer. Bone marrow-derived mononuclear cells (BM-MNCs) isolated from MM-positive patients showed upregulation in vascular endothelial growth factor (VEGF)-A (an angiogenic growth factor) and suppressed miR-15a/16 expression, suggesting the association of miR-15a/16 with the progression of MM.96 Furthermore, it was observed that miR-15a/16 decreased the proliferation of human MM U266 cells by downregulating Bcl-2 (an anti-apoptotic factor). miR-15a/16 was also found to repress VEGF-A at the post-transcriptional level and decrease IL-17 expression, revealing the role of miR-15a/16 against angiogenesis and enhancing antitumor immune response, respectively.97 As both VEGF and Bcl-2 are regulated by the STAT3 signaling pathway, the role of miR-15a/16 in targeting STAT3 cannot be overruled. In accordance, another study demonstrated that IL-17 facilitated cell proliferation and migration and inhibited apoptosis by triggering the regulatory feedback loop involving miR-192-targeted IL-17Rs (IL-17RE and IL-17RA) in MM cells.98 IL-17 is also known to induce NF-κB99 and MAPK100; therefore, it is possible that miR-192 is also regulated by IL-17 via the upstream binding site of NF-κB or MAPK. Another possibility is that IL-17-induced IL-6 activates STAT3, which might subsequently result in cancer pathogenesis.98

**IL-23**

IL-23 is a heterodimeric pro-inflammatory type 1 cytokine that plays a critical role in tumorigenesis by inducing CRI.95,100 IL-23 is composed of the IL-12/p40 subunit and p19 subunit belonging to the superfamily of IL-6. It has been documented that overexpression of IL-23 was observed during various cancer conditions, and was shown to promote tumor metastasis.101,102 For example, IL-23 was found to facilitate metastasis in hepatocellular carcinoma via NF-κB-mediated upregulation of MPP9.102 Similarly, IL-23-induced metastatic melanoma brain has also been reported via the upregulation of MPP2.103 Members of the MPP family are associated with cancer invasion and angiogenesis, and thus upregulation of MMPs might be a possible mechanism elicited by IL-6-induced cancer cells for invasion and migration. Suzuki et al.104 showed the role of IL-23 in...
inducing proliferative and invasive activities of the colorectal carcinoma DLD-1 cell line via TGF-β production.

It has been speculated that IL-23 regulates miRNA expression. For example, IL-23 induces the expression of the miR-133B/miR-206 cluster in IL-17-producing T cells, contributing to T cell differentiation.105 Indeed, it was shown that miR-133B/miR-206 and IL-17A share regulatory elements and are co-regulated by IL-23 via the STAT3 signaling mechanism. Also, IL-23 was found to upregulate the expression of miR-25 in thyroid cancer cells (TCCs).106 Overexpressed miR-25 inhibits suppressor of cytokine signaling (SOCS) by directly binding to its 3’ UTR region and promotes the invasion and migration of TCCs,106 suggesting SOCS-mediated negative feedback regulation of IL-23-induced cancer progression.

**TGF-β**

TGF-β is a multifunctional cytokine that signals via protein kinase receptors.107 TGF-β promotes or inhibits tumorigenesis by regulating carcinoma initiation, metastasis, and progression.108 The importance of TGF-β has been established in the inflammation associated with cancer.108 Wang et al.109 showed that miR-16 inhibits TGF-β1-induced EMT through the activation of autophagy in NSCLC cells. Conversely, it has been noted that TGF-β controls human leukocyte antigen (HLA)-G expression in gastric cancer (GC) cells, where miR-152 plays a key role. TGF-β stimulates HLA-G expression in the course of inhibiting miR-152 in GC, and it was suggested that miR-152 might have a therapeutic role in the treatment of GC.110 TGF-β has an effect on cancer cell propagation, especially in breast cancer cells. miR-106b is upregulated by TGF-β1 in highly invasive breast cancer cells. Enhanced levels of miR-106b define the influencing paradox of TGF-β in breast cancer cells.111 In another study, Qiu et al.112 demonstrated that TGF-β plays a noteworthy function in tumor metastasis through the expression of miRNA. miR-182 is a key molecule in the regulation of cancer development, especially gallbladder cancer (GBC) metastasis. It has been found that miR-182 negatively regulates cell adhesion molecule 1 (CADM1) expression in GBC.111,112 It has also been observed that the loss of the function of miRNA, such as miR-142, through the hypermethylation process could cause TGF-β-mediated tumor metastasis and growth in HCC.113

**GM-CSF**

Granulocyte macrophage colony-stimulating factor (GM-CSF) is a pro-inflammatory cytokine and a WBC growth factor produced by macrophages, T cells, endothelial cells, and NK cells. This cytokine is a monomeric glycoprotein. The gene of this cytokine is located at the chromosome region 5q31. Moreover, GM-CSF is known as a haemopoietic growth factor and can trigger the activation of neutrophils and peripheral monocytes.27,114 GM-CSF is also significant for the development of inflammatory responses during different inflammatory diseases14 as well as in cancer.115,116 A genetically engineered pancreatic ductal adenocarcinoma mouse model showed that GM-CSF secreted from tumors plays an important role in regulating inflammation and immune suppression in the tumor microenvironment.117 Importantly, it has been observed that alterations in GM-CSF-induced signaling pathways resulted in acute myeloid leukemia (AML).118 More importantly, Favreau and Sathyanarayana119 observed that GM-CSF, along with IL-3 and GCSF, regulates (both upregulates and downregulates) the expression of various miRNAs in an AML progenitor cell model (AML-193 cell line). Upregulated miRNAs include miR-219-5p and miR-590-5p, while downregulated miRNAs include miR-15b and miR-628-5p. Among upregulated miRNAs, miR-590-5p targets bone morphogenetic protein receptor type II (BMPR2) and poly(C) binding protein 2 (PCBP2); both of these proteins are known to possess tumor-suppressive properties. Another upregulated miRNA, miR-219-5p, targets TGF-β/BMP-induced signaling protein Smad4, which binds to Hoxa9 and inhibits Hoxa9-Nup98-induced AML. Among downregulated miRNAs, miR-628-5p targets Foxo3/Foxo3a, whereas miR-15b targets Bcl-2. It has been shown that elevated expressions of Foxo3 or phosphorylated (p)-Foxo3 have an adverse effect on AML prognosis.120,121 Therefore, targeting cytokines regulated by miRNAs may be instructive against CRI, and thus may provide therapeutic interventions against cancer progression.

**miRNA Mediated Regulation of Other Major Players in CRI**

In addition to the major cytokines involved in CRI, there are other significant players that are associated with CRI and are in crosstalk with miRNAs (Figure 4).

**Transcription Factors**

**NF-κB**. NF-κB is a combined term, which refers to dimeric transcription factors related to an important protein family called the Rel family.122 In the cytoplasm, NF-κB occurs in an inactive form (inactive complex NF-κB-inhibitory NF-κB [IκB]), where the IκB subunit acts as an inhibitor for NF-κB and prevents it from nuclear localization. Upon stimulation by external stimuli, the IκB subunit undergoes rapid phosphorylation, ubiquitination, and, finally, proteolytic degradation. Upon the release of the IκB form, the NF-κB-IκB complex allows NF-κB to translocate into the nucleus and regulate targeted gene transcription. Several studies have established NF-κB as a key molecule for inducing inflammation and as a regulator of innate immunity. Moreover, NF-κB has been implicated as a hallmark of carcinogenesis.123 NF-κB is vital for tumor cell development and also crucial for the inflammatory cells. In the inflammatory cells, NF-κB triggers different genes that encode for inflammatory/pro-inflammatory cytokines and other molecules such as adhesion molecules, inducible nitric oxide synthase (iNOS), and COX-2.123 Some clear evidence indicates that NF-κB is involved in the initiation and progression of tumor cells and tissues, where CRI normally occurs.124 However, the NF-κB pathway is firmly controlled by some inhibitors that function at different phases of the pathway. There is some emerging evidence that miRNAs are examples of these inhibitors and have regulatory control over the NF-κB signaling pathway in cancer. For instance, it has been demonstrated that miR-181d regulates the mesenchymal (MES) phenotype through the NF-κB pathway in GBM. In the absence of miR-181d, the MES subtype of GBM displays a more malignant phenotype.125 In another study, Wang et al.126
The binding of ligands induces conformational/structural changes in STAT3, by the signaling cascade of Janus-activated kinases (JAK) activating and regulating STAT family transcription factors, especially STAT3. It is well established that cytokines can control other significant proteins (other than the Cytokines) associated with CRI (NF-κB, STAT3, HIF1α, iNOS, COX-2, PPARγ).

**Figure 4. Schematic Diagram Shows miRNAs That Control Other Significant Proteins (Other Than the Cytokines) Associated with CRI (NF-κB, STAT3, HIF1α, iNOS, COX-2, PPARγ)**

**STAT3.** Identical to NF-κB, STAT3 is a point of junction for various oncogenic signaling pathways. It is well established that cytokines can activate and regulate STAT family transcription factors, especially STAT3, by the signaling cascade of Janus-activated kinases (JAK). The binding of ligands induces conformational/structural changes in cytokine receptors, stimulating the associated JAKs and consequently phosphorylating and triggering STAT signaling. In numerous solid tumors, JAK/STAT activation has been acknowledged as a significant characteristic. However, the mechanism of activation of the pathway is not well understood. However, it is well established that the deregulation of a network of JAK/STAT signaling causes cancer. This key signaling cascade is very crucial in immune cells as well as in tumor cells engaged in oncogenesis. The STAT3 protein is known to inhibit apoptosis. Promising evidence has proven that miRNAs control the STAT3 pathway in different types of cancer. It has been noted that the deletion of miR-139-5p might stimulate NF-κB, MAPK, and STAT3 signaling and promote colorectal cancer and intestinal inflammation. Another miRNA entitled miR-146b has been shown to inhibit NF-κB-mediated production of IL-6 and, consequently, the activation of STAT3 in cancer. A study proposed crosstalk between STAT3 and the NF-κB signaling pathways during the occurrence of inflammation in oncogenesis.  

**HIF1α.** HIF1α is a subunit of a heterodimeric transcription factor, is a mediator of oxygen homeostasis and has a compelling role in cell survival and tumor invasion. HIF1 plays an important role in inflammation and leukocyte adhesion. Increasing evidence has suggested that HIFs, in addition to supervising glycolytic energy production, can act as a governing switch for innate immunity, pro-inflammatory gene expression, and cell migration. The HIF2α protein is intensively expressed in tumor-associated macrophages and is in the detectable range for human cancers. The status of a cell determines the crosstalk between proteins, NF-κB, and HIF1α during a response. It has been documented that some pro-inflammatory cytokines, such as IL-1β, TNF-α, and others, activate HIF1α in an NF-κB-dependent manner. The activated form of HIF1α then plays a pivotal role in linking the oncogenic and inflammatory pathways. miRNAs have a role in regulating the expression of HIF1α. miR-21 is an onco-miRNA that influences the expression of different genes of malignant melanoma. Noticeably, this miRNA controls PTEN, HIF1α, and TIMP3 during angiogenesis. It has also been noted that another miRNA, miR-182, augments HIF1α signaling in prostate cancer via targeting PHD2 and FIH1. In melanoma, miR-199a-5p inhibits tumor proliferation by involving HIF1α. miR-373 is associated (positively associated) with HIF1α and TWIST and controls metastasis through miR-373-TXNIP-HIF1α-TWIST signaling in breast cancer.

**COX-2.** COX-2 is an enzyme, and the expression of COX-2 might be regulated by a variety of stimuli (such as pro-inflammatory cytokines, including TNF and IL-1). It is also overexpressed in several types of cancer. COX-2 has been proposed as a linker between inflammation and cancer. Nevertheless, the exact role of COX-2 in CRI is not fully known. It has been reported that miRNAs can enhance COX-2 expression during inflammation. miR-155 is shown to enhance COX-2 expression in inflammation, and its inhibition displayed a deleterious effect on tumorigenicity. Therefore, miR-155 might be considered a promising target for antagonizing COX-2 expression in colorectal and other cancers. It has been found that miR-101 regulates prostate cancer cells through COX-2 modulation in vivo. Therefore, more detailed studies on miR-101-mediated COX-2 modulation might offer new cancer therapy.

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## Table 1. miRNAs Related to Major Cytokines Signaling and CRI

| Cytokine Cascades | Pro-inflammatory/Inflammatory Role | miRNAs       | Remark                                                                 | References |
|-------------------|------------------------------------|--------------|------------------------------------------------------------------------|------------|
| TNF-α             | pro-inflammatory role              | miR-145      | supposed to be a tumor suppressor, and it is downregulated in multiple cancers | 54         |
|                   |                                    | miR-145      | this miRNA supports TNF-α-induced apoptosis in triple-negative breast cancer | 55         |
|                   |                                    | miR-15a, miR-29a, miR-181a | miRNAs regulate the TNF/TNFα gene superfamily in chronic lymphocytic leukemia | 58         |
|                   |                                    | miR-19a      | connected with lymph node metastasis                                    | 62         |
|                   |                                    | miR-130a     | this miRNA regulates cervical cancer cells; TNF-α may induce NF-kB activity, which may activate miR-130a | 60         |
|                   |                                    | miR-21       | cell propagation in cervical cancer                                      | 63         |
|                   |                                    | miR-765      | TNF-α inhibited the metastasis of OSCC through the miR-765-EMP3-p66Shc axis | 64         |
| IL-1              | pro-inflammatory role              | miR-181a     | IL-1β stimulated the expression of miR-181a, which regulates colon cancer | 70         |
|                   |                                    | miR-155      | induced by IL-1β in melanoma cells                                      | 72         |
|                   |                                    | miR-101      | IL-1β mediated suppression of this miRNA in particle-induced lung cancer | 73         |
|                   |                                    | miR-425      | IL-1β induces the upregulation of this miRNA in gastric cancer           | 71         |
|                   |                                    | miR-101      | vital for inflammation formation, especially for lung cancer tumorogenesis | 74         |
| IL-6              | inflammatory role                  | miR-21       | this miRNA regulates the PDCD4 gene, and IL-6 inhibits expression of PDCD4 in prostate cancer cells | 76         |
|                   |                                    | miR-146b     | inhibits NF-kB-mediated production of IL-6 and consequent activation of STAT3 in breast cancer cells | 77         |
|                   |                                    | miR-26       | role in the regulation of IL-6 in tumorigenicity and inflammation       | 83         |
|                   |                                    | miR-26a      | represses metastasis and tumor growth of HCC through the IL-6/STAT3 pathway | 86         |
|                   |                                    | miR-26a      | upregulation of IL-6 provides the decrease of this miRNA expression in HCC | 85         |
| IL-17             | pro-inflammatory role              | miR-181a-5p  | VCAM-1 expression by this miRNA under IL-17 introduction; this miRNA causes tumor cell migration and cell proliferation | 92         |
|                   |                                    | miR-221      | role in papillary thyroid carcinoma                                     | 93         |
|                   |                                    | miR-15a/16   | this miRNA reduces IL-17 and VEGF-A levels where it acts as a tumor suppressor in multiple myeloma (MM) | 94         |
|                   |                                    | miR-192      | regulatory feedback loop related to IL-17/miR-192/IL-17Rs in MM progression | 95         |
| IL-23             | pro-inflammatory role              | miR-25       | this miRNA is overexpressed in cancer cells and is involved in IL-23-associated cell migration and invasion in thyroid cancer cells | 106        |
| TGF-β             | pro-inflammatory role              | miR-16       | this miRNA inhibits TGF-β-1, which controls epithelial-to-mesenchymal transition through the creation of autophagy in NSCLC cells | 109        |
|                   |                                    | miR-152      | TGF-β stimulates HLA-G expression in the course of inhibiting this miRNA in gastric cancer | 111        |

(Continued on next page)
Table 1. Continued

| Cytokine Cascades | Pro-inflammatory/Inflammatory Role | miRNAs | Remark | References |
|------------------|----------------------------------|--------|--------|------------|
| GM-CSF           | pro-inflammatory role            | miR-790-5p, miR-219-5p, miR-15b, miR-628-5p | expression of these miRNAs control by GM-CSF and G-CSF in acute myeloid leukemia | 114 |

TNF-α, tumor necrosis factor α; TNFR, tumor necrosis factor receptor; NF-kB, nuclear factor κB; OSCC, oral squamous cell carcinoma; EMP3, epithelial membrane protein 3; IL-1β, interleukin 1β; PDCD4, programmed cell death protein 4; STAT3, signal transducer and activator of transcription 3; HCC, hepatocellular carcinoma; VCAM-1, vascular cell adhesion protein 1; TGF-β1, transforming growth factor β1; NSCLC, non-small-cell lung carcinoma; HLA-G, human leukocyte antigen G; GM-CSF, granulocyte macrophage colony-stimulating factor.

Receptors

PPARγ. Peroxisome proliferator-activated receptor γ (PPARγ), a type II nuclear receptor, is involved in inflammation, cell differentiation, as well as cell proliferation. miRNAs regulate this nuclear receptor, which also participates in the regulation of transcription factors such as NF-κB. PPARγ has a tumor-suppressive function. In addition, several studies also suggested the implication of PPARs in inflammatory processes and specific cancers.147,148 During inflammation, the expression of miR-223 is controlled through direct binding of PPARγ with PPAR response elements (PPREs) within the promoter of pre-miR-223. For macrophage polarization, it has been noted that miR-223 and its target genes (such as Rasa1 and genuine) are significant effectors.149 Both miR-130b and miR-27a also have the ability to target PPARγ and reduce its expression, resulting in an enhanced cancer cells growth and aggressiveness during inflammation in cancer.150

Therapeutic Possibilities of miRNA Against CRI

Presently, miRNAs are known to regulate critical cellular processes by simultaneously modulating multiple targets and have been regarded as a possible therapeutic tool.151 It has been observed that oncogenic miRNAs are overexpressed in different human cancers or CRI. Thus, the inhibition or downregulation of these miRNAs might re-establish the normal functioning of a gene. There are several strategies to inhibit the miRNAs, such as the use of antisense anti-miR oligonucleotides (AMOs), locked nucleic acid (LNA) anti-miRNAs, miRNA sponges, antagonism, and miRNA masks. Another effective alternative strategy to re-establish the normal function of a gene is the use of “miRNA mimics.” Moreover, SMIRs (small molecule inhibitors of miRNAs) can actively block miRNA-target interaction or can inhibit miRNA biogenesis. Another method used is to agitate the mode of transport and to block extracellular miRNAs in exosomes. It has been observed that GW4869, a small molecule, is an inhibitor of neutral sphingomyelinase and can inhibit miRNA and exosome secretion.152 It may be concluded that miRNA-based therapeutics have great promise for the treatment of CRI, as they are highly specific and perfect candidates for targeted therapies.

Challenges for miRNA-Based Therapeutics

The development of miRNA-based therapeutic systems may encounter various challenges. As it is well known that the efficacy of miRNA-based therapeutics depends on the successful delivery of miRNAs into the target site, finding a suitable delivery system is one of the major challenges.153 Various factors might affect the successful delivery of miRNAs into the target cancer site. These include the leaky structure of tumor vessels, slow diffusion of miRNAs in the solid tumor due to the complex or higher interstitial fluid pressure, and non-specific uptake of miRNAs by non-malignant cells.154 However, even if some miRNAs reach the tumor site, they may get degraded by the endosomes or lysosomes in the cancer cells.155 Therefore, measures for endosomal escape and the release of therapeutic miRNA cargo into the cytoplasm must be taken into account.

The short half-life and instability of naked miRNAs, as they are prone to degradation by nucleases present in the blood, are other issues to be resolved before using miRNAs in cancer therapy.156 Moreover, systemic miRNA delivery might trigger the secretion of undesirable inflammatory cytokines and interferons,157 leading to the activation of the innate immune system that might induce side effects and toxicities, such as neurotoxicity.158 Besides immunogenicity, off-target gene silencing is also one of the biggest hurdles, as miRNAs can interact with complementary 3’ UTRs of non-target genes regulating multiple pathways.159 Thus, strategies should be utilized that must minimize the side effects and toxicities mediated by therapeutic miRNAs by reducing off-target gene silencing.

Conclusion

CRI appears to be one of the greatest challenges faced by medical scientists who are performing research in the area of current medicines and new drug discovery. It is very apparent from the research data that miRNA-mediated regulation might play an important role in the development of CRI. The identified miRNA candidates associated with CRI have already offered an indication that key molecular mechanisms are involved with the inflammation and cytokine signaling pathways (Table 1). Moreover, several
miRNAs associated with CRI that are involved in regulating the key factors (NF-κB, STAT3, HIF1α) of molecular pathways during the course of inflammation have also been acknowledged (Table 2). However, studies on the roles of miRNAs in CRI are still in the early stages, and several questions remain to be answered about the key regulatory events mediated by miRNAs such as (1) how a single miRNA or miRNA family regulates CRI, (2) whether a single miRNA can perform different functions during the regulation of CRI, and (3) clarifying the complex network between the miRNA, cytokines, and CRI. miRNAs that regulate CRI might have the potential to prevent migration of the cells toward the tumor site. This knowledge might re-educate us about tumor cell inflammatory infiltrates. We hypothesize that a better understanding of the miRNA-mediated regulation mechanisms linking inflammation and cancers will be beneficial to the development of efficient prevention and therapies for CRI. In-depth knowledge about the miRNA controlled CRI might provide a potential approach for reversing tumor-related inflammation, which could be the start of a new era for anticancer therapies, especially for CRI.

**AUTHOR CONTRIBUTIONS**
C.C. and A.R.S researched data for the article, substantively contributed to the discussion of content, and contributed to writing the article. G.S. significantly contributed to the discussion of content, generated the figures, and reviewed the manuscript. S.-S.L. reviewed and edited the manuscript before submission.

**CONFLICTS OF INTEREST**
The authors declare no competing interests.

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