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MicroRNAs and Epithelial Immunity

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Abstract

MicroRNAs are required for development and maintenance of the epithelial barrier. It is hypothesized that microRNAs are involved in regulating epithelial anti-microbial defenses by targeting key epithelial effector molecules and/or influencing intracellular signaling pathways. Additionally, aberrant microRNA expression has been implicated in the pathogenesis of various diseases at the skin and mucosa. Increased understanding of the role of microRNAs in epithelial immunoregulation and identification of microRNAs of pathogenetic significance will enhance our understanding of epithelial immunobiology and immunopathology.

Keywords

microRNAs; non-coding RNAs; Epithelium; Immunoregulation

INTRODUCTION

Epithelial cells of the skin and mucosa represent the host's first line of defense against microbial infection. Beyond the role of epithelial cells in creating a physical barrier to infection, epithelial cells are critical in the initiation, regulation, and resolution of both innate and adaptive immune responses [1,2]. Toll-like receptors (TLRs) expressed by epithelial cells recognize distinct pathogen-associated molecular patterns (PAMPs) and evoke diverse responses including anti-microbial peptide and cytokine release [3]. Epithelial cells also express a wide range of proteins associated with the immune response, including major histocompatibility complex (MHC) class I and II, costimulatory molecules, chemokines, cytokines, and prostaglandins, which together coordinate a strong adaptive immune response [4,5]. This epithelial immune response to infection is finely controlled and reflects a delicate balance between effector functions and their potential to cause damage to healthy tissue. Disturbance of this delicate balance may result in devastating consequences to the host, such as tissue damage due to an inappropriate immune response or an immune response that is insufficient to clear the pathogen [6-8]. Despite the obvious critical nature of epithelial cells in preserving host well-being, the study of immune responses triggered by epithelial cells is in its infancy [6,7].

The importance of microRNAs (miRNA) in regulating normal cellular functions is becoming increasingly clear as more miRNA targets are discovered and the molecular mechanisms underlying miRNA gene regulation becomes unraveled [8,9]. Modulation of miRNA expression has been studied *in vitro* as well as *in vivo* and has been used to ascribe important roles for miRNAs in epithelial function [10-15]. Emerging studies implicate specific miRNAs in controlling epithelial cell processes such as regulation of cellular differentiation, determination of epithelial cell fate (cell death and proliferation), initiation and regulation of

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anti-microbial immunity, fine-control of inflammatory responses and activation of intracellular signaling pathways[10,12-14,16-24]. Such control of epithelial cell functions is likely vital to fine-tuning of the epithelial immune response against infection. This review will highlight recent advances in the identification and expression of epithelial cell miRNAs. A brief summary of these exciting and newly emerging findings is listed in Table 1. In addition, we will discuss the functional significance of miRNA expression in immunoregulation of epithelial cells in health and disease [25-28].

MicroRNAs are abundant in epithelial cells at skin and mucosal sites

MicroRNAs are endogenous, single-stranded RNA molecules of approximately 22 non-coding nucleotides that regulate target genes at the post-transcriptional level [29,30]. A total of around 2000 miRNAs have been identified in over 80 species including plants, animals and virus (miRBase, Release 13.0, http://microrna.sanger.ac.uk). It is predicted that the human genome has 800-1000 miRNAs. Approximately 700 human miRNAs have been identified and these miRNAs are postulated to control 20 ~ 30% of human genes [31].

MicroRNAs have been identified in most human cell types that have been tested thus far. Distinct miRNA expression signatures are observed in a tissue-specific manner, suggesting that expression of these molecules is exquisitely controlled. For example, miR-192, miR-194, miR-204, miR-215 and miR-216 are preferentially expressed in human kidney, while these miRNAs are expressed at minimal levels in other tissues such as heart, spleen, lung and prostate [32]. Studies on numerous human cell lines derived from normal epithelial cells further confirmed the abundant expression of miRNA molecules in epithelial cells. Unique miRNA expression profiles have been described in normal epithelial cells from lung, breast, stomach, prostate, colon, and pancreas [33]. Additionally, miRNA signatures in cancer cell lines of epithelial origin are unique from those derived from normal epithelial cells [34,35]. The unique expression patterns of these powerful gene regulators in a tissue- and differentiation-specific manner further solidifies the critical nature of miRNAs in host homeostasis and defense from pathogens.

MicroRNAs are involved in epithelium development and are required for epithelial barrier integrity

The high level of expression of miRNAs in epithelial cells suggests a critical role for the miRNAs in regulating epithelial cell functions. One of the earliest demonstrations of the significance of miRNAs in epithelial barrier development was described in studies investigating the function of Dicer in morphogenesis and maintenance of hair follicles. Dicer knockout mice, which are incapable of processing precursor miRNAs into mature, functional miRNAs, experience abnormal skin morphogenesis [16,17]. Yi et al. developed a skin-targeted conditional Dicer knockout mouse to repress miRNA expression in skin epithelium. Although the epidermal barrier of these conditional Dicer 1 knockout mice was intact at birth, epidermal barrier integrity became compromised [16]. At P6.5, the skin of the conditional knockout mice developed hair follicle cysts indicative of increased proliferation. Other stratified epithelial tissues also experienced gross abnormalities. Andl et al. also found that mice carrying an epidermal-specific Dicer deletion developed an evagination of hair germs rather than invagination, accompanied by the loss of key signaling molecules Sonic hedgehog (Shh) and Notch expression [17]. Harris et al. used mice with the Shh^{cre} allele to inactivate Dicer in the lung epithelium shortly after the initiation of lung branching [18]. These Dicer-deficient mice experienced gross developmental defects compared to control mice. Instead of forming the typical branching pattern, the epithelial cells of the lungs of mutant mice formed large fluid-filled sacs. Additionally, the epithelium was not consistently attached to the mesenchyme as is observed in control mice. Increased epithelial cell death was also observed in distal regions of lungs of Dicer-inactivated mice. Because this increased epithelial cell death occurred at a

later stage of development than the branching defect, it cannot account for the defects in epithelial morphogenesis in the Dicer-inactivated lung.

These initial studies examining the impact of Dicer on epithelial cell morphogenesis opened the field to study the spatiotemporal expression of miRNAs during epithelium development [19-21]. Using human intestinal epithelial cells, Kimihiro et al. demonstrated dynamic miRNA expression profiles in these cells during differentiation. MicroRNA-194 was significantly upregulated in intestinal epithelial cells during induced differentiation *in vitro*. The induction of miR-194 is postulated to be controlled by hepatocyte nuclear factor −1α (HNF-α), a critical regulator of intestinal epithelial gene expression [19].

MicroRNA-17-92, a polycistronic miRNA cluster, has recently been discovered to be important for proliferation of lung epithelial progenitor cells. By comparing the miRNA expression profiles of lung tissue at different developmental stages, Lu et al. observed a progressive decline in miR-17-92 cluster expression as development proceeded. Ectopic expression of miR-17-92 cluster expression in embryonic lung epithelium resulted in accumulation of proliferative epithelial progenitor cells and inhibition of epithelial cell differentiation. Despite this knowledge, the mechanism by which the miR-17-92 cluster promotes proliferation and inhibits differentiation of lung epithelial progenitor cells remains unclear. There are 7 discrete miRNAs in the mi-R-17-92 cluster and each may target multiple genes, thereby increasing the complex regulatory interactions that may be occurring [20].

MicroRNA-203 is highly expressed in mature skin cells but minimally expressed in skin precursor cells. To test the impact of aberrant (that is, premature) miR-203 expression in skin, transgenic mice were generated using the keratin 14 promoter to drive miR-203 expression. These transgenic mice had significantly thinner back skin epidermis than their wild-type littermates. Blocking studies *in vitro* using primary cells suggest that p63 may be a target of this miR-203. p63, an important regulator of stem cell maintenance in stratified epithelial tissues, is not repressed in the absence of either Dicer or miR-203 [21]. The study also showed that miR-203 induced the cell-cycle exit and impaired the proliferative potential of epithelial stem cells, but had little effect on terminal differentiation marker expression. Thus, miR-203 appears to act as a switch between proliferation and terminal differentiation via a mechanism repressing progenitor cell proliferation. Given that epithelial progenitor cells provide a continuous source of differentiated epithelial cells, these studies highlight the importance of miRNAs in the maintenance of homeostasis of various epithelial barriers [19-21].

Studies by Yi et al. [21] provided novel insight into how miRNAs function in concert in a tissue-specific manner. By comparing the unique miRNA expression profiles found in epidermis and hair follicles. MicroRNAs were classified into groups according to the similarity of their 5′ends. Although miRNAs within a single group may be independently transcribed from separate genes, they appeared to be coordinately expressed. For example, five members of the miR-200 family and four members of the miR-19/20 family were predominately expressed in epidermis, while miR-199 family members were exclusively expressed in hair follicles. The co-expression of multiple miRNAs with similar seed sequences in the same lineage suggests that the miRNAs function together to permit effective suppression of specific target genes within the cells and thus may be important in maintaining specific-tissue characteristics.

Expression of microRNAs in epithelial cells is finely regulated in response to extracellular stimuli

Alterations in miRNA expression following immune stimulation were first described in macrophages and monocytes [36,37]. Because of the alterations described in miRNA expression following immune stimulation of monocytes and macrophages, it has been

postulated that miRNAs are involved in response to extracellular stimuli including pathogen infection [36]. So far, miR-146 is one of the best studied NF-κB-dependent miRNAs in immune cells. Expression of miR-146 in macrophages and monocytes is induced via NF-κB activation following lipopolysaccharide (LPS) stimulation [36]. While there are no studies demonstrating LPS induction of miR146 in epithelial cells, it was recently reported that IL-1β could induce miR-146a expression in A549 cells (cell line derived from human epithelial lung carcinoma) via NF-κB activation. IL-1β-induced miR-146a expression was further confirmed in primary bronchial epithelial cells and in a SV40 transformed bronchial Beas2B epithelial cell line [10]. Because this induction was only observed at high IL-1β concentrations, it was postulated that miRNA-146a plays a role in severe inflammation [10]. Triggering the downstream signaling pathways of the Toll/interleukin(IL)-1 receptor (TIR) superfamily members is key to initiating and activating immune responses in many cell types [38].

Similarly, following exposure to high dose IL-1β, lung alveolar epithelial cells downregulated at least six miRNAs including miR-26b, miR-104, miR-195, miR-296, miR-299 and *let-7g* [10]. Other data suggests that TLR/MyD88/NF-κB-mediated and tissue type-dependent expression of specific miRNAs expression may apply to several miRNAs. For example, miR-155 expression is regulated by TLR/MyD88/NF-κB signaling in macrophages and monocytes [37], but not in lung epithelial cells [10,11]. Alterations in miRNA expression are not solely limited to upregulation of miRNA expression. Activation of the TLR/MyD88/NF-κB pathway has been reported to downregulate certain miRNAs in some cell types as well. Recently we showed that activation of TLR/MyD88/NF-κB decreased *let-7* expression in H69 cells (SV40 transformed normal human biliary epithelial cells) [12].

Besides TIR-mediated signaling, cytokines and chemokines may also regulate miRNA expression in epithelial cells during immune reactions. Given the redundant, synergistic, and antagonistic nature of the soluble mediator network, it is difficult to clearly elucidate the roles of specific miRNAs during immune responses. Nevertheless, several recent studies have attempted to address this complex issue. Treatment of human hepatocytes with IFN-α induced significant alterations in expression of ~30 miRNAs [13]. Specifically, miR-1, miR-30, miR-128, miR-196, miR-296, miR-351, miR-431 and miR-448, were upregulated. Conversely, several miRNAs, including miR-122, a liver-specific miRNA, were downregulated [13]. Recently we examined the effect of IFN-γ treatment on miRNA expression in human biliary epithelial (H69) cells demonstrating that IFN-γ induced a universal downregulation of miRNA expression in these cells [14]. MicroRNA-mediated translational silencing is also compromised in human bronchial epithelial BEAS-2B cells following stimulation with IL-4 and TNF-α [15]. Together, the current literature demonstrates the responsiveness of miRNA expression to immune stimuli that are both pathogen- (i.e., LPS) and host-derived (i.e., IL-4).

MicroRNAs may target key components of signaling pathways and alter cell surface proteins involved in immune responses in epithelial cells

While the previous section described the impact of immune stimulation via either PAMPs or host immunomodulators on miRNA expression, miRNAs also appear to impact the signaling pathways directly. Potential targets of miR-146 are IL-1 receptor-associated kinase 1 (IRAK1) and TNF receptor-associated factor 6 (TRAF6) [36], both of which are key components of the TLR/NF-κB signaling pathway [38,39]. Upregulation of miR-146 following LPS stimulation is postulated to be a negative feedback regulator inhibiting TLR/NF-κB signaling in macrophages and monocytes [36]. MicroRNA-146a was also induced in human lung alveolar epithelial cells by exposure to high concentrations of IL-1β [10]. Transfection of the alveolar epithelial cells with miR-146 precursor prior to cytokine exposure *in vitro* decreased IL-8 and CCL5 release, indicating that miR-146 is likely involved in regulating release of mediators involved in the early phases of an immune response, either directly or indirectly. Conversely,

transfection of the same cells with anti-miR-146a increased the release of these two cytokines. The effect of miR-146a on IL-1β-induced IL-8 and CCL5 release in lung epithelial cells appears to be independent of both IRAK1 and TRAF6. Transfection of these cells with miR-146a precursor did not decrease IRAK1 or TRAF6 levels. Furthermore, although three genes involved in secretion (syntaxin-3, synaptotagmin-1 and sec23 interacting protein) are also the predicted targets for miR-146a, their protein levels were also not affected by miR-146a precursor transfection. Together these findings demonstrate that miRNA-mediated gene regulation remains a field dominated by complex interactions, many of which remain undefined.

In addition to delivering intracellular signals, miRNAs have also been implicated in regulating expression of membrane proteins important in modulating immune reactions. B7-H1, a member of the B7 costimulatory molecule family, is critical in regulating cell-mediated immune responses including epithelial-T cell interactions [14]. Our recent work showed that B7-H1 expression was suppressed at the translational level in resting human biliary epithelial cells *in vitro* and transfection of these cells with anti-miR-513 induced B7-H1 protein expression. Downregulation of miRNA-513 was required for IFN-γ-induced B7-H1 protein expression. Transfection of miR-513 precursor decreased IFN-γ-induced B7-H1 expression, demonstrating that miR-513 downregulation was key to IFN-γ-induced B7-H1 induction. Moreover, transfection of biliary epithelial cells with the miR-513 precursor inhibited B7-H1-associated apoptotic cell death in co-cultured human T cells, demonstrating the functional significance of miR-513 in biliary epithelial cell-T cell interactions during an immune response.

Exosomes are small membrane vesicles derived from multivesicular bodies or endocytic-like lipid raft domains of the plasma membrane and are found in many cell types including epithelial cells. There is an emerging concept that exosomes mediate cell-cell communication via exosomal shuttle of molecules including miRNAs [40,41]. MicroRNAs have been identified in exosomes released from cultured mast cells [40]. Epithelial cell secreted exosomes have been shown to express high levels of MHC-peptide complexes, capable of modulating immune responses [42,43]. Given that miRNAs have been shown to impact immune responses, it would be interesting to determine if exosomes from epithelial cells also contain miRNAs and thus modulate epithelial-immune cell interactions via exosomal delivery of miRNAs.

MicroRNAs are involved in the regulation of epithelial anti-microbial defense

The role of epithelial cell miRNAs in the control of microbial infections has recently been investigated. Otsuka et al. demonstrated that Dicer knockout mice were highly susceptible to vesicular stomatitis virus (VSV) infection [22]. By fusing different segments of VSV sequence to the 3′UTR of a luciferase reporter gene, three VSV genome sequences were identified that decreased reporter gene expression. Four miRNAs (miR-24, miR-93, miR-146 and miR-378) were expressed by host epithelial cells with the potential to target VSV. Transfection of epithelial cells with either anti-miR-24 or anti-miR-93 resulted in 4- to 5-fold decrease in virus titer. Although it remains to be determined if these miRNAs inhibit VSV replication in the virus's natural hosts, the abundant expression of these specific miRNAs at the site of VSV replication in the epithelial layer suggests that miR-24 and miR-93 may participate in defense of the epithelial barrier.

In hepatocytes, eight IFN-inducible miRNAs (miR-1, miR-30, miR-128, miR-196, miR-296, miR-351, miR-431 and miR-448) have been shown to have nearly perfect complementarities between their seed sequences and the hepatitis C virus (HCV) RNA genome [13]. Transfection of HCV replicon-containing hepatocytes with precursors of these 8 miRNAs decreased the levels of HCV RNA accumulation. Functional inhibition of these particular miRNAs abrogated the inhibitory effect of IFN on HCV replication in hepatocytes. IFN-β treatment also decreased

miR-122 expression, a liver specific miRNA essential for HCV replication in hepatocytes [23]. The downregulation of miR-122 in response to IFN-β further enhanced the antiviral effects of this cytokine. Together the data suggest a novel mechanism involving miRNA-mediated gene targeting to fight HCV infection in hepatocytes [13].

The initial data derived from these *in vitro* studies are not compatible with some *in vivo* data thus far. Magdalena et al. examined miR-122 levels in liver biopsies from 42 patients with chronic hepatitis C (CHC) undergoing IFN treatment. Pretreatment levels of miR-122 in non-responders were several times lower than miR-122 levels in responders. Given the results from *in vitro* studies suggesting that miR-122 is crucial for efficient replication of HCV in hepatocytes [23], this finding in CHC patients is unexpected and suggests that the impact of miR-122 on HCV replication may be less pronounced *in vivo* than it is *in vitro*, probably a result of the complex *in vivo* interactions that are difficult to model in tissue culture [24],

MircoRNAs have also been implicated in epithelial immune responses against other pathogens, including parasites. We recently reported that *C. parvum* infection decreased *let-7* expression in human cholangiocytes [12]. Downregulation of *let-7* was dependent on TLR/MyD88/NF-κB pathway activation and enhanced TLR4 expression. Since TLRs recognize PAMPs and are key modulators of epithelial cell immune responses to microbial infection, these data raise the possibility that miRNAs may be critical to host-cell regulatory responses to microbial infection in general. Moreover, experimental manipulation of *let-7i* expression caused reciprocal alterations in the infection dynamics of *C. parvum in vitro* [12].

Aberrant expression of microRNAs has been implicated in the pathogenesis of various inflammatory diseases at skin and mucosal sites

There is increasing evidence implicating deregulation of miRNA expression in epithelial cells at sites of sustained inflammation, a hallmark of many chronic inflammatory diseases at skin and mucosal sites. Sonkoly et al. examined miRNA expression profiles in the skin from patients with psoriasis, a common chronic inflammatory skin disease [25]. MicroRNA-203 was significantly up-regulated in skin from patients with psoriasis. Interestingly, miR-203 has 10-nucleotides with complementarity to the 3′UTR of SOCS-3 mRNA. Decreased SOCS-3 protein expression, but not SOCS-3 mRNA, was also found in psoriasis skin compared with healthy skin, suggesting posttranscriptional repression of SOCS-3. Further supporting a role for miR-203 in SOCS-3 regulation, a mutually exclusive expression pattern of miR-203 and SOCS-3 was observed in the skin from healthy subjects and patients with psoriasis. These data suggest that downregulation of miR-203 may induce relief of posttranscriptional suppression of SOCS-3 expression in keratinocytes in patients with psoriasis. Since SOCS-3 is a negative regulator of IL-6 and IFN-γ-induced signaling [44], upregulation of SOCS-3 could result in constitutive activation of STAT3, a downstream effector of the IL-6 and IFN-γ receptor signaling pathways. This impaired negative feedback regulation in keratinocytes may consequently contribute to prolonged skin inflammation [25]. Nevertheless, further investigations are needed to directly and fully demonstrate the consequences of miR-203 deregulation in psoriasis.

To test a potential role for miRNAs in inflammatory diseases of the intestine, Wu et al. examined miRNA expression profiles in skin of patients with chronic inflammatory bowel diseases [26]. Eleven miRNAs were differentially expressed in patients with active ulcerative colitis (UC). MicroRNA-192, one of three miRNAs that were significantly downregulated, was found to be predominantly localized to colonic epithelial cells. In addition, *in situ* hybridization revealed that miR-192 expression was inversely correlated to macrophage inflammatory peptide (MIP)-2α expression in the epithelial layer. Functional data implicate miR-192 as directly targeting the 3′UTR of MIP-2α and inhibiting MIP-2α expression via TNF-α in human colonic epithelial cells. Thus, these data suggest that miR-192 functions as a

negative regulator of MIP-2 alpha expression and dysregulation of miR-192 may contribute to uncontrolled inflammation in chronic inflammatory bowel diseases.

Cigarette smoking alters gene expression in bronchial airway epithelium; many of these genes are involved in regulation of oxidant stress, xenobiotic metabolism, inflammation and tumorigenesis [45]. Schembri et al. analyzed whole-genome miRNA expression in bronchial airway epithelium from individuals who were current smokers and individuals who never smoked [27]. This study identified upregulation of 23 miRNAs and downregulation of five miRNAs in the bronchial airway epithelial cells from the smokers. Interestingly, expression of many of these miRNAs was inversely correlated with expression of their predicted targets in bronchial epithelial cells. Specifically, functional manipulation of miR-218, a miRNA downregulated by smoking in bronchial epithelial cells, was sufficient to cause reciprocal alterations in the protein expression of its predicted targets including small Maf protein G (MAFG). MAFG is a key player in inflammatory responses [46] and MAFG binding sites are found in the promoters of many genes whose expression are altered by smoking [27]. Transfection of bronchial epithelial cells with the miR-218 precursor diminished cigarette smoke condensate-induced MAFG expression. Together, these data suggest that miRNAs are involved in the overall epithelial response to tobacco smoke exposure [27]. Specifically, miRNAs may modulate bronchial epithelial cell responses to cigarette condensate and participate in the pathogenesis of smoking related diseases.

It has long been suggested that the persistent inflammation plays a crucial role in cancer development. Although the direct evidence for this hypothesis is minimal, recent studies suggest that miRNAs may serve as the bridge between inflammation and tumorigenesis, including cancer development at mucosal sites [28]. MicroRNA-146a expression appears to be driven by the transcription factor NF-κB, which has been implicated as an important causal link between inflammation and carcinogenesis. While elevated miR-146a expression promotes cancer cell proliferation, several studies showed that miR-146a expression in metastatic cancer cells markedly impaired invasion and migration capacity of the cancerous cells [47,48]. Liu et al. found that miR-146a overexpression protected the human bronchial epithelial cells from apoptosis in response to TGF-β1 plus cytomix stimulation [28]. Interestingly, whereas miR-146a mimic had little effect on epithelial-mesenchymal transition (EMT) induction in response to inflammatory stimulation, the anti-miR-146a significantly augmented EMT, suggesting endogenous expression of miR-146a is critical to control EMT [28]. Thus, it would be attractive to speculate that the balance between the expression levels of various miRNAs would be key determinants in regulating the response of epithelial cells to inflammatory stimulation.

CONCLUSION AND PERSPECTIVES

Study of miRNAs is flourishing in the decade after their discovery. It is clear that miRNAs have the potential to affect every aspect of cellular function, from cell differentiation and proliferation to apoptotic death. MicroRNAs appear to regulate a diverse spectrum of epithelial cell functions including epithelial cell developmental, refining intracellular signaling and controlling epithelial immune responses to inflammatory stimuli and pathogens. Aberrant miRNA expression has been implicated in the pathogenesis of various inflammatory diseases of the skin and mucosa. In the near future, distinct miRNA signatures involved in fine-control of intracellular signaling and expression of proteins including anti-microbial peptides, cytokines and chemokines, adhesion and costimulatory molecules, should define the role of miRNAs in epithelial immune responses. Further, identification of miRNAs of significant pathogenic significance in persistent inflammatory reactions of the skin and at mucosal sites could provide rationale for the design and implementation of new immunotherapeutic strategies for treatment of the diseases. Unraveling the regulatory circuits of miRNAs in epithelial biology

is in its infancy, but will likely yield new insights into our understanding of epithelial immunobiology and immunopathology.

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Abbreviations

TLR, Toll-like receptor
PAMPs, pathogen-associated molecular patterns
MHC, Major histocompatibility complex
miRNAs, microRNAs
3′UTR, 3′-untranslated region
NF-κB, nuclear factor-kappa B
IRAK1, interleukin-1 receptor-associated kinase 1
IL, interleukin
TRAF6, TNF receptor associated factor 6
CCL5, CC motif ligand 5
IFN, interferon
CIS, cytokine-inducible Src Homology 2-containing protein
TIR, Toll/IL-1 receptor
MYD88, myeloid differentiation primary response gene 88
LPS, lipopolysaccharide
MIP-2, macrophage inflammatory peptide-2
MAFG, Maf protein G
UC, ulcerative colitis
CHC, chronic hepatitis C

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Table 1

Experimental charactering of miRNAs in epithelial cells

MicroRNAs	Potential functions in epithelial cells	References
miR-17-92,	Involved in lung epithelium morphogenesis.	[20]
MiR-203	Involved in skin Morphogenesis by targeting p65. Decreased in psoriasis and targeting SOSC3.	[21],[25]
MicroRNA-146a/b	Maintenance of lung epithelium homeostasis during inflammation. Modulation of cytokine production in lung epithelial cells. Induced by IL-1β and TGF-β1 plus cytomix.	[10],[28]
miR-1, miR-30, miR-128, miR-196, miR-296, miR-351, miR-431, miR-448	Inhibition of HCV replication by targeting virus genome in hepatocytes. Induced by interferon beta.	[13]
miR-122	Permissive of HCV replication *in vitro*. Positively correlated with interferon therapy.	[23] [24]
miR-24,miR-93	Inhibition of VZV replication by targeting virus genome.	[22]
let-7	Promotes of *C. parvum* infection clearance in biliary epithelial cells. Induced by LPS and *C. parvum* infection.	[12]
miR-513	Regulation of immune response in biliary epithelial cells by targeting costimulatory molecular B7H1. Decrease by INF-γ.	[14]
miR-218	Decreased by smoking in lung epitheliumand and targeting MAFG.	[27]
miR-192	Decreased in inflammatory bowel diseases and targeting MIP-2.	[26]