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MicroRNAs in intestinal barrier function, inflammatory bowel disease and related cancers — their effects and therapeutic potentials

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Abstract

The initiation and development or inflammatory bowel disease (IBD) and associated colorectal cancers, have been linked to inflammation. MicroRNAs are non-coding regulators of gene expression that have gained great attention due to their capability to regulate the expression of a number of target transcripts. It is now generally admitted that microRNAs are instrumental in gut pathologies, in particular through their targeting of transcripts encoding proteins of the intestinal barrier (IB) and their regulators. Intense research is conducted to identify microRNAs susceptible to be used as biomarkers and to design new therapeutic approaches based upon using synthetic microRNA mimics and inhibitors as well as finding new drugs capable to restore or modify microRNA expression in the context of gut pathologies.

Introduction

Food digestion and nutrient absorption rest on the activity of intestinal epithelial cells (IECs) and of a plethora of microorganisms, collectively referred to as the microbiota. The greatest proportion of microbiota corresponds to commensal bacteria that both participate to the digestion of nutrients and help to keep the gut healthy by competing with pathogens for the same ecological niche. Interactions between the microbiota, IECs and immune cells modulate the renewal of the epithelium and the activation status of immune cells.

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Immune cells must tolerate commensal bacteria and antigens produced from food digestion while retaining their full activation capacity to fight invading pathogens. The health of the gut thus rests on a delicate equilibrium between IECs loss and proliferation, on one hand, and immune cells activation or tolerance, on the second hand. When this equilibrium is broken, inflammatory conditions can occur and induce gut pathologies such as Inflammatory bowel disease (IBD). IBD is a group of chronic idiopathic, relapsing and remitting immune disorders of the gastrointestinal tract in genetically susceptible individuals exposed to environmental risk factors [1]. IBD present with two main forms: Crohn's disease (CD), that may affect any part of the gastrointestinal tract, and ulcerative colitis (UC), that is confined to the colon [2].

The critical role played by the intestinal barrier (IB) on gut health and function came to light recently, although whether intestinal barrier defect is a cause or a consequence of IBD remains debated [3–5]. The semi-permeable IB established by IECs must allow the captation of nutrients while avoiding the passage of pathogens. This double function depends on the production of a luminal mucosal barrier, that restricts the access of bacteria to intestinal epithelium, and the presence of different types of IECs that concur to IB homeostasis [6,7]. Organized in a single layer, IECs are linked by three types of junctions, namely, from apical to basal, tight junctions, adherens junctions and desmosomes. Tight junctions are implicated in blocking the transit of bacteria and food while facilitating paracellular flux through the pore pathway and the leak pathway [8]. Chronic, enhanced inflammation can damage IB, allowing unwanted bacteria and molecules to cross IB and further exacerbate the immune response, depending on the quality of mucosal layer and tight junctions, the composition of the microbiota, and ultimately the genotype of each individual.

MicroRNAs are small non-coding RNAs that regulate the translation and/or stability of target transcripts. Micro-RNAs control the expression of tens to hundreds of transcripts, either directly through binding or indirectly by targeting transcripts encoding transcription factors, epigenetic regulators or effectors of signal transduction pathways. As target transcripts usually contain one short sequence partly complementary to targeting microRNAs, one can predict, with a certain risk of error, the targeting of a given transcript by a given microRNA. MicroRNAs are major regulators of cell function and homeostasis, and their aberrant expression has been found in virtually all diseases, including IBD, CD, UC and cancers. Therefore, molecules that would allow targeting of specific micro-RNAs in a specific context should improve the efficiency of existing treatments. In this review, we will emphasize results of the last 2–3 years that implicate microRNAs in IBD and inflammation-related gut cancers, and summarize the therapeutic potential of using specific micro-RNAs as biomarkers and/or therapeutic agents in these pathologies.

MicroRNAs in IBD

Frozen nondysplastic colonic mucosa collected from CD and UC patients showed differential expression of micro-RNAs, implicated in the regulation of genes encoding proteins of epithelial adhesion junctions, integrin, glycolysis and cell cycle [9••]. Altered microRNA expression profiles were found between inflamed and non-inflamed ascending colon mucosae of CD patients [10••], and microRNAs of the *miR-200* family showed

enhanced expression in UC dysplastic lesions [11,12]. Patients with pediatric CD showed enhanced duodenal expression of *miR-146*, *miR-155* and *miR-122* [13,14]. MicroRNAs regulated cytokine production in regulatory T cells of UC patients [15], *miR-155* targeted *Jarid2* transcripts in Th17 cells in an experimental dextran sulfate sodium (DSS)-induced colitis in mouse [16], and increased *miR-511-3p* expression in mouse macrophages has been linked to intestinal inflammation [17]. By contrast, *miR-31* expression increased while *miR-21*, *miR-155* and *miR-146a* levels decreased in colonic $CD3^+$ T cells in UC remission [18]. Table 1 presents microRNAs with validated target transcripts in gut mucosa or cells of the immune system in the context of IBD or in different mouse models [16,19,20•,21••,22–32].

MicroRNAs in IB

Patients with IBD and their healthy relatives have increased intestinal permeability, suggesting that barrier dysfunction might contribute to inflammation in IBD and other inflammatory-related gut pathologies [4,33,34]. IB external, mucosal layer is represented by glycosylated mucins and less abundant proteins secreted by goblet cells. Tight junctions that regulate paracellular transport require the presence of proteins such as Claudins, Occludin, MarvelD2/Tricellulin, MarvelD3, Zona occludens (Z0)-1-3 and the regulator of tight junction permeability myosin light chain kinase (MLCK) [5,35]. Paneth cells have a very active autophagy pathway and secret antibacterial peptides, including Lysozyme, RegIIIA and αDefensins such as HD5 and HD6. Abnormal expression of genes encoding barrier proteins has been linked to the development of IBD, CD, UC and other inflammatory-related diseases [5,7,34]. Several microRNAs, whose expression changed in IBD [16,19,20•,21••, 22–32,36] have been shown to target transcripts encoding some of the above proteins in the context of gut inflammatory diseases. For example, by targeting *Claudin 8*, pro-inflammatory *miR-223* was instrumental in allowing IL23 pathway to initiate trinitrobenzene sulphonic acid (TNBS)-induced colitis in mice [32]. Computer analysis using Targetscan software (http://www.targetscan.org) allowed us to predict microRNA–mRNA interactions possibly implicated in IB homeostasis and dysfunction (Table 2). Interestingly, transcripts encoding IB proteins Claudin 1, Occludin, MarvelD3, ZO-1, MYLK, Catenin delta1/p120, VEZT, and Desmocolin 3 are likely target of the highest number of microRNAs, suggesting that micro-RNA deregulation might be an initiating or aggravating factor for IBD. Taken all together, microRNAs listed in Table 2 do not show any preference between the six classes of transcripts (Figure 1). By contrast, other micro-RNAs should preferentially target specific components of tight junctions, adherens junctions, desmosomes, or factors implicated in the immune response. Thus, it is likely that deregulation of different microRNAs will have differential effects on paracellular permeability, cell–cell adhesion or the level of inflammation, and thus should be associated with different intestinal pathologies. IB is now considered a key therapeutic target [3–5], therefore any treatment susceptible to restore normal microRNA expression is likely to improve the treatment of gut diseases. Nevertheless, certain genes encoding important barrier proteins or mucins that are not listed in Table 2 have a very short 3′-untranslated region and likely are not directly regulated by microRNAs.

MicroRNAs in inflammation-related cancers

Chronic UC has been associated with increased risk of colonic neoplasia, and microRNAs are critical players in molecular circuitries linking inflammation and cancer [37]. Changes in expression or glycosylation of proteins of tight junction, adherens junction or desmosomes have the potential to turn them from tumor suppressors to tumor promoters [38–40]. The expression of several microRNAs implicated in IBD is deregulated in colon cancer. For example, the levels of microRNAs of the *miR-200* family increased in UC dysplastic lesions [11], and *miR-200-3p* showed higher expression in colorectal cancer complications [11]. In IBD, downregulation of *miR-200* microRNAs correlated with increased Snail and Slug, a hallmark of epithelium-to-mesenchyme transition [41]. Archetypal oncogenic *miR-21* was found upregulated in patients with colitis-associated colorectal cancer as well as in a mouse model of this pathology [42,43]. Inflammation can trigger a *miR-34a*-Numb feed-forward loop that enhances asymmetric stem cell division in intestine and colon cancer [44•]. Inhibiting *miR-214*, a microRNA highly expressed in colon samples of patients with UC or UC-associated colorectal cancer, reduced the number and size of tumors of mice given azoxymethane in a DSS-induced colitis model [45]. *MiR-301a* targets BTG anti-proliferation factor 1 (BTG1), thus favoring intestinal inflammation and colitis-associated cancer development [46••]. Neuropeptide Y from enteric neurons promotes inflammation-induced cancer, both by activating cell proliferation through the PI3-K/AKT pathway and by down-regulating *miR-375*, a microRNA pro-apoptotic in IECs [47]. By contrast, microRNAs such as *miR-193a-3p* and *4728-3p* were down-regulated in patients with UC-associated colorectal cancer, and behaved as tumor suppressor in colon cancer cells, by respectively targeting interleukin 17 receptor D (ILR17D) and focal adhesion signaling [48,49]. Nevertheless, *miR-31*, not express in normal IECs but highly deregulated in mouse and human colorectal cancers, can function both as an oncogenic or a tumor-suppressor microRNA depending on the context, and its deletion has been shown to promote UC-associated cancer in mouse [50]. Interestingly, two different E-cadherin- p120 complexes have been identified at the junctions of polarized epithelial cells, the apical one containing the factor PLEKHA7 that is implicated in stabilization of adherens junctions. Remarkably, apical PLEKHA7 complex, through its association with the microprocessor components Drosha and DGCR8, was able to regulated the levels of a subset of microRNAs such as *miR-24*, *miR-30a*, *miR-30b* and *let-7g*. Owing to the presence of microprocessor, apical PLEKHA7 complex was able to control the processing of at least the precursor (pri-*miR-30b*) of *miR-30b* [51••], a microRNA, known to inhibit epithelium-to-mesenchyme transitions. It is now clear that microRNAs targeting transcripts encoding components of cell–cell junctions are instrumental in IB dysfunction associated with both IBD and IBD-associated tumors (Figure 2).

MicroRNAs as biomarkers and therapeutic targets

In the light of the above considerations, one can expect microRNAs to represent valuable biomarkers. Indeed, *miR-26b*, up-regulated in colon biopsies of patients with UC and UC-associated cancer, was conversely down-regulated in sporadic colon cancers [52]. The levels of *miR-320a*, a microRNA that inhibits *Escherichia coli*-induced damage to IB, were increased in blood samples of CD patients and UC mice [53•]. The expression of

miR-221-5p, that reduces IL6-receptor expression and decreases inflammation, was higher in biopsies of UC but not of CD patients [54]. Polymorphisms in *miR-122*, *miR-196a2* and *miR-124a* genes have been associated with different IBD clinical phenotypes [55]. MicroRNA mimics and antisense inhibitory RNAs (antagomiRs) should allow to compensate for endogenous microRNA deregulation, and several pre-clinical and clinical assays are already under way. For example, microvesicles-delivered *miR-200b* attenuated experimental colitis-associated intestinal fibrosis by inhibiting TGF-β1 mediated epithelium-to-mesenchyme transition in IECs and in a rat model of 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced intestinal fibrosis [56]. Nevertheless, caution should be exerted for the treatment of long-lasting pathologies. In particular, in long-lasting treatments, the risk of off-target effects should not be minimized, especially given the potential of microRNAs to be secondly transported toward non-target cells. Also caution should be exerted considering that microRNAs have repeatedly been shown to reduce the levels of their target transcripts in a dose-dependent manner. For example, only low levels of pro-inflammatory *miR-155* translated into targeting *Quaking* transcripts in lipopolysaccharide (LPS)-challenged macrophages [57]. Thus, except when mutations incapacitate endogenous microRNA(s) of interest, it remains of great importance to develop new drugs capable to modulate ‘on demand’ the expression of particular microRNA(s) while causing minimal harmful consequences.

Conclusion

During the last 15 years, many publications have unraveled the enormous potential of microRNAs to provide new, powerful biomarkers that can be used to define ever more subtle sub-categories within patients with major pathologies such as cancer or autoimmune, metabolic, neuro-degenerative and behavioral diseases. This versatility brings hopes to develop new drugs capable, through the manipulation of endogenous microRNA populations, to deliver maximal beneficial effects with minimal iatrogenic consequences, or, in specific contexts, to directly deliver microRNA mimics or antagomiRs to pathological cells, ultimately leading to truly ‘personalized’ medicine. On the other hand, a number of phytochemicals that can be provided by dietary intake or food supplementation have been identified as being beneficial for the body. Although few epidemiological studies and intervention trials are available, experiments conducted on cell cultures or in animals have established that some of these phytochemicals deliver at least some of their antioxidant, anti-inflammatory and/or anti-proliferative effects through the modification of the composition of endogenous microRNA populations. For example, catalpol, an iridoid glucoside found in plants of genus *Rehmannia*, has been shown to reduce endoplasmic reticulum stress in UC through the down-regulation of *miR-132* [58], while salvianolic acid B, extracted from *Salvia miltiorrhiza*, restored impaired IB in a rat model of TNBS-induced colitis likely through inducing downregulation of MLCK by *miR-1* [59]. Also, flavonoid and non-flavonoid poly-phenols found in different fruits and berries present antioxidant, anti-inflammatory and/or anti-proliferative effects on cell cultures or in murine models, including cases of gut inflammation or colon cancer. Many of these polyphenols appear to modify the expression of endogenous microRNAs [60]. Considering that polyphenols do not behave as classical, purified drugs and seem to act in many different ways through many different

mechanisms, they are often considered as non-effective and not relevant. Nevertheless, polyphenols such as resveratrol that do not display harmful properties might possibly be used as diet supplement to regulate the function of micro-RNAs, especially those present in EICs. Altogether, maintaining or restoring normal microRNA expression in IECs should prove beneficial in health as well as in disease.

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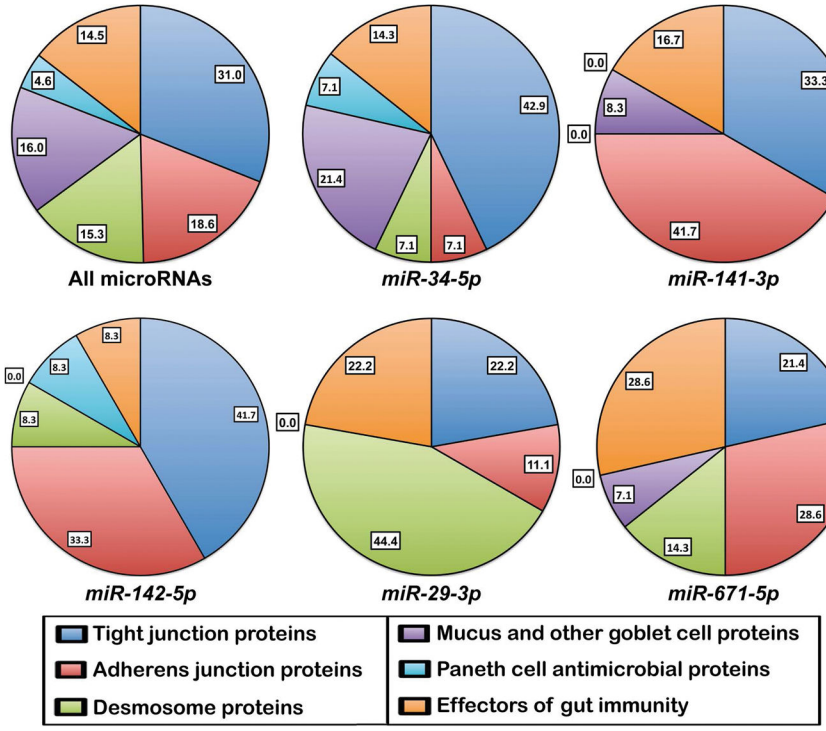

Figure 1.

Percentages of transcripts belonging to the six classes of transcripts encoding proteins involved in IB and gut immunity (listed in Table 2) that are potentially targeted by microRNAs whose expression changes in IBD. 'All microRNAs' refers to microRNAs in Table 2. The name of five microRNAs representative of microRNAs that show class-preference are given under the pie charts.

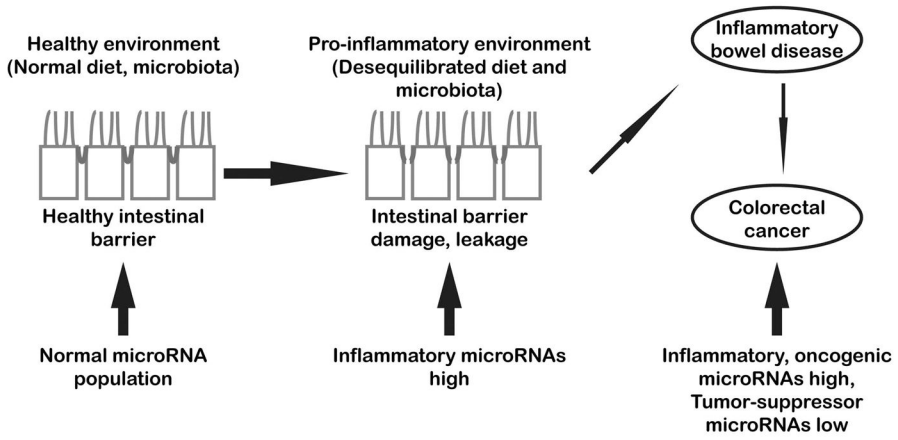

Figure 2.

Schematic diagram summarizing the main results and concepts discussed in this review. MicroRNAs are powerful regulators of cell homeostasis and function. Following IB damage, persistent inflammatory conditions can alter microRNA expression, initiating or accelerating the development of IBD. On the long run, chronic deregulation of microRNAs targeting transcripts encoding key components of IB as well as of oncogenic and tumor-suppressors microRNAs may lead to the development of colorectal cancer.

Table 1

Validated target transcripts of microRNAs implicated in IBD.

MicroRNA(s)	Target transcript(s)	Proteins	Pathology	References
miR-132, miR-223	*FOXO3*	Forkhead box O3	IBD	[19]
miR-223	*NLRP3*	NLR family pyrin domain containing 3	IBD	[20]
miR-320	*NOD2*	Nucleotide binding oligomerization domain containing 2	IBD	[21]
miR-665	*XBP1/ORMDL3*	X-box binding protein 1/ORMDL sphingolipid biosynthesis regulator 3	IBD	[22]
miR-31	*IL-25*	Interleukin 25	CD	[23]
miR-124	*AHR*	Aryl hydrocarbon receptor	CD	[24]
miR-29b	*MCL1*	MCL1, BCL2 family apoptosis regulator	CD fibrosis	[25]
miR-16	*ADORA2A*	Adenosine A2a receptor	UC	[26]
miR-206	*ADORA3*	Adenosine A3 receptor	UC	[27]
miR-429	*MARCKS*	Myristoylated alanine rich protein kinase C substrate	UC	[28]
miR-155	*FOXO3*	Forkhead box O3	UC	[29]
miR-155	*Ship-1/INPP5D*	Inositol polyphosphate-5-phosphatase D	Spontaneous colitis[a]	[30]
miR-155	*Jarid2*	jumonji and AT-rich Interaction domain containing 2	Induced colitis[b]	[16]
miR-193a-3p	*PepT1*	Solute carrier family 15 (oligopeptide transporter), member 1	Induced colitis[b]	[31]
miR-223	*CLDN8*	Claudin 8	Induced colitis[c]	[32]

[a] Bacteria-induced spontaneous colitis in mouse.

[b] Mouse model of dextran sulfate sodium (DSS)-induced colitis.

[c] Mouse model of 2,4,6-trinitrobenzene sulphonic acid (TNBS)-induced colitis.

Table 2

MicroRNAs whose expression changed in IBD [16,19,20•,21••,22–32] or a mouse model of colitis [36] potentially[a] target transcripts encoding proteins of IB and gut immunity.

Proteins	Target transcripts	MicroRNAs	Number of targeting microRNAs
Tight junction proteins			
Claudin 1	*CLDN1*	29a-5p; 29-3p; 34-5p; 142-5p; 144-5p; 155-5p; 194-5p; 196-5p; 449-5p; 455-5p; 483-3p; 584-5p; 1290; 4725-3p	14
Claudin 2	*CLDN2*	29a-5p; 34-5p; 122-5p; 142-3p; 449-5p; 483-3p; 1291; 3622a-3p; 3622b-3p	9
Claudin 3	*CLDN3*	455-3p	1
Claudin 4	*CLDN4*	142-3p; 144-5p; 455-3p.1; 483-3p; 1291; 4793-3p	6
Claudin 5	*CLDN5*	122-5p; 671-5p; 1291	3
Claudin 7	*CLDN7*	122-5p; 140-3p; 223-3p; 483-5p; 483-3p	3
Claudin 8	*CLDN8*	21-5p; 34-5p; 155-5p; 142-5p; 143-3p; 144-5p; 181-5p; 223-3p; 449; 455-3p	3
Occludin	*OCLN*	29-3p; 122-5p; 142-5p; 142-3p.1; 144-3p; 155-5p; 181-5p; 192-3p; 200b-3p; 200c-3p; 429; 455-5p; 455-3p.2; 584-5p; 3622b-5p	15
MARVEL domain containing 2/ Tricellulin	*MARVELD2*	29a-5p; 141-3p; 145-5p; 194-5p; 200b-3p; 200c-3p; 223-3p; 429; 671-5p; 3622b-5p; 3622a-3p; 3622b-3p; 4793-3p	13
MARVEL domain containing 3	*MARVELD3*	29a-5p; 34-5p; 93-5p; 106-5p; 122-5p; 141-3p; 142-3p.1; 145-5p; 155-5p; 200a-3p; 200b-3p; 200c-3p; 429; 449-5p; 455-3p.2; 483-5p; 1290; 3622a-3p; 3622b-3p	19
Tight junction protein 1/ZO-1	*TJP1*	34-5p; 141-3p; 142-5p; 142-3p.1; 144-3p; 145-5p; 194-5p; 200a-3p; 200b-3p; 200c-3p; 429; 449-5p; 455-5p; 1290; 4725-3p	15
Myosin light chain kinase	*MYLK/MLCK*	34-5p; 93-5p; 106-5p; 141-3p; 142-5p; 142-3p.1; 142-3p.2; 144-5p; 145-5p; 155-5p; 194-5p; 200b-3p; 200c-3p; 221-3p; 222-3p; 429; 449-5p; 584-5p; 671-5p; 1290; 3622b-5p; 4793-3p	22
Adherens junction proteins			
Cadherin 1/E-cadherin	*CDH1*	93-5p; 98-5p; 106-5p; 140-5p; 142-5p; 146-5p; 181-5p; 221-3p; 222-3p; 483-3p; 671-5p; let-7-5p	12
Catenin alpha 1	*CTNNA1*	140-3p.2; 141-3p; 142-3p.2; 144-3p; 181-5p; 200a-3p; 671-5p	7
Catenin beta 1	*CTNNB1*	141-3p; 142-5p; 142-3p.2; 146-5p; 200a-3p; 483-3p.1; 483-3p.2	7
Catenin delta 1/p120	*CTNND1*	29-3p; 34-5p; 93-5p; 106-5p; 141-3p; 142-3p; 145-5p; 155-5p; 181-5p; 200b-3p; 200c-3p; 223-3p; 429; 449-5p; 455-5p; 671-5p; 1290	17
Pleckstrin homology domain containing A7	*PLEKHA7*	93-5p; 106-5p; 141-3p; 142-5p; 196-5p; 200a-3p; 455-3p; 671-5p	8
Vezatin, adherens junctions	*VEZT*	29a-5p; 93-5p; 98-5p; 106-5p; 122-5p; 141-3p; 142-5p; 144-3p; 145-5p; 155-5p; 181-5p; 194-5p; 196-5p; 200a-3p; 200b-3p;	28
transmembrane protein		200c-3p; 221-3p; 222-3p; 429; 455-3p.1; 483-5p; 483-3p.1; 584-5p; 1290; 3622b-5p; 3622a-3p; 3622b-3p; let-7-5p	
Desmosome proteins			
Desmoglein 2	*DSG2*	29-3p; 93-5p; 106-5p; 122-5p; 155-5p; 223-3p; 483-3p.1; 671-5p; 4725-3p; 4793-3p	10

Proteins	Target transcripts	MicroRNAs	Number of targeting microRNAs
Desmoglein 3	*DSG3*	29-3p; 93-5p; 98-5p; 106-5p; 144-3p; 221-3p; 222-3p; 223-3p; 483-5p; 584-5p; 671-5p; 3622a-3p; 3622b-3p; 4793-3p; let-7-5p	15
Desmoglein 4	*DSG4*	29-3p; 93-5p; 106-5p; 142-5p; 142-3p.1; 142-3p.2; 144-3p; 192-5p; 455-5p; 4725-3p; 4793-3p	11
Desmocollin 2	*DSC2*	29a-5p; 29-3p; 142-3p.2; 144-3p; 181-5p; 194-5p; 455-3p.2; 1290; 1291	9
Desmocollin 3	*DSC3*	29a-5p; 34-5p; 93-5p; 98-5p; 106-5p; 145-5p; 200b-3p; 200c-3p; 223-3p; 429; 449-5p; 455-5p; 455-3p.2; 584-5p; 4725-3p; 4793-3p; let-7-5p	17
Mucus and other goblet cell proteins			
Mucin 1, cell surface associated	*MUC1*	122-5p; 145-5p; 455-3p.1; 1291; 3622a-3p; 3622b-3p	6
Anterior gradient 2, protein disulphide isomerase family member	*AGR2*	34b-5p; 194-5p; 196-5p; 431-5p; 449-5p; 483-3p.2	6
Zymogen granule protein 16	*ZG16*	34-5p; 93-5p; 98-5p; 106-5p; 122-5p; 142-3p.1; 145-5p; 155-5p; 181-5p; 194-5p; 196-5p; 431-5p; 449-5p; 455-3p.1; 455-3p.2; 483-3p.1; 584-5p; 1290; 4793-3p; let-7-5p	20
Cystic fibrosis transmembrane conductance regulator	*CFTR*	34-5p; 142-3p.2; 144-3p; 145-5p; 200b-3p; 200c-3p; 223-3p; 429; 449-5p; 455-3p.2; 671-5p	11
Autophagy related 16 like 1	*ATG16l1*	29a-5p; 93-5p; 98-5p; 106-5p; 141-3p; 142-3p.1; 142-3p.2; 181-5p; 200a-3p; 455-5p; 483-3p; 1291; let-7-5p	13
Autophagy related 3	*ATG3*	29a-5p; 142-3p.2; 155-5p; 194-5p; 221-3p; 222-3p; 431-3p; 455-5p; 584-5p; 1290; 3622b-5p	11
Paneth cell antimicrobial proteins			
Defensin alpha 5	*DEFA5/HD-5*	155-5p	1
Defensin alpha 6	*DEFA6/HD-6*	142-5p	1
Lysozyme	*LYZ*	140-5p; 142-3p.1; 455-3p.2; 483-3p.1	4
Angiogenin	*ANG*	21-5p; 34-5p; 34b-5p; 93-5p; 106-5p; 122-5p; 142.5p; 144-5p; 146-5p; 155-5p; 192-5p; 455-3p.2; 483-3p.1; 584-5p	14
Effectors of gut immunity			
Signal transducer and activator of transcription 3	*STAT3*	29-3p; 34-5p; 93-5p; 98-5p; 106-5p; 122-5p; 181-5p; 192-5p; 196-5p; 221-3p; 222-3p; 449-5p; 671-5p; let-7-5p	14
Signal transducer and activator of transcription 5A	*STAT5A*	29a-5p; 141-3p; 200a-3p; 223-3p; 483-3p; 3622b-5p	6
Signal transducer and activator of transcription 5A	*STAT5B*	141-3p; 194-5p; 200a-3p; 221-3p; 222-3p; 455-5p; 483-5p; 671-5p; 1291; 3622b-5p	10
Nucleotide binding oligomerization domain containing 2	*NOD2*	29a-5p; 34b-5p; 122-5p; 142-5p; 192-5p; 431-5p; 449-5p; 483-5p; 483-3p.1; 671-5p	10
C-type lectin domain containing 7A/ DECTIN1	*CLEC7A*	29-3p; 144-3p; 192-5p; 200b-3p; 200c-3p; 429; 3622b-5p; 4793-3p	8
TNF receptor superfamily member 1B	*TNFRSF1B/TNFR2*	93-5p; 98-5p; 106-5p; 122-5p; 142-3p.1; 431-5p; 671-5p; 1291; let- 7-5p	9

[a] As determined using the Targetscan software.