Immune function of miR-214 and its application prospect as molecular marker

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Abstract: MicroRNAs are a class of evolutionarily conserved non-coding small RNAs that play key regulatory roles at the post-transcriptional level. In recent years, studies have shown that miR-214 plays an important role in regulating several biological processes such as cell proliferation and differentiation, tumorigenesis, inflammation and immunity, and has become the one of focuses of miRNA study. In this review, the regulatory functions of miR-214 in the proliferation, differentiation and functional activities of immune-related cells, such as dendritic cells, T cells and NK cells, were briefly reviewed. Also, the mechanisms of miR-214 involved in tumor immune, inflammatory regulation and antivirus were discussed. Finally, the value and application prospects of miR-214 as a molecular marker in inflammation and tumor related diseases were analyzed briefly. We hope it can provide a theoretical reference for further study on the mechanisms and application of miR-214.

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Introduction

MicroRNAs (miRNAs) are a kind of evolutionarily highly conserved non-coding small RNA that bind to the 3′-untranslated region (3′-UTR) of the target gene mRNA and regulate gene expression at the post-transcriptional level. In immune responses, miRNAs can act as signal-regulating molecules after immune-related receptor activation, and affect the expression of immune-related genes (Bosisio D et al., 2019; Mehta Arnav & Baltimore David et al., 2016), thus extensively participating in various aspects of the immune response.

MiR-214 is one of the key miRNAs involved in the immune responses. MiR-214 is widely distributed in fish, amphibians, birds, mammals and other vertebrates (Thomas Desvignes et al., 2014). Human miR-214 is located in the dynamin-3 gene of chromosome 1 q24.3. Pre-miR-214 can encode two mature miRNAs: miR-214-5p and miR-214-3p, and there are functional differences between them (Bartel DP, 2004; Deng ZF et al., 2019; Teng JW et al., 2018; Wang P

et al.,2019; Li Hd et al., 2018) (Fig. 1). Recently, a number of literatures have reported the functions and mechanisms of miR-214 in the fields of immune response, tumor, cardiovascular, development, neurology, and metabolism, and become one of the hotspots in the field of miRNA research. This review focuses on the immune functions and application prospects of miR-214 as molecular marker, so as to provide theoretical references for the in-depth study of miR-214.

Survey Methodology

We used the PubMed database to search the keyword "miR-214", combined with "immune", "inflammation", "T cell", "tumor immunity", "virus" and "molecular marker" to obtain relevant articles and summarized them. The selected articles are directly or indirectly related to miR-214.

1 MiR-214 and immune cells

MiR-214 can regulate the functions and characteristics of a variety of immune cells including dendritic cells (DCs), T cell, natural killer (NK) cell, and macrophages, etc., thus participate in the immune response processes widely.

MiR-214 is a key miRNA that regulates the function of DCs. Studies have found that DCs immune activity is inhibited by regulatory T (Treg) cells(Alexander Mildner & Steffen Jung, 2014; Pandey G et al., 2013; Svajger Urban et al., 2014), and the down-regulation of miR-214 can enhance the expression of heat shock protein 27 (HSP27), while the up-regulation of HSP27 can inhibit the differentiation of Treg cells(Huan Y et al., 2017), so the overexpression of miR-214 can promote the differentiation of Treg cells and enhance the inhibitory effect on DCs

55 immune activity. Interestingly, when miR-214 expression is down-regulated, it also induces
56 immune tolerance in DCs(Gordon JR et al., 2014; Fändrich F, 2010), because miR-214-3p can
57 target the 3'UTR of the *β-catenin*, which in turn this gene is regulated, and *β-catenin* is a key
58 regulator of DCs tolerance (Gu C et al., 2015). Therefore, miR-214 comprehensively affects the
59 immune status of DCs by regulating the expression of *β-catenin* and the differentiation of Treg
60 cells, thereby regulating the balance of immune activity and tolerance of DCs, suggesting that
61 miR-214 may have potential application value in the rejection of organ transplantation and the
62 prevention and treatment of autoimmune diseases (Fig. 2).

63 MiR-214 plays an important regulatory role in cellular immune response by regulating the
64 activation, proliferation and differentiation of T cells. For example, PTEN protein can negatively
65 regulate T cell activation and is a regulator of the PI3K-AKT signaling pathway(Buckler JL et al.,
66 2008). MiR-214 attenuates its inhibitory effect on PI3K by targeting PTEN protein, while up-
67 regulation of PI3K activates AKT, ultimately enhancing the activity of the PI3K-AKT signaling
68 pathway, thereby promoting T cell activation(Velasco A et al., 2006). Moreover, the up-
69 regulation of miR-214 in activated T cells can also enhance the proliferation capacity of T
70 cells(Jindra PT et al., 2010). Interestingly, miR-214 can also inhibit T cell activation because T
71 cell activation requires the integration and transduction of signals by the T cell receptor (TCR)-
72 CD3 complex, and CD3ζ plays a key role in signal transduction. MiR-214 can target the 3'-UTR
73 of CD3ζ gene mRNA and negatively regulate T cell activation by inhibiting CD3ζ
74 expression(Xiao Y et al., 2019). Therefore, miR-214 can also play a key regulatory role in

balancing the activation of T cells (Fig. 2). In addition, miR-214 in chicken thymus is significantly up-regulated under immunosuppressive conditions, and whether miR-214 up-regulated expression is related to T cell suppression in thymus is worth further study(Zhou Y et al., 2019). It is worth mentioning that miR-214 can also regulatory the differentiation of certain T cells. MiR-214 plays a key role in inducing differentiation of naive T cells to Th17 cells during the relapse and remission phases of multiple sclerosis (MS) patients; MiR-214 may be a negative regulator of Th17 cell differentiation to inhibit its differentiation, and the imbalance of Th17 cells is a key factor leading to MS(Brucklacher-Waldert V et al., 2009), therefore miR-214 may have important research value in the future prevention and treatment of MS(Ahmadian-Elmi M et al., 2016).

MiR-214 plays an important role in regulating functions of NK cells and macrophages. NK cells are closely related to the occurrence and maintenance of pregnancy(Bezman NA et al., 2010; Jabrane-Ferrat Nabila, 2019). MiR-214 is differentially expressed in peripheral blood and NK cells of uterus decidual, and it may affect the NK cells differentiation and the process of pregnancy(Carlino C et al., 2018). Because of NK cells playing a key role in pregnancy complications, in-depth research on miR-214 regulating NK cell function will help understand the pathological mechanisms of pregnancy injury at the molecular cell level. It is well known that macrophages are important immune cells with phagocytic function and mediate the transition from innate immunity to adaptive immunity (Arango Duque G & Descoteaux A, 2014). Study has found that virus mimics polyriboinosinic polyribocytidylic acid (pIC) can induce up-

95 regulation of 10 miRNA expression in Atlantic cod macrophages, including miR-214-1-5p,
96 suggesting that miR-214 may be involved in macrophages and play an important role in the
97 antiviral immune response (Eslamloo K et al., 2017).

98 In short, miR-214 plays an important regulatory role in DCs immune activity and tolerance,
99 T cell proliferation and differentiation, NK cells and macrophage functions (Table 1). Therefore,
100 in-depth research on the function and application of miR-214 in immune cells may have positive
101 theoretical and practical significance for the prevention and treatment of various diseases such as
102 organ transplantation, autoimmune disease, pregnancy injury, immune tolerance and
103 immunosuppression.

104 **2 MiR-214 and tumor immunity**

105 Immune system plays an important role in the development of tumor, while miR-214 plays
106 a key regulatory role in the proliferation, invasion and metastasis of tumor cells (Yin Y et al.,
107 2014). For example, in the tumor microenvironment, the tumor secretes microbubble structures
108 containing miRNAs which are novel regulators between tumor cells and immune cells (Kasinski
109 Andrea L et al., 2011). In recent years, research has found that Treg cells play an important role
110 in mediating tumor cell immune escape and have become important targets for tumor
111 immunotherapy(Ahmetlić F et al., 2019). Moreover, miR-214 expression is up-regulated in a
112 variety of tumor cells (eg, lymphoma, lung cancer, etc.) and can be encapsulated into
113 microcapsules and secreted outside the cells. After circulating microcapsules enter $CD4^{+}$T cells,
114 miR-214 can target to down-regulate PTEN(Yang H et al., 2008; Zhang Y et al., 2010), which

115 can inhibit tumor by antagonizing phosphorylase activity such as tyrosine kinase(Myers MP et
116 al., 1998). In addition, since the activities of Treg cells are often up-regulated in tumor patients
117 and the immune activities of DCs are inhibited by Treg cells(Alexander Mildner & Steffen Jung,
118 2014; Pandey G et al., 2013; Svajger Urban et al., 2014), the immune response to tumor cells
119 appears to an inhibitory effect, thereby promoting the development of tumors. If miR-214
120 activity is blocked or down-regulated in microcapsules, PTEN expression is reduced and Treg
121 cell activity is down-regulated, DCs cell immune activity is up-regulated, and tumor growth may
122 be inhibited. For example, Yin et al. used microcapsules to inoculate anti-miR-214 antisense
123 oligonucleotides to tumor mice via tail vein, which can significantly inhibit Treg cell
124 proliferation and tumor growth, indicating that the use of miR-214 for tumor micro-regulation of
125 Treg cells and PTEN proteins in the microenvironment can effectively inhibit tumor proliferation
126 and metastasis(Yin Y et al., 2014) (Table 1).

127 Programmed cell death receptor ligand 1 (PDL1) can interact with programmed cell death
128 protein 1 (PD-1), inhibit T cell activation, induce apoptosis of effector T cells, and ultimately
129 damage anti-tumor immunity(Dong H et al., 1999; Ceeraz S et al., 2013), which is important for
130 avoiding harmful autoimmune reactions(Zhang J et al., 2018; Wang CJ et al., 2019). MiR-214
131 can inhibit the expression of PDL1 by targeting 3'UTR(Song MK et al., 2019). It is known that
132 urothelial carcinoma associated 1 (UCA1) (a long non-coding RNA overexpressed in various
133 human cancers（Sun JR et al., 2019）) can inhibit miR-214, miR-26a/b and miR-193a through
134 direct interaction and then up-regulate PDL1 expression, thereby overexpression of UCA1 can

protect PDL1 expression from miRNA inhibition, promote gastric cancer (GC) cell proliferation and migration, and inhibit apoptosis, which helps GC cells immune escape and miR-214 can be used as GC treatment potential new therapeutic targets(Wang H et al., 2017). In addition, in diffuse large b-cell lymphoma (DLBCL), miR-214 also targets PDL1 to regulate T cells and further mediate the immune response of tumor cells(Song MK et al., 2019) (Table 1).

Multiple myeloma (MM) is related to macrophage polarization, and lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) and B7-H3 (it is induced in tumors and related to tumor immunogenicity and development(Fauci JM et al., 2012; Wang L et al., 2014; Mao Y et al., 2017) are upregulated and miR-214 is significantly downregulated in MM patients. NEAT1 directly targets miR-214, and miR-214 directly binds to B7-H3. If NEAT1 is silenced, it will inhibit the expression and release of B7-H3, and inhibit the polarization of M2 macrophages by inhibiting JAK2/STAT3 signaling(Gao Y et al., 2020). Therefore, miR-214 plays an important role in the polarization pathway of M2 macrophages (Table 1).

With the deepening of research, tumor therapeutic agents that target miRNAs including miR-214 for clinical cancer treatment will be developed. Therefore, a thorough understanding of the molecular interaction network mechanism of miR-214, the development of new preparations, the molecular mechanism of tumor treatment, and the feasibility of treatment may be issues that need to solve urgently at this stage.

3 MiR-214 and inflammation

MiR-214 plays a key regulatory role in promoting inflammation. For example, adenosine A2A receptors (A2AR) have anti-inflammatory effects, and up-regulation of miR-214 expression in inflammatory cells can inhibit adenosine A2AR expression. The decrease of A2AR expression also weakens the inhibition of nuclear factor kappa-B (NF-κB) through PKA, that is, the anti-inflammatory effect of A2AR is weakened. Meanwhile, weakened inhibition of NF-κB promotes its further up-regulation of miR-214 to amplify the inflammatory response(Zhao L et al., 2015). In addition, miR-214 can also promote the release of inflammatory factors. For example, Adipose-derived stem cells (ADSCs) inhibit the inflammation of microglia by secreting tumor necrosis factor-inducible gene 6 protein (TSG-6). TSG-6 can inhibit the release of pro-inflammatory factors such as IL-1β, IL-6 and TNFα, while *TSG-6* is negatively regulated by miR-214-5p, so miR-214 increases proinflammatory factor release by inhibiting TSG-6(Hu Y et al., 2018). Furthermore, miR-214 plays a key regulatory role in the inflammatory response and calcification of human aortic valve interstitial cells (AVICs). M1 macrophages transmit miR-214 to valvular interstitial cells through microbubbles, miR-214 directly targets Twist1 and down-regulates it, thereby promoting calcification of valve interstitial cells(Li XF et al., 2016). Further research found that miR-214 is related to the expression level of MyD88 protein. Up-regulation of miR-214 can promote the expression of MyD88 and NF-κB, while MyD88 up-regulation can increase the secretion of pro-inflammatory factors and increase the number of calcified nodules. Therefore, miR-214 promotes calcification by promoting MyD88/NF-κB signaling pathway in AVIC(Zheng D et al., 2019). And miR-214 can be selectively inhibited by 17β-estradiol (E2) or progesterone (P), while E2 and P can indirectly inhibit apoptosis and inflammation-related gene

translation. It is speculated that E2 and P suppress inflammation by inhibiting miR-214 expression(Herzog R et al., 2017). Besides, miR-214 is down-expressed in the post-menopausal women's epithelial-mesenchymal transition (EMT) process and the development of interstitial cystitis (IC), and mitofusin 2 (Mfn2) is the target gene of miR-214, so miR-214 down-regulation can promote the EMT process and bladder wall fibrosis, leading to IC in postmenopausal women(Lv JW et al., 2017). However, miR-214-3p is up-regulated in the kidney, pancreas and serum of hyperlipidemic pancreatitis (HP) rats. Up-regulation of miR-214-3p can inhibit PTEN expression, but can increase the level of P-Akt in HP kidneys, which may be a possible mechanism for inducing severe symptoms of pancreatitis, and may exacerbate HP-induced pathological changes, kidney and pancreas damage, and fibrosis. Therefore, miR-214-3p as the target for the treatment of acute renal injury of HP can provide an effective treatment for the clinic(Yan Z et al., 2020).

Interestingly, miR-214 also plays a regulatory role in inhibiting inflammation. Substantial interstitial inflammation caused by renal cysts is often overlooked. MiR-214 is upregulated in cystic kidney of autosomal dominant polycystic kidney disease (ADPKD) patients(Lakhia R et al., 2020). The mechanism is mainly the pro-inflammatory TLR4/IFN-γ/STAT1 pathways to activate the miR-214 host gene (miR-214 comes from a long non-coding RNA (lncRNA) called dynamin 3 opposite strand (DNM3OS)(Watanabe Tet al., 2008)). In turn, miR-214 upregulates and directly inhibits TLR4 expression, inhibiting the inflammatory response. Therefore, the up-regulation of miR-214 is a compensatory protective response of the cyst microenvironment,

195 which can inhibit inflammation and cyst growth.

196 In summary, miR-214 plays different roles in multiple inflammatory response pathways
197 (Table 1). Studying the pro-inflammatory and anti-inflammatory functions of miR-214 can
198 provide a positive theoretical basis for understanding the molecular mechanism of inflammatory
199 action and developing new strategies for the diagnosis and treatment of inflammatory diseases.

200 **4 MiR-214 and virus**

201 MiRNAs can directly target RNA virus genes or affect the replication and pathogenesis of
202 virus by altering the host transcriptome(Trobaugh DW & Klimstra WB, 2017). It is found that
203 miR-214 is differentially expressed in virus-infected tissues. For example, the expression of
204 miR-214 is up-regulated in the plasma and myocardial cells of patients with viral myocarditis
205 (VM) infected with coxsackievirus, but the specific mechanism is still unclear(Chen ZG et al.,
206 2015). Coxsackie adenovirus receptor (CAR) protein is an adenovirus receptor, and miR-214 can
207 inhibit adenovirus replication by targeting the 3'-untranslated region of early region 1A (E1A)
208 mRNA(Yanagawa-Matsuda A et al., 2012). Therefore, in-depth study of the mechanism and
209 biological effects of miR-214 expression changes in virus-infected tissues may have important
210 theoretical and practical significance for the prevention and treatment of viral diseases including
211 viral myocarditis.

212 Recent studies have found that miR-214 can inhibit the replication of fish viruses. For
213 instance, miR-214 can effectively inhibit siniperca chuatsi rhabdovirus (SCRV) replication,

214 which provides a new approach for the development of effective SCRV infection prevention
215 strategies(Zhao Y et al., 2019). In addition, miR-214 can also target the coding regions of viral N
216 and P to inhibit snakehead vesiculovirus (SHVV) replication(Zhang C et al., 2017). Another
217 study has found that miR-214 can also target glycogen glycogen synthase (GS) gene can inhibit
218 SHVV replication, because GS gene is the key gene for SHVV replication, indicating that miR-
219 214 can inhibit SHVV replication from multiple aspects through multiple target genes(Zhang C
220 et al., 2019).

221 **5 MiR-214 and molecular markers**

222 In recent years, the application value of miR-214 as a diagnostic marker has gradually
223 attracted widespread attention.

224 In inflammatory diseases, miR-214 is one of the three lowest expressed miRNAs in gingival
225 tissue inflammation in Japanese dental patients. It can be determined that abnormal expression of
226 miR-214 is associated with chronic periodontitis, which provides a basis for the diagnosis of
227 periodontal inflammatory diseases(Ogata Y et al., 2014). MiR-214 can also be used as a non-
228 invasive biomarker for the diagnosis of ankylosing spondylitis (AS). The expression level of
229 miR-214 in serum of AS patients is significantly lower than that of normal people. The level is
230 significantly correlated with the active C-reactive protein (CRP) of AS disease. Therefore, the
231 expression level of miR-214 as a diagnostic marker of AS disease can provide a powerful help
232 for the treatment and prevention of AS(Kook HY et al., 2019). Upregulation of STAT6
233 expression in intestinal mucosa of ulcerative colitis (UC) and increase of its phosphorylation are

234 involved in the pathogenesis of UC(Rosen MJ et al., 2011). STAT6 is a direct target of miR-214-
235 3p. Upregulation of STAT6 can promote the secretion of proinflammatory cytokines in intestinal
236 epithelial cells, and then participate in the inflammation response to induce UC. Therefore,
237 targeting STAT6 pathway by miR-214-3p may become a new therapeutic target for UC(Li JA et
238 al., 2017).

239 In tumor diseases, the expression of miR-214 in the plasma of gastric cancer (GC) patients
240 is significantly higher than that of normal people, and GC patients with high miR-214 expression
241 may have larger tumor lymphatic metastasis and tumor node metastasis (TNM) stage, higher
242 levels of CEA (Carcinoembryonic antigen) and carbohydrate antigen 19-9 (CA19-9), the survival
243 rate is low. The high sensitivity and specificity of miR-214 for GC has high application value in
244 the diagnosis and prognosis of GC(Ji B et al., 2019). In addition, miR-214 expression is down-
245 regulated in human cholangiocarcinoma exosomes, sinonasal inverted papilloma (SNIP), and
246 bladder cancer (BC), but the expression of miR-214 is up-regulated in difuse large B cell
247 lymphoma (DLBCL), which suggests that miR-214 has potential as a molecular marker and
248 therapeutic target(Kitdumrongthum S et al., 2018; Xie Y et al., 2017; Lim EL et al., 2015; Teng
249 Y et al., 2018). In breast cancer cells overexpressed with miR-214 in vitro, the cell proliferation
250 and migration ability decrease, and are induced to apoptosis and interfered with the cell
251 cycle(Liu B et al., 2016). Similar to the performance in breast cancer, miR-214-5p expression in
252 hepatocellular carcinoma (HCC) tissues and cells also shows a reduced form. The
253 overexpression of miR-214-5p can down-regulate cell proliferation, reduce cell migration and

block the cell cycle in G0/G1 phase (Pang J et al., 2018). These results indicate that miR-214 plays a key role in inhibiting breast cancer and HCC, and may become a potential biomarker and therapeutic target. MiR-214 was significantly down-regulated in esophageal squamous cell carcinoma (ESCC), and overexpression of miR-214 may impair the invasion and migration ability of Eca109, TE1 and KYSE150 cells. Therefore, miR-214 may have potential application value as a diagnostic marker and therapeutic target of ESCC(Lu Q et al., 2016). In addition, miR-214 expression is down-regulated in colon cancer tissues and cells. MiR-214 can inhibit the cell viability and development of colon cancer by inhibiting ADP-ribosylation factor-like protein 2 (ARL2) and mitochondrial transcription factor A (TFAM)(Long LM et al., 2015; Wu K et al., 2018). Therefore, miR-214 may be an important target for the treatment of colon cancer.

In other diseases, miR-214-3p expression is upregulated in chronic kidney disease. Mitochondrial dysfunction is related to the pathogenesis of chronic kidney disease. MiR-214 has a pathogenic role in chronic kidney disease by disrupting mitochondrial oxidative phosphorylation, so miR-214 has the potential to become a therapeutic target and diagnostic biomarker for chronic kidney diseases such as nephritis(Bai M et al., 2019). In addition, 6 miRNAs including miR-214-3p are found to be dysregulated in diabetic kidney disease (DKD). And these miRNAs are involved in the pathogenesis of apoptosis, fibrosis, and accumulation of extracellular matrix related to the pathogenesis of DKD, which indicates that miR-214 may have the potential to represent the disease biomarker(Assmann TS et al., 2018). In addition, Wang et al. explored the key miRNAs in the pathogenesis of myocardial ischemia/reperfusion (I/R) injury

and found that 8 miRNAs including miR-214-5p are significantly up-regulated, which is developed for myocardial I/R damage prevention miRNA diagnostic biomarkers provide new targets(Wang X et al., 2016). MiR-214 also plays an important role in fibrotic diseases. Increasing the expression of miR-214 will reduce the expression of collagen αl and connective tissue growth factor (CTGF) in endometriosis matrix and endometrial epithelial cells, which provides another treatment for endometrium heterotopic fibrosis(Wu D et al., 2018). Interestingly, miR-214 also plays an important role in musculoskeletal metabolism, bone formation, and other bone diseases. Specifically, miR-214 can mediate skeletal muscle myogenesis and the proliferation, migration and differentiation of vascular smooth muscle cells. MiR-214 also regulates bone formation by targeting specific molecular pathways and expression of various osteoblast-related genes(Sun Y et al., 2018). For example, osteoclast-derived exosome miR-214-3p transferred to osteoblasts can inhibit bone formation(Li D et al., 2016). MiR-214's role in primary osteoporosis may be through inhibiting the expression of osterix to inhibit bone formation(Mohamad N et al., 2019). So miR-214 may be an important potential target for the treatment of bone diseases.

In brief, more and more studies have shown the potential values and application prospects of miR-214 as a diagnostic marker in diseases such as inflammation and tumor (Table 2). It is believed that in the near future, miR-214 can truly appear in clinical practice detection as a diagnostic marker and play its due value for the diagnosis and treatment of clinically relevant diseases.

6 Conclusions

With the deepening of research, the function and mechanism of miR-214 in the fields of immune cell regulation, inflammatory response, tumor immunity and antivirus are gradually revealed. Moreover, the potential clinical application value of miR-214 as a biomarker has attracted increasing attention. According to the research status, miR-214 has promising prospects in the following aspects: Firstly, miR-214 may have in-depth research value in the prevention and treatment of diseases such as organ transplant rejection, autoimmune disease and immune tolerance through affecting DCs tolerance and T cell activation; Secondly, miR-214 regulates tumor microenvironment Treg cells and PTEN proteins to make it have the ability to inhibit the immune escape of tumor cells and its potential application value; Thirdly, miR-214 has abnormal expression in virus-infected tissues and has antiviral ability against fish SCRV and SHVV, which makes it a good development prospect in the diagnosis and treatment of viral diseases; Finally, miR-214 has potential application value as a diagnostic marker and therapeutic target in diseases such as periodontitis, ankylosing spondylitis, kidney disease and various tumors. In short, deep study on the regulatory relationship and molecular regulatory mechanism of miR-214 not only can provide important theoretical basis for scientific issues such as immune regulation, tumor treatment, inflammation diagnosis, and antivirus, but also pave the way for actively developing new strategies for the prevention and treatment of these diseases. It is believed that miR-214 will have great research value and bright application prospects whether it is used as a drug target for disease treatment or as a molecular marker for disease diagnosis and prognosis.

314

315 **Competing Interests**

316 The authors declare that there are no competing interests associated with the manuscript.

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Table 1(on next page)

Table 1 Expressional changes and biological effects of miR-214 in immune and inflammatory responses

miR-214	Expressional change	Target gene	Biological effect	Reference
miR-214-3p	Up	*HSP27*	Promote Tregs cell differentiation	Huan Y et al. (2017)
miR-214-3p	Down	*β-catenin*	Induce DCs tolerance and inhibit ovarian cancer	Gordon JR et al. (2014), Fändrich F (2010) and Gu C et al. (2015)
miR-214-3p	Up	*PTEN*	Promote T cell activation and proliferation, inhibit Tregs cell proliferation and tumor growth	Velasco A et al. (2006), Jindra PT et al. (2010), Yin Y et al. (2014), Yang H et al.(2008), Zhang Y et al. (2010) and Myers MP et al. (1998)
miR-214-3p	Up	*CD3ζ*	Inhibit T cell activation	Velasco A et al. (2006), Jindra PT et al. (2010), Yin Y et al. (2014), Yang H et al.(2008), Zhang Y et al. (2010) and Myers MP et al. (1998)
miR-214-3p	Down	*PDL1*	Regulate T cells and further mediate the immune response of tumor cells	Song MK et al. (2019), Sun JR et al. (2019) and Wang H et al.(2017)
miR-214-3p	Down	*B7-H3*	Regulate the polarization pathway of M2 macrophages	Fauci JM et al. (2012)
miR-214-3p	Up	*A2AR*	Amplify inflammatory effect	Zhao L et al. (2015)
miR-214-5p	Up	*TSG-6*	Promote proinflammatory factor release	Hu Y et al. (2018)
miR-214-3p	Up	*TWIST1*	Promote aortic valve stromal cell calcification	Li XF et al. (2016)
miR-214-3p	Up	*MyD88*	Increase the secretion of pro-inflammatory factors and the number of calcified nodules	Zheng D et al. (2019)

miR-214-3p	Down	*Mfn2*	Promote EMT process and bladder wall fibrosis, induce IC development	Lv JW et al. (2017)
miR-214-3p	Up	*TLR4*	Inhibit inflammation and cyst growth	Lakhia R et al. (2020)

Table 2(on next page)

Table 2 Biological functions of miR-214 as a molecular marker

miRNA	Related disease	Expressional change	Application prospect	Reference
miR-214-3p	Periodontitis	Down	Biomarker for the diagnosis of periodontitis-related diseases	Ogata Y et al. (2014)
miR-214-5p	Ankylosing spondylitis	Down	Non-invasive biomarker for the diagnosis of ankylosing spondylitis	Kook HY et al. (2019)
miR-214-3p	Ulcerative colitis	Down	Therapeutic target for ulcerative colitis	Rosen MJ et al. (2011)
miR-214-3p	Gastric cancer	Up	Biomarker value in the diagnosis and prognosis of gastric cancer	Ji B et al. (2019)
miR-214-3p	Cholangiocarcinoma	Down	Biomarker for the diagnosis and treatment of cholangiocarcinoma	Kitdumrongthum S et al. (2018)
miR-214-3p	Bladder cancer	Down	A potential therapeutic target for the treatment of bladder cancer	Xie Y et al. (2017)
miR-214-5p	Difuse large B cell lymphoma	Up	Biomarker for good prognosis of difuse large B cell lymphoma	Lim EL et al. (2015)
miR-214-3p	Sinonasal inverted papilloma	Down	Biomarker for the diagnosis and treatment of sinonasal inverted papilloma	Teng Y et al. (2018)
miR-214-5p	Hepatocellular carcinoma	Down	Potential biomarker and therapeutic target for HCC	Pang J et al. (2018)
miR-214-3p	Esophageal squamous cell carcinoma	Down	Potential diagnostic marker and therapeutic target of ESCC	Lu Q et al. (2016)
miR-214-3p	Colon cancer	Down	Potential target for the treatment of colon cancer	Long LM et al. (2015) and Wu K et al. (2018)
miR-214-3p	Nephritis	Up	Therapeutic target and diagnostic biomarker for chronic kidney	Bai M et al. (2019)

			disease	
miR-214-3p	Diabetic kidney disease	Up	Potential diagnostic marker for diabetic kidney disease	Assmann TS et al. (2018)
miR-214-5p	Ischemia/reperfusion	Up	Biomarker for the diagnosis and treatment of myocardial I/R injury prevention	Wang X et al. (2016)
miR-214-3p	Fibrotic diseases	Up	Potential target for treatment of endometrium heterotopic fibrosis	Wu D et al. (2018)
miR-214-3p	bone diseases.	Up	Potential target for the treatment of bone diseases	Sun Y et al. (2018), Sun Y et al. (2016) and Mohamad N et al. (2019)

1

2

Figure 1

Fig. 1 Pre-miR-214 and its mature miRNAs (miR-214-5p and miR-214-3p)

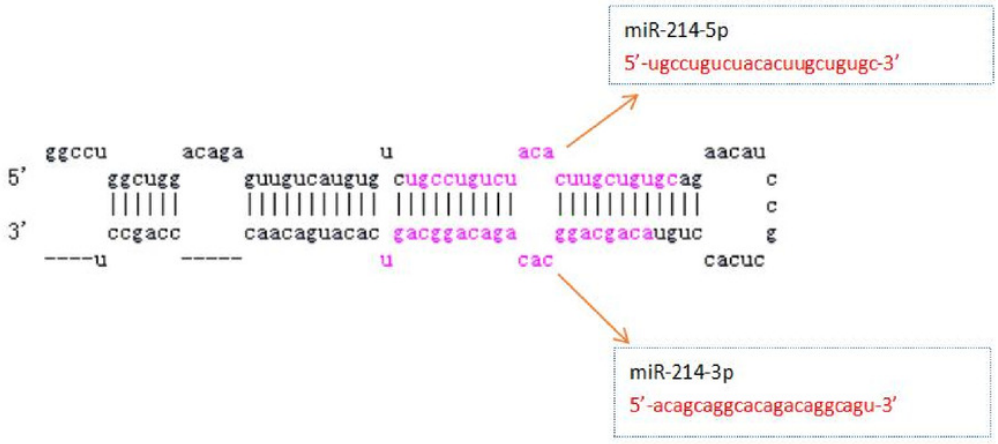
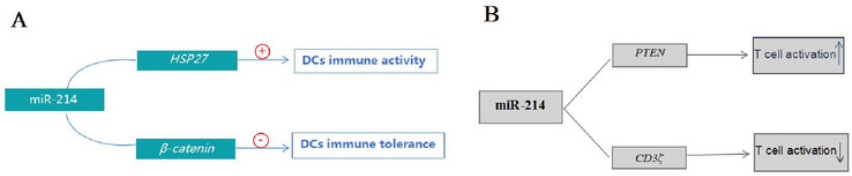

miR-214-5p
5'-ugccugucuacacuugcugugc-3'
ggccu acaga u aca aacau
5' ggcugg guugucaugug cugccugucu cuugcugugcag c
3' ccgacc caacaguacac gacggacaga ggacgacauguc g
----u ----- u cac cacuc
miR-214-3p
5'-acagcaggcacagacaggcagu-3'

Figure 2

Fig. 2 Pathways of miR-214 in regulating the functions of DCs and T cells

A: The pathways of miR-214 in regulating DCs functions; B: The pathways of miR-214 in regulating T cells activities.


A
HSP27
DCs immune activity
miR-214
β-catenin
DCs immune tolerance
B
PTEN
T cell activation
miR-214
CD3ζ
T cell activation