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MicroRNA regulation and host interaction in response to *Aspergillus* exposure

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Abstract: *Aspergillus* is a group of conidial fungi, isolated from soil and litter, cause serious diseases in humans and animals. This ubiquitous fungus is prevalent in the air and inhalation of fungal spores is common. Fungal diseases from *Aspergillus* became a major health problem and are difficult to manage because they tend to be chronic and invasive, hard to diagnose and difficult to exterminate with antifungal drugs. Although, immune responses play vital roles in monitoring the fate of fungal infections and regulation of the immune responses against fungal infections might be an effective approach for controlling and reducing the pathological damages. Recent studies have shown that microRNAs (miRNAs) are assembly of regulators which modulates the immune responses during fungal infections through diversified cellular mechanisms. These small non-coding RNA sequences regulate gene expression, mostly at the post-transcriptional level and have emerged as the controller of gene expression of at least 30% human genes. Therefore, miRNAs might be considered as one of the potential goals in immunotherapy for fungal infections. The objective of this review is to explore the role of miRNAs in host recognition processes and understanding the modulation of regulatory pathways in response to *Aspergillus* exposure.

Introduction

Fungi are eukaryotic and ubiquitous microorganisms found in soil, animals, faeces, water, plant debris or other surfaces and are present in almost all the surroundings. It is estimated that out of 1.5 million of fungal species, mostly are saprophytes obtaining their nutrients from organic material, among which some are primary or opportunistic pathogens (Hawksworth, 2001). Fungi have a complex cellular organization that is surrounded by a firm cell wall; and its complexity and functionality is crucial to the development of new therapeutic and prophylactic strategies. The cell wall plays several key functions in fungal pathobiology as varied factors, such as cell shape, encapsulation, and rigidity, influence measures during interaction with the host (Gow *et al.*, 2017).

The fungal cell wall has a flexible and an indispensable structure that is highly complex and intricately organized of α- and β- linked glucans, chitin, glycoproteins, and pigments (Gow *et al.*, 2017). Fungal life forms broadly diverge from unicellular yeasts to multicellular filamentous hyphae that collectively form mycelium. Most fungi are adapted to aerial dispersion and replicate by non-motile asexual and sexual spores. Fungal spores and hypha fragments are ubiquitous components of the atmosphere and impact human health as triggers of allergic reactions or as the cause of infectious disease. Fungal spores can be aerosolized when agitated and in some occupational settings the airborne concentration may exceed from 1×10^5 spores/m^3 (Eduard, 2009).

Fungi are one of the acknowledged biological factors and those who are pathogenic in nature have a destructive impact on human health (Hardin *et al.*, 2003). The airborne spores of these microorganisms, when inhaled, are alleged to contribute to negating conditions from pulmonary sinus, and subcutaneous infections to respiratory ailments that may consist of hypersensitivity pneumonitis, allergy, and asthma (Eduard, 2009), in individuals who are susceptible to irritant effects of exposure, and immunocompromised patients susceptible to infections. Generally fungi cause mild infections consequences in immunocompetent hosts, but immunocompromised patients face occurrence of pathological indices that can be a substantial cause to a mortality up to 40% (Brown *et al.*, 2012). The frequency of

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fungal infections also shows variations with socioeconomic conditions, geographic region, and cultural habits. Superficial infections of the skin and nails are communal fungal diseases in humans and affect approximately 25% of the general population globally (Havlickova *et al.*, 2009) that are primarily caused by dermatophytes, which give rise to well-known conditions such as athlete's foot, and ringworm of the scalp. Mucosal infections of the oral and genital tracts are also common in the regions with limited health care provisions and in individuals who take steroids for asthma, have leukaemia, received transplant or undergoing chemotherapy or radiotherapy (Cornely *et al.*, 2017; Enoch *et al.*, 2017; Lien *et al.*, 2018).

Invasive fungal infections (IFIs) are of greater concern than superficial infections because they are associated with inadmissibly high mortality rates and annually impose large costs, involving 2 million people every year globally (Brown *et al.*, 2012). Many species of fungi are responsible for these invasive infections and the most emphasized species that are gaining importance are *Candida albicans* (candidiasis), *Pneumocyctis jirovecii* (pneumocyctosis), *Cryptococcus neoformans/gattii* (cryptococcosis), and *Aspergillus fumigatus* (aspergillosis). According to the World Health Organization (WHO; http://www.who.org), candidiasis, pneumocyctosis, cryptococcosis and aspergillosis are among the top 20 significant and deadly fungal infections in AIDS patients worldwide. *Aspergillus* species are the primary reason of health apprehension in immunocompromised beings, and this ubiquitous and opportunistic fungi cause invasive to allergic aspergillosis. Among the *Aspergillus* species, *A. fumigatus* has been found to be the most pathogenic to humans and accountable for more than 90% of *Aspergillus* induced infections. The morphotypes of *Aspergilli* such as conidia, mycelia or hyphae provide virulence and pathogenicity to fungi and help them to invade into hosts by secreting enzymes, proteins or toxins. The global burden of allergic bronchopulmonary aspergillosis (ABPA) obscuring asthma likely to be 5 million, out of which 0.4 million are estimated to have chronic pulmonary aspergillosis (CPA) (Denning *et al.*, 2013). The mortality rates for invasive pulmonary aspergillosis (IPA) exceed 90% if not treated and when treated aggressively with antifungals, fatality rates of 50% are common in intensely immunosuppressed individuals such as people with leukaemia and transplant recipient. This high mortality rate subsequent to *A. fumigatus* infection is a consequence of the availability of suboptimal diagnostic tool, delay in diagnosis and comparative ineffectiveness and toxicity of antifungal drugs against *Aspergillus* induced infections. The various combinations of antifungals are used but they can only lessen the fungal load in the hosts and the cure from the infection can rarely be achieved. Therefore, it is extremely difficult to treat aspergillosis and hence, the treatment and management of pulmonary aspergillosis has become the most importance topic of concern.

The immune system of healthy individuals has effective mechanisms for preventing fungal infections, and the hefty incidence of invasive diseases is largely a result of extensive escalations over the last few decades in immunosuppressive infections, such as HIV/AIDS, and modern immunosuppressive and invasive medical intrusions. The surge of broad-spectrum antibiotic usage and other medical and therapeutic approaches, concern has been raised towards invasive opportunistic fungal infections as nosocomial infections in the hospital site that may be life-threatening for dangerously ill persons (Bajwa and Kulshrestha, 2013). Therefore, fungal life-threatening infections are the major challenge to the health system in both developed and developing countries. Due to cross-reactivity of many fungal allergens that complicate the diagnosis of fungal sensitization, it is very important to characterize compromised innate and adaptive immune responses (Crameri *et al.*, 2009). Moreover, earlier research has engrossed on host reactions in exposed fungal models by examining immunological, functional, and histological parameters, and also considerable studies have been conducted on the design of antifungal vaccines (Nami *et al.*, 2019). Also, during the recent decade, novel immunotherapeutic strategies are under development such as cytokine/pattern recognition receptors (PRRs) ligand therapy, and antigen trained dendritic cells (DCs) (Goncalves *et al.*, 2016; Datta and Hamad, 2015). In this direction, many studies have been published that have explored the role of microRNAs (miRNAs) in pulmonary immunological responses to acute and chronic exposures to fungal spores. Therefore, understanding the role of miRNAs as the major immune regulators would be beneficial. This review compiles the state-of-knowledge of regulatory role of miRNAs in relation to the host response following *Aspergillus* exposure, with the emphasis placed on the mechanistic insights.

Host Immune Responses to *Aspergillus* Exposure

Aspergillus spp. encompasses a diversity of environmental filamentous fungus found in miscellaneous ecological niches worldwide. Among this genus, *A. fumigatus* is the most predominant species and is mainly accountable for the increased frequency of invasive aspergillosis with high mortality tolls in immunocompromised patients (Garcia-Rubio *et al.*, 2017). *A. fumigatus* is accountable for a hefty ratio of nosocomial opportunistic fungal infections in immunocompromised hosts, specifically during cytotoxic chemotherapy and after bone marrow transplantation, and is currently a foremost cause of death in leukaemia patients. *Aspergillus* conidia (resting spores) are ubiquitous in the environment, often inhaled and quickly phagocytised by alveolar macrophages and neutrophils of an immunocompetent host. However, the consequences of failure of immunocompromised individuals to immaculate germinating conidia can be invasive pneumonia and disseminated infection (Marr *et al.*, 2002). Due to its clinical significance; it has become a model for studying filamentous fungus cell wall and understanding its role in evolution and pathogenesis.

A. fumigatus releases abundant conidia in air which are constantly inhaled by humans. The first barrier for *A. fumigatus* conidia is airway mucociliary cells followed by the alveolar macrophages in the alveolar lumen before they undergo germination (Latgé, 1999). The host's innate immune system, consists of mononuclear monocytes and macrophages (MQs), polymorphonuclear neutrophils (PMNs), epithelial cells (EPs), dendritic cells (DCs) and soluble mediators such as complement cascade and defensins battle against fungal particles, and PRRs such as

TLRs recognize the PAMPs such as zymosan and glucans (Netea *et al.*, 2008). Following the recognition of Aspergillus antigens, specific signaling pathways are triggered through different molecules (Fig. 1), which eventually lead to stimulation of adaptive immune responses through cytokines and chemokines (Kawai and Akira, 2011) (Fig. 3). The host's immune response varies with the erratic composition of the cell wall that depends on different stages of fungal growth (Lee and Sheppard, 2016). Dormant conidia have an outer layer formed of immunologically inert proteins such as RodA hydrophobins and dihydroxynaphthalene-melanin that mask the inner components of the fungi cell wall and protects conidia from phagocytic activity (Amin *et al.*, 2014; Bayry *et al.*, 2014). After phagocytosis of conidia by alveolar macrophages, hydrophobins are degraded and the cell wall polysaccharides become exposed to trigger a potent immune response.

The β-1,3-glucan has a stimulatory effect on the host immune system and is recognized by a PRR, Dectin-1, expressed on phagocytic cells including macrophages and neutrophils (Goodridge *et al.*, 2009). After inhalation, the conidia swell and, if they are not cleared, produce germ tubes that eventually extend to form filamentous hyphae, thereby exposing β-glucan on the surface of *Aspergillus* germ tubes and hyphae and thus detected by Dectin-1 (Goodridge *et al.*, 2009). Consistent with this, germinating spores induce neutrophil recruitment to the airways and cytokine and chemokine production by alveolar macrophages. These Dectin-1-dependent responses are more pertinent in germinating conidia and young hyphae that are exposing higher levels of β-1,3-glucans than in mature hyphae where it is covered by exopolysaccharides (Gravelat *et al.*, 2013). Galactosaminogalactan is an important exopolysaccharide and an adhesin that facilitates binding of hyphae to macrophages, neutrophils, and platelets (Fontaine *et al.*, 2011; Rambach *et al.*, 2015). It has been additionally related to an immunosuppressive activity concealing cell wall β-glucans from recognition by Dectin-1, diminished polymorphonuclear neutrophil apoptosis via an NK cell–dependent mechanism and ROS production (Gravelat *et al.*, 2013; Robinet *et al.*, 2014) and stimulated fungal development in immunocompetent mice due to its immunosuppressive activity associated with reduced neutrophil infiltrates (Fontaine *et al.*, 2011). These polysaccharides inhibit Th1 and Th17 shielding response towards Th2 in humans, thus upholding IL-1Ra secretion by human peripheral blood mononuclear cells (Gresnigt *et al.*, 2014).

Dendritic cell-specific ICAM-3-grabbing non-integrin (DC-SIGN), type II C-type lectin, is an adhesion receptor and used by viral and bacterial pathogens to gain admittance to human DC (Fig. 1). It is reported that DC-SIGN unambiguously interacts with clinical isolates of *A. fumigatus*. The binding and internalization of *A. fumigatus* conidia is associated with DC-SIGN cell surface expression levels and is abolished with the occurrence of *A. fumigatus*-derived cell wall galactomannans (Serrano-Gómez *et al.*, 2004). Thus,

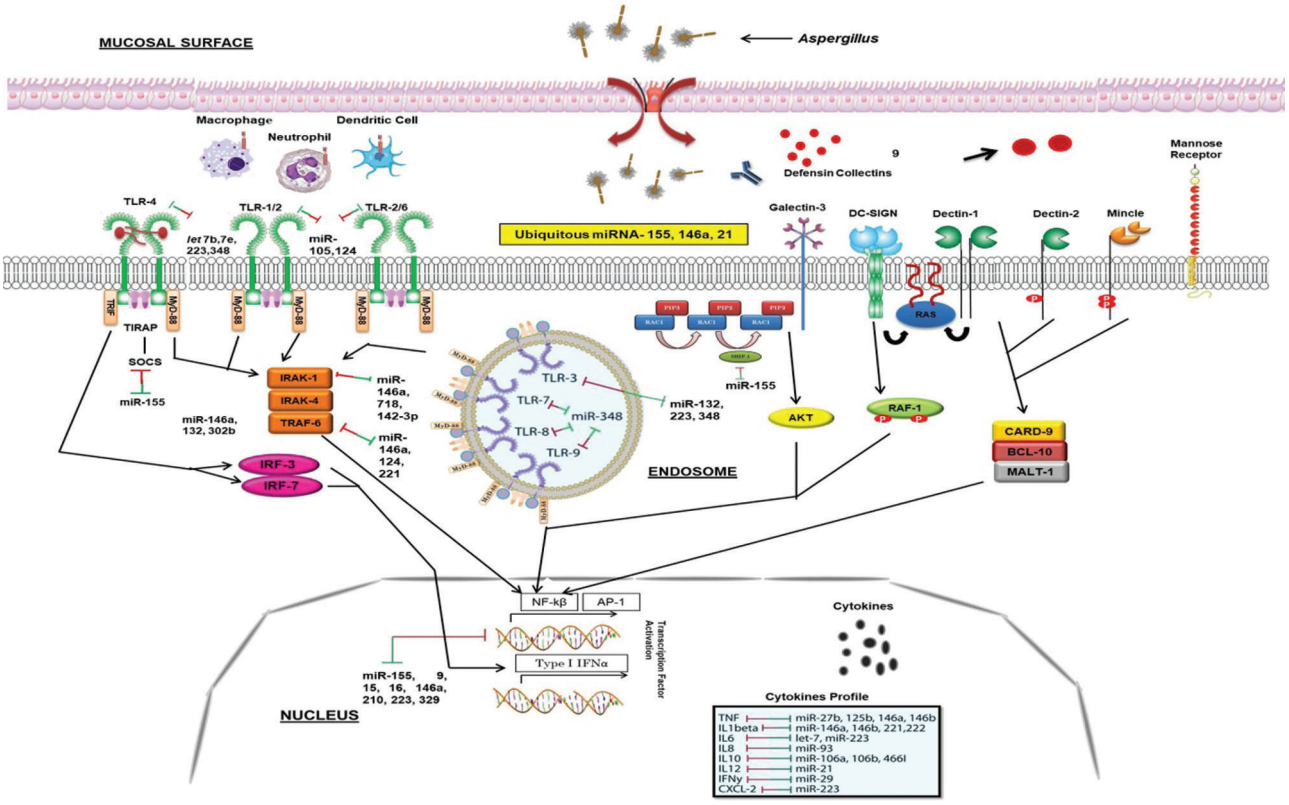

FIGURE 1. Innate immune responses to the *Aspergillus* and miRNA interactions. Different PRRs, mainly TLRs and dectins which expressed on the APCs, recognize fungal PAMPs, and their interaction triggers the stimulation of downstream signaling pathways such as MyD-88, CARD-9, IRAK, TRAF. This further stimulates transcription factor (NF-κB, AP-1) which secrete inflammatory cytokines IL-1, IL-6, IL-17, TNF-α. Several miRNAs interact with these processes (presented by two-way arrows) and double-ended arrows by green and red colour represents up-regulation and down-regulation of target mRNAs. MicroRNA-155, -146 and -21 are the most known miRNAs that fine-tune the innate immune response to ubiquitous fungal pathogen.

galactomannan also has a damaging effect in the host immune system by favouring fungal infection. There is an another receptor, Dectin-2, (Fig. 1) that recognizes α-mannans of cell wall and has an important role in conidia and hyphae binding by THP-1 macrophages which leads to TNF-α (Tumor necrosis factor) and IFN-α (Interferon) release as well as heightened antifungal activity by plasmacytoid DC (Loures *et al.*, 2015).

However, no host receptor for chitin, the inner component of the *Aspergillus* cell wall, has yet demonstrated. The immune response to chitin is disputatious and the exact mechanisms determining its inflammatory response are poorly understood. It was shown to have pro-inflammatory as well as anti-inflammatory properties subject to the presence of co-stimulatory pathogen-associated molecular patterns and immunoglobulins (Becker *et al.*, 2016).

MicroRNAs

MicroRNAs (miRNAs) are a complex of about 18–23 bp non-coding single stranded ribose nucleic acids (RNAs) that are involved in the regulation of nearly every basic molecular or cellular process by governing the levels of mRNA and post-transcriptional gene expression (Pakshir *et al.*, 2020). The first miRNA was discovered over 20 years ago has led to a new era in molecular biology (Hammond, 2015). Now, there are over 2000 miRNAs that have been discovered in humans, collectively control one third of the genes in the genome (Hammond, 2015). Most miRNAs are transcribed from DNA sequences and following the reception of stimulatory signals at the cell nucleus, RNA polymerase II (RNA pol II) triggers the generation of primary miRNAs (pri-miRNAs) that further administered in the nucleus by the microprocessor complex Drosha-DGCR8 to release hairpin structured precursor miRNAs (pre-miRNAs) (O'Brien *et al.*, 2018; Pakshir *et al.*, 2020) (Fig. 2). Then these pre-miRNAs are exported into the cytoplasm via Exportin-5 where they are further transformed by Dicer and catalysed the production of mature miRNA duplex that subsequently loaded onto the RNA-induced silencing complex (RISC), final functional tuner complex, which transcriptionally/post-transcriptionally regulates the target mRNA (O'Brien *et al.*, 2018; Pakshir *et al.*, 2020) (Fig. 2).

MicroRNAs function to regulate gene expression in animals, plants and protozoa, and function post-transcriptionally through base-pairing to the mRNA 3'-untranslated regions (Fabian *et al.*, 2010). Depending on the level of complementarity of base-pairing, target mRNA molecules are silenced or gene expression is repressed by one or more of the processes such as cleavage of the mRNA strand into two pieces, destabilization of the mRNA strand through shortening of its polyA tail, no effective translation of mRNA into proteins by ribosomes (Bartel, 2009), affecting DNA methylation or histone acetylation, or targeting transcription factors (Iorio *et al.*, 2010; Sato *et al.*, 2011; Feng *et al.*, 2011), as observed in humans, animals and plants. These single-stranded tuners are endogenously articulated by all metazoan eukaryotes and have emerged as the master gene expression controllers of at least 30% human genes (Mehta and Baltimore, 2016; Masotti *et al.*, 2009; He and Hannon, 2004). The human genome is predicted to encode as many as 1000 miRNAs in a large variety of physiological environments (Zeng, 2006; O'Connell *et al.*, 2012). Studies have shown that a single miRNA can be regulated from one to multiple genes, and also multiple miRNAs can regulate the same gene (Bartel, 2009; Friedman *et al.*, 2009; Rajewsky, 2006; Krek *et al.*, 2005).

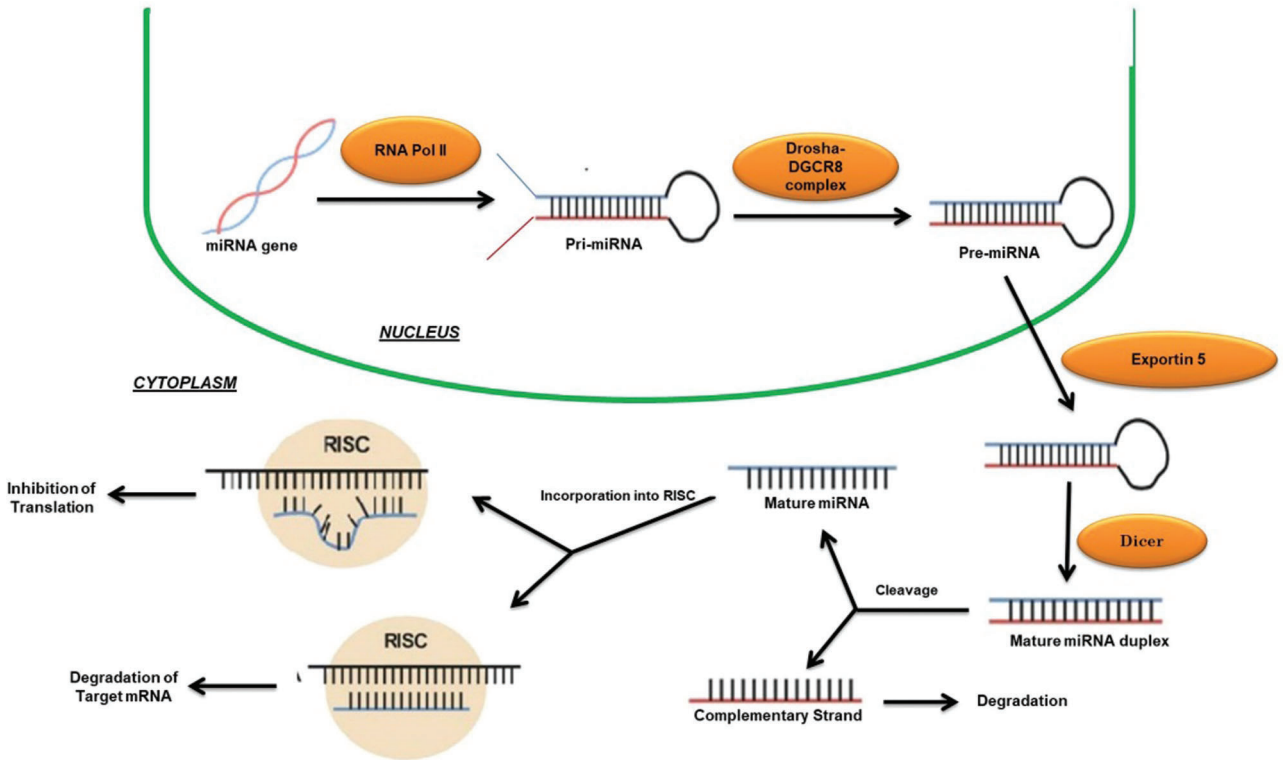

FIGURE 2. Biogeneis and mechanism of action of miRNAs.

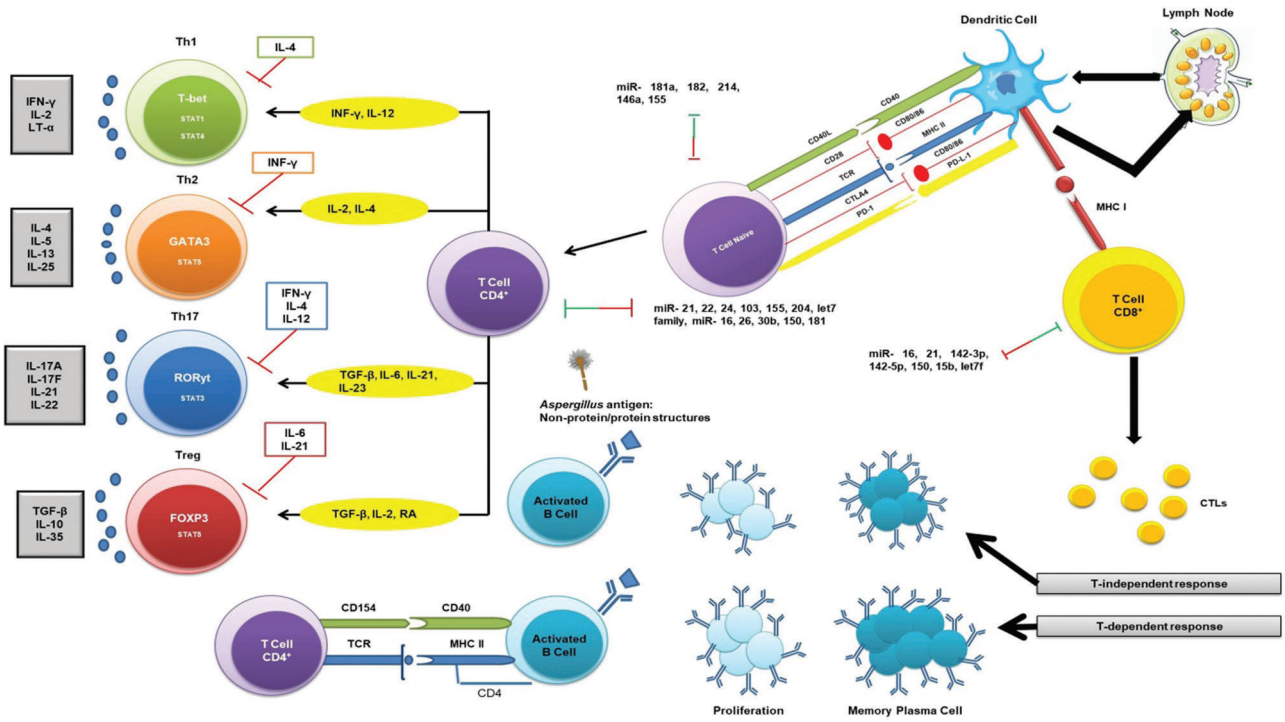

FIGURE 3. Adaptive immune response to the fungal pathogen (*Aspergillus*) and miRNA interactions. Several miRNAs interact with T-dependent and T-independent processes shown via two-way arrows and these double-ended arrows by green and red indicate up-regulation and down-regulation of miRNAs on target mRNAs, respectively.

Few studies have also indicated that miRNA can also trigger the translation of certain target mRNA (Li *et al.*, 2006; Janowski *et al.*, 2007; Vasudevan *et al.*, 2007). Several miRNAs have been broadly examined and characterized in cancer models, aging, heart disease, apoptosis and immune responses to inflammatory provocations (Place *et al.*, 2008; Lu and Rothenberg, 2013; Van Rooij and Olson, 2007; Hackl *et al.*, 2010; Leopold and Maron, 2016; Posch *et al.*, 2017).

In general, post-transcriptional mechanisms of miRNAs are supposed to regulate around two thirds of all human genes (Filipowicz *et al.*, 2008; Esteller, 2011). Recently, amplified information of proteomics has established that single miRNAs function can edge the production of numerous proteins via reduction of mRNA levels and limiting the translational disarray (Filipowicz *et al.*, 2008; Baek *et al.*, 2008; Selbach *et al.*, 2008).

This mechanism indicates that miRNAs do not extinguish gene expression, but instead they are fine-tuners of the key regulatory proteins. Also, under specific circumstances, miRNAs unpredictably govern the upregulation of the target mRNAs (Vasudevan *et al.*, 2007) or directly intervene the target gene transcription (Kim *et al.*, 2008).

MicroRNAs and Immune Responses

MicroRNAs are referred to as key controllers for animal development and many biological processes (Fu *et al.*, 2013), and play pivotal roles in regulating immune reactions to fungi. The importance of miRNA roles has been demonstrated by investigations on Dicer-knockout model of mice, that enforce a cell mediated immune deficiency (Muljo *et al.*, 2005), and also micro-array analysis (Gantier *et al.*, 2007; Taganov *et al.*, 2006). Additionally, miRNAs are shown to be detectable in cell-free body fluids like serum and plasma samples (Chen *et al.*, 2008; Zen and Zhang, 2012) and these circulating miRNAs are shielded from blood RNAses either by prevailing membrane-derived vesicles like exosomes or by making complex with lipid-protein carriers such as high-density lipoprotein (HDL) (Valadi *et al.*, 2007; Gallo *et al.*, 2012; Vickers *et al.*, 2011). Also, the majority of miRNAs in plasma is protected from degradation due to their complex formation with the AGO2 protein which is required for RNA-mediated gene silencing by the RNA-induced silencing complex (RISC) (Arroyo *et al.*, 2011; Li *et al.*, 2012). Therefore, these circulating miRNAs might be ideal biomarker attributable to their disease-specific dysregulation and their relative stability compared with mRNAs. Hence, we categorize and discuss the potential miRNAs in each sort of the immune response against the fungal pathogen, innate and acquired immunity (Tab. 1).

Influence of miRNA on allergic reactions

Allergic inflammatory responses include a wide range of conditions including asthma, allergic rhinitis, atopic dermatitis, and more recently eosinophilic esophagitis (Maddox and Schwartz, 2002; Broide, 2008; Blanchard and Rothenberg, 2008; Boguniewicz and Leung, 2011; Gelfand, 2004). Each of these diseases involves continued inflammation that is linked with visible histological changes as well as molecular alterations in gene and protein expression. The pathway employed in regulating and fine-tuning these practices represents a striking area for microRNA studies.

The let-7 family is the substantial respiratory miRNAs and has been recognized in studies examining cancer, diabetes, and aging (Frost and Olson, 2011; Su *et al.*, 2012; Jun-Hao *et al.*, 2016; Brennan *et al.*, 2017; Pal and Kasinski, 2017). Let-7 is a

TABLE 1

Immune system interactions with miRNAs

iRNA-immune system member	miRNA(s)	Target	Mechanism(s) of action	References
miRNA-PRRs	**miR-155**	• Signaling proteins: MyD88, IRAK1-2, mAL, TRAF6, TAB2 and BTK • Negative regulators: SHIP1 and SOCS1	• Directly regulate the signaling proteins • Triggering inflammatory regulators and miRNAs characterized by miR-155 (mute the negative regulators such as; SHIP1 and SOCS1, and induce AKT and IFN responses)	(Casadevall *et al*., 2002; He and Hannon, 2004)
	miR-146a	Signaling proteins: MyD88, IRAK1, IRAK2, mAL, TRAF6, TAB2 and BTK	• Negative feedback regulators that silent the immune response • Repressing the expression of the mRNAs encoding TRAF6 and IRAK1, which down-regulates the NF-κB activation • Reduces the production of IL-6 and TNF-α during innate immune responses	(He and Hannon, 2004; Zhao and Srivastava, 2007; Androulidaki *et al*., 2009)
	miR-21	Signaling proteins: MyD88, IRAK1-2, mAL, TRAF6, TAB2 and BTK	• Negative feedback regulators that silent the immune response • Repress the NF-κB signaling in IL-10 dependent manner	(He and Hannon, 2004)
	miR-223, let-7i, let-7e	TLR4 mRNA	Fine tuning the target mRNA	(Zhao and Srivastava, 2007; Masotti *et al*., 2009; O'Connell *et al*., 2012)
	miR-223	TLR3 and TLR4 mRNAs		(Masotti *et al*., 2009)
	miR-105	TLR2 mRNA		(Carissimi *et al*., 2009)
	miR-348	BTK mRNA TLR4, TLR7-9 signaling pathways to NF-κB stimulation	Indirectly stimulates the NF-κB of TLR4, TLR7, TLR8 and TLR9 dependent pathways	(Cai *et al*., 2004)
	miR-9, miR-132	Different TLRs	Targeting NF-κB 1 gene (miR-9) and the gene encoding acetylcholinesterase (AcHE) (miR-132)	(Cai *et al*., 2004; Boldin *et al*., 2011)
miRNA-Cytokine	**miR-27b**	TNF gene	NF-κB dependent induction of miR-27b up-regulates the secretion of TNF	(Casadevall, 1995)
	miR-125b	TNF gene	Up-regulation of TNF by TLR-dependent manner	(Lagos *et al*., 2010)
	miR-146a/b	TNF and IL-1 gene	Translational regulation of target genes	(Chen *et al*., 2004)
	miR-106a	IL-10 gene	miR-106 triggers the expression of IL-10 and reduced levels of IL-10 triggers further expression of 8 miRNAs, mainly miR-106a and -106b	(Marson *et al*., 2007)
	miR-21	IL-12p35 subunit	Up-regulation of IL-12	(Netea *et al*., 2008)
	Let-7	IL-6 mRNA	Up-regulation of target mRNA	(Kawai and Akira, 2011)
	miR-16, -155, -125b, -221, -369-3, -579	TNF mRNA	Fine tuning the target mRNA	(Antachopoulos and Roilides, 2005; Bartel, 2009; Mehta and Baltimore, 2016)
miRNA-Myeloid	**miR-146**	Inflammatory mediators in psoriasis	Depleting elevated levels of inflammatory mediators	(Lee *et al*., 2004)
	miR-155, -146a, and -223	NF-κB, AKT1, MEF2C	Regulation of myelocytes via affecting the targets	(Mehta and Baltimore, 2016)

(Continued)

Table 1 (continued).

iRNA-immune system member	miRNA(s)	Target	Mechanism(s) of action	References
miRNA-T cell	**miR-181a, -182, -214, -146a**	T cell associated genes	Up- and down- regulation of T cells regulatory proteins	(Cobb *et al.*, 2005; O'Connell *et al.*, 2007; Sonkoly *et al.*, 2007; Ma *et al.*, 2010)
	miR-16, -142-3p, -21, -150, -15b, -142-5p, and let-7f	Naïve T cells	Manipulating miRNA profiles for driving differentiation of naïve T cell to $CD8^+$ T cells	(Cobb *et al.*, 2006)
	miR-21	$CD8^+$ T cells	Up-regulation of $CD8^+$ T cells	(Liston *et al.*, 2008; O'Neill *et al.*, 2011)
	Anti-CD3 antibodies	T cells	*In vitro* application of anti-CD3 antibodies triggers the up-regulation of miR-21-22, -204, -24, -155, and –103 in T cells	(Stittrich *et al.*, 2010)
			In vitro application of anti-CD3 antibodies triggers the down-regulation of let-7 family members, miR-26, -16, -30b-c, -181, and -150 in T cells	(Li *et al.*, 2007)
	miR-155	T cells	Fine tuning the production of DC-mediated T cells miR-155 is essential for the polarization of Th1 and Th17 profiles	(Wu *et al.*, 2007; Lu *et al.*, 2010)
		$Foxp3^+$ Tregs	miR-155 and $Foxp3^+$ Tregs fine tune each other	(Asangani *et al.*, 2008; Marioto *et al.*, 2017)
miRNA-B cell	**mir17~92**	Pro B cells	Fine tuning the functions of B cells especially pro-B cells	(Lee *et al.*, 2004; Li *et al.*, 2014)
	miR-155	B cells	miR-155-deficient mice shows the impaired B cell functions after immunization via dinitrophenylated LPs	(Pillai *et al.*, 2007)
	miR-142, -146a, -155, -217	B cells precursors	Triggering B cells differentiation	(Foster *et al.*, 2013; Zhang *et al.*, 2015; Mehta and Baltimore, 2016)

vital tumor suppressor miRNA, which is articulated across various animal species from worms to flies, to humans (Pasquinelli *et al.*, 2000; Ruby *et al.*, 2006). The human let-7 family of miRNA comprises 12 members of miRNA and is highly conserved in human tissues (Su *et al.*, 2012). The *let-7* miRNAs target interleukin (IL)-13 in *in vivo* and *in vitro* fungal exposed models (Lu and Rothenberg, 2013). Also, miR-21 is another broadly studied miRNA and has been known to take part in the inflammatory response elicited by different stimuli, comprising of doxycycline-induced allergic airway inflammation (Lu *et al.*, 2009). miR-21 is one of the firsts identified cancer-promoting oncomiRs, affecting numerous tumour suppressor genes associated with proliferation, apoptosis and invasion (Feng and Tsao, 2016). The recent studies are focusing on the diagnostic and prognostic value of miR-21 as well as its implication in the drug resistance of human malignancies. miR-21 is also one of the most up-regulated miRNAs in patients suffering from allergic eosinophilic esophagitis (Lu *et al.*, 2012a; Lu *et al.*, 2012c), which is related to the investigations that stated miR-21 and miR-223 as controllers of development of eosinophil in an *ex vivo* specimen of bone-derived eosinophils (Lu *et al.*, 2013a; Lu *et al.*, 2013b). Down regulation in miR-375 in epithelial cells from patients with eosinophilic esophagitis has been reported. This leads to modulation of IL-13 associated immunoinflammatory pathways in epithelial cells demonstrating the role of miR-375 as a fine-tuner of IL-13-mediated responses (Lu *et al.*, 2012b).

The studies on rodent models, that allowed to expose to house dust mite allergen, have been reported the increased expression of microRNAs miR-126, miR-106a and miR-145 which ultimately contribute to allergic inflammation (Mattes *et al.*, 2009; Collison *et al.*, 2011; Sharma *et al.*, 2012). The airborne pollutants such as cigarette smoke, contribute to pulmonary inflammation in rodent models through down-regulation of let-7c and 7f, miR-34b, -34c and miR-222 (Izzotti *et al.*, 2005; Izzotti *et al.*, 2009a; Izzotti *et al.*, 2009b). Research scrutinizing anomalous miRNA depiction in asthmatic patients also showed new miRNAs that give rise to allergic airway infection. In a study, $CD4^+$ T cells have been isolated from the bronchoalveolar lavage fluid from human patients with asthma and showed that miR-19a had

the extreme expression stimulating a cell response mediated through Th2, a known reaction furnishing to allergic asthma (Simpson *et al.*, 2014). In an another study, upregulation of miR-221 and miR-485-3p in peripheral blood of pediatric asthmatic patients indicated that these miRNAs add to the development of asthma (Liu *et al.*, 2012). A chemical allergen murine model on dermal exposure to toluene 2,4-diisocyanate showed increased dermal expressions of miR-21, -22, -27b, -31, -126, -155, -210 and miR-301a. This study showed miRNAs that are known to be related to immune responses with asthmatic host (miR-21, -31, -126, and miR-155), and also proposed new miRNAs as potential biomarkers (miR-22, -27b, -301a, and miR-210) for allergic sensitization to toluene 2, 4-diisocyanate (Anderson *et al.*, 2014).

miRNA regulation on B-cell and T-cell

In the immune system, microRNAs give the impression to have a key role in the stimulation, function and maintenance of the regulatory T-cell lineage, and differentiation of B cells, dendritic cells and macrophages via toll-like receptors. The miR-17/92 cluster is among the broadly studied microRNA clusters, important in cell cycle, proliferation, apoptosis and other crucial processes and is often dysregulated in cardiovascular, immune and neurodegenerative diseases. The miR-17~92 cluster induces immune responses from Th1 type together with impeding regulatory T-cell differentiation (Jiang *et al.*, 2011) and the consequences of overexpression of miR-17~92 are enhanced B-cell proliferation and survival (Xiao *et al.*, 2008). Similarly, miR-181 and miR-150 has also been shown to regulate B-cell differentiation and responses. Ectopic expression of miR-181 has been shown to decrease T-cell numbers as well as substantial increase in $CD19^+$ B-cells (Chen *et al.*, 2004). The miR-150 is generally expressed at low quantity in initial B-cell progenitors and its aberrant expression marks a developmental block at the pro-B to pre-B transition by targeting the transcription factor c-Myb (Xiao *et al.*, 2007; Zhou *et al.*, 2007). In B-cell malignancies in humans, miR-155 has been found to be highly expressed that control important aspects of B-cells but not their early differentiation (van den Berg *et al.*, 2003; Metzler *et al.*, 2004). There is also the requirement of miR-155 for regular and active working of B and T lymphocytes, and dendritic cells (Rodriguez *et al.*, 2007).

MiRNAs play significant roles in T-cell growth by knocking down of Dicer/Drosha in immature thymocytes that leads to a severe reduction in total thymocytes as well as in peripheral $CD4^+$ numbers (Cobb *et al.*, 2005). Following PAMP-PRR interactions and stimulation of different cytokines, fungal antigens are also presented to $TCD4^+/TCD8^+$ (via MHC-TCR interaction) (Fig. 3). Moreover, fungal antigens trigger humoral immune responses through interaction between B and $TCD4^+$ cells and these responses are in two forms: T-dependent and T-independent (Fig. 3). There are several studies suggested the effect of miR-181a, -182, -214, and miR-146a in regulating the T-cell responses (Li *et al.*, 2007; Stittrich *et al.*, 2010; Jindra *et al.*, 2010; Lu *et al.*, 2010; Boldin *et al.*, 2011). The pivotal roles of miR-21, -16, -142-5p, -142-3p, -15b, -150, and let-7 family miRNAs has been studied in manipulating the differentiation of naïve T cells to effector and memory $CD8^+$ T cells (Wu *et al.*, 2007). Also, several studies have indicated the chief roles of miR-21 in the effector CD^+ T cells (Asangani *et al.*, 2008; Li *et al.*, 2014; Sonkoly *et al.*, 2008). It is also mentioned that miRNAs also have the same interactions with $CD4^+$ T cells and regulatory T cells (Cobb *et al.*, 2005). A study revealed that mice with miR-155 deficiency were unable to unveil T cell response through dendritic cells signaling onsets (Rodriguez *et al.*, 2007). Since deficit miR-155 did not distress the Th2 profiles, therefore, miR-155 elicits the polarization of Th1 profile and production of pro-inflammatory cytokines, considering that (Rodriguez *et al.*, 2007). Additionally, miR-155 activates the polarization of Th17 cell that are the main operators to compel inflammatory responses, and DCs deficient with miR-155, causes lower levels of IL-6 and IL-23 (O'Connell *et al.*, 2010a). Both the thymic and peripheral stimulation of regulatory T cells are enhanced by miRNAs (Lu and Liston, 2009).

Studies indicated the diminution of specific miRNA profiles causes the compromised function of regulatory T cells, which ultimately leads to autoimmunity (Liston *et al.*, 2008; Zhou *et al.*, 2008). Also, miR-155 is directly regulated by Foxp3+ regulatory T cells (Marson *et al.*, 2007; Zheng *et al.*, 2007). In an animal model of eosinophilic rhinosinusitis, the expression of miR-125b is greater than before that further resulted in amplified interferon IF-γ and a Th1 type immune response (Zhang *et al.*, 2012) and also, miR-125b overexpression persuaded macrophage surface activation (Chaudhuri *et al.*, 2011). MiR-19a has also been critical in modifying Th1 type responses through the production of IF-γ succeeding antigen induction in a mouse model (Jiang *et al.*, 2011).

MiR-19a is a member of miR-17-92 cluster and its up-regulation has been shown to cause increased inflammation and promoted a Th2 type response (Simpson *et al.*, 2014). MiR-106-363 cluster has been found to regulate Th17 cell differentiation (Kästle *et al.*, 2017) and also, Th17 cell-mediated inflammation was induced by miR-326 and miR-21 in an experimental autoimmune encephalomyelitis (Liston *et al.*, 2008; Murugaiyan *et al.*, 2015).

miRNAs trigger TLR signaling

Toll like receptors (TLRs) have been reported to detect the pathogen invasion and induce either immuno-stimulatory or immune-modulatory biological response (Dwivedi *et al.*, 2011). TLRs perform a fundamental role in the innate immunity by distinguishing pathogen-associated molecular patterns (PAMPs) expressed on pathogens and signaling for the production of cytokine to excite an immune reaction. These TLRs contribute in macrophage activation and have been shown to persuade miR-155, -146, -147, -9, and -21 (O'Connell *et al.*, 2010b; O'Neill *et al.*, 2011). MicroRNAs administer the TLR signaling by directly targeting specific signaling proteins, mainly MyD88, mAL, IRAK1, IRAK2 and TRAF6 (O'Neill *et al.*, 2011) (Fig. 1). An up-regulation of miR-21 has been noticed in both primary human airway epithelial cells (Lu *et al.*, 2009), and through an IL-13Rα1-dependent mechanism in an IL-13 transgenic mouse model (Case *et al.*, 2011). A study showed that miR-21 expression has inhibited murine pulmonary inflammation by subduing TLR2 signaling (Case *et al.*, 2011). It has also been reported

that miR-21 and miR-29a interact with TLR7 and TLR8 on secretion from tumour cells (Chen *et al.*, 2013).

Upon lipopolysaccharide stimulation, miR-146a/b was made known to regulate TLR and cytokine signaling, and TNF and IL-1 through targeting their receptors (Taganov *et al.*, 2006). It has been remarkably specified that miR-146a is a key tuner of TLRs through TRAF6 and IRAK1 signaling pathways and NF-κB (O'Connell *et al.*, 2012; Boldin *et al.*, 2011; Zhao *et al.*, 2011) (Fig. 1). The pivotal roles of miR-146 has been studied on diminishing the over elevated levels of inflammatory mediators that were strongly associated with psoriasis, chronic inflammatory disease of skin which is strengthened by *Malassezia* species (Sonkoly *et al.*, 2007). However, miR-146a decreases the secretion of pro-inflammatory cytokines during innate immune responses (Boldin *et al.*, 2011; Zhao *et al.*, 2011). In TLR signaling, miR-21 is a key player which is induced by MyD88-dependent signaling of NF-κB during TLR4 induction of macrophages and also, accelerates repression of NF-κB signaling in IL-10 dependent manner (O'Connell *et al.*, 2012). Moreover, it has been indicated that TLR signaling and TNF-α lipopolysaccharide (LPS)-triggered mechanism are targeted and modulated by miR-9 and miR-27b (Jennewein *et al.*, 2010). Similarly, TLR-signaling-mediated expression of TNF-α was elicited by miR-125b (Tili *et al.*, 2007). In addition, studies showed that miR-223 was involved in TLR4 and TLR3 expression (Chen *et al.*, 2007), and miR-105 regulated TLR2 mRNA (Benakanakere *et al.*, 2009) (Fig. 1). Further investigation suggested that the gene encoding acetylcholinesterase (AChE) targeted by miR-132 to regulate TLR signaling (O'Connell *et al.*, 2012; Sonkoly *et al.*, 2008; O'Neill *et al.*, 2011) (Tab. 2). Another study showed that miR-106 controlled the expression of IL-10 gene, and the reduced levels of IL-10 triggers added expression of miR-106a and miR-106b (Sharma *et al.*, 2009).

MicroRNAs Profiles Following *Aspergillus* Exposure

Although the role of miRNA has been explored and established in a number of disorders, their utility in understating the immunological response on pulmonary and systemic exposure to fungus is in nascent state. It has been assumed that fungal pathogen may manipulate the miRNA genetic network signaling and change their expression profiles during the progression of disease. Members of *Aspergillus* are prominent etiological agents and in the past decades the occurrence of aspergillosis has increased (Ruhnke *et al.*, 2018; Badiee and Hashemizadeh, 2014). MicroRNAs emerged as significant endogenous regulators of almost all basic biological processes. Recent researches have estimated the potential of free circulating miRNAs in diagnostic approaches as biomarkers in extrapolative diseases. During infection, hypoxia related miRNAs, miR-26a, -26b, -21 and -101 were considered when lung hypoxia has been established by an ischemic microenvironment, vascular invasion, thrombosis, antiangiogenic factors such as gliotoxin, that were significantly considered as virulence factor of *A. fumigatus* (Dix *et al.*, 2017; Saliminejad *et al.*, 2019; Xu *et al.*, 2017). For the investigation of miRNAs role during *A. fumigatus* infection, a study has been conducted for the analysis of two major miRNAs expression, miR-132 and miR-155 in human monocytes and dendritic cells (Gupta *et al.*, 2014). It was demonstrated that miR-132 and miR-155 were differentially articulated in monocytes and DCs upon induction with *A. fumigatus* or bacterial lipopolysaccharide. Surprisingly, miR-132 was stimulated by *A. fumigatus* but not by LPS in both monocytes and DCs and hence, suggested that miR-132 may be a substantial regulator of the immune response focussed against *A. fumigatus* (Gupta *et al.*, 2014) (Tab. 3).

TABLE 2

miRNAs and TLR interactions

miRNA	TLRs	Target cell type	Underlying mechanism via signaling proteins	References
miR-21	TLR4	B-cells, lung tissues, BMDMs, cholangiocytes	Up-regulation of miR-21 in target cell types via MyD88, TRIF, NF-κB signaling molecules	(Taganov *et al.*, 2006; Chen *et al.*, 2017)
miR-125b		Splenocytes, BMDMs, DCs	Down-regulation of miR-125b in target cell types via NF-κB, AKT1 signaling molecules	(Cai *et al.*, 2004; Cameron *et al.*, 2008a)
		Cholangiocytes, LPS-tolerized THP1 cells	Up-regulation of miR-125b in target cell types via NF-κB signaling molecules	(Boldin *et al.*, 2011; Chen *et al.*, 2017; Dix *et al.*, 2017)
Let-7i		H69 cholangiocytes	Down-regulation of let-7i in target cell types via NF-κB, C/EBPβ signaling molecules	(Taganov *et al.*, 2006; Cameron *et al.*, 2008b; Gantier, 2010)
Let-7e		Peritoneal macrophages	Up-regulation of let-7e in target cell types via AKT1 signaling molecules	(Sonkoly *et al.*, 2008)
miR-98		H69 cholangiocytes	Down-regulation of miR-98 in target cell types	(Landgraf *et al.*, 2007)

(Continued)

Table 2 (continued).

miRNA	TLRs	Target cell type	Underlying mechanism via signaling proteins	References
miR-27b		Human macrophages	Up-regulation of miR-27b in target cell types via NF-κB signaling molecules	(Ni *et al.*, 2014)
miR-223		Inflammed lung tissue, DCs	Up-regulation of miR-223 in target cell types	(Moschos *et al.*, 2007; Sonkoly *et al.*, 2008)
miR-132	TLR4, TLR9	Human MO and MQ, BMDMs, THP1 cells, splenocytes	Up-regulation of miR-132 in target cell types	(Moschos *et al.*, 2007; Zhou *et al.*, 2009)
miR-146	TLR2, TLR3, TLR4, TLR5	THP1 cells, macrophages, BMDMs, T cells	Up-regulation of miR-146 in target cell types via MyD88, NF-κB signaling molecules	(Casadevall, 1995; Taganov *et al.*, 2006; Moschos *et al.*, 2007; Sabina *et al.*, 2013)
miR-155	TLR2, TLR3, TLR4, TLR9	Human MO and MQ, BMDMs, THP1 cells, DC, B cells, Tregs, splenocytes	Up-regulation of miR-155 in target cell types via MyD88, JNK, TRIF, NF-κB, KSRP and AP1 pathways	(Cai *et al.*, 2004; Brown *et al.*, 2007; Moschos *et al.*, 2007; Carissimi *et al.*, 2009; Ruggiero *et al.*, 2009; Zhou *et al.*, 2009; Iliopoulos *et al.*, 2010; Chen *et al.*, 2017)
miR-147	TLR2, TLR3, TLR4	BMDMs, alveolar MQ, THP1 cells	Up-regulation of miR-147 in target cell types via MyD88, NF-κB, TRIF and IRF3 signaling molecules	(O'Carroll *et al.*, 2007)
miR-9	TLR2, TLR4, TLR7, TLR8	Human monocytes, and granulocytes	Up-regulation of miR-9 in target cell types via MyD88, NF-κB signaling molecules	(Vigorito *et al.*, 2007)

TABLE 3

Analysis of miRNAs on different host cell types

miRNA	Host cell types	*Aspergillus* strain	*Aspergillus* culture/ Sample preparation	Time of exposure	Methods of miRNA quantification	References
miR-155, -132	Human Monocytes and DC	*A. fumigatus* isolate ATCC 46645	Conidia of the *A. fumigatus* were prepared by adding sterile distilled water and passed through a cell strainer. Germ tubes and hyphae were grown by incubating conidia in RPMI 1640 medium without FCS at 200 rpm and room temperature overnight followed by incubation at 37°C until the respective fungal morphology was microscopically visible.	Immune cells were stimulated with *A. fumigatus* conidia, germ tubes or hyphae with monocytes for 2, 4 and 6 h and with DCs for 4, 6 and 9 h.	Quantification of the specific miRNAs was performed by qPCR with TaqMan probes according to manufacturer (miRNA RT kit and miRNA-specific TaqMan miRNA assays).	(Morton *et al.*, 2011; Gupta *et al.*, 2014)
miR-142-3p, -142-5p, -26b 5p, -21-5p	Human peripheral blood samples		Classical mycology of bronchoalveolar lavage (BAL) was performed in the case of 8 patients in whom there was a suspicion of bacteremia or aspergillosis.		TaqMan qRT-PCR was used to detect miRNA expression.	(Tolnai *et al.*, 2020)

(Continued)

Table 3 (continued).

miRNA	Host cell types	*Aspergillus* strain	*Aspergillus* culture/ Sample preparation	Time of exposure	Methods of miRNA quantification	References
mmu-miR-124-3p, -29c-5p, -21a-3p, -3473b, -3473e, -150-3p, -29c-5p, mmu-let-7b-3p	Lung tissues of mice	A clinical isolate of *A. fumigatus*	Conidia were harvested from *A. fumigatus* grown on PDA through washing by sterile 0.1% Tween 20 phosphate buffer saline and filtered through nylon membrane.	Mice were intratracheally administered with conidia of *A. fumigatus* and were monitored every 6 h post-inoculation.	qRT-PCR was used to detect miRNA expression.	(Chen *et al.*, 2019)
miR-511-5p, -142-3p, -155-5p, -451a, -21-5p, -146-5p, -143-3p, -204-5p, -184	Human corneas	*A. flavus*	Eleven post-transplant corneas were obtained during surgery from keratitis patients who were culture positive for *A. flavus*.		qRT-PCR was used to detect miRNA expression.	(Boomiraj *et al.*, 2015)
miR-23b-3p, -29a-3p, -30c-5p, -677-3p, -2137, -1947-3p, -29a-3p	Lungs of mice	*A. fumigatus* strain B5233/ ATCC 13073	Conidia were inoculated on malt extract agar and harvested and filtered through sterilized endotoxin-free water. Autoclaved Mahatma brown rice was inoculated with conidia and incubated and heat inactivated conidia were prepared by autoclaving the *A. fumigatus* laden rice cultures.	Three groups of naïve B6C3F1/N mice were exposed via inhalation of *A. fumigatus* viable conidia, heat inactivated conidia or HEPA-filtered air through nose only for 13 weeks. Total RNA was isolated from whole lung 24 and 48 h post final exposure.	qRT-PCR was used to detect miRNA expression.	(Croston *et al.*, 2016)

The immune response against *A. fumigatus* is dependent on the morphology of fungus that is conidia are covered by hydrophobins that prevent the immune sensing but upon germination, the loss of this rodlet layer leads to the fungal recognition by immune cells (Aimanianda *et al.*, 2009). MiR expression was supported by stimulating monocytes and DCs with different *A. fumigatus* morphologies (Gupta *et al.*, 2014). Conidia were unable to induce miR-132 expression in both cell types, whereas both germ tubes and hyphae amplified miR-132 levels.

In a study (Tab. 3), a significant association was confirmed between invasive aspergillosis and miRNAs, miR-142-3p, -142-5p, -26b-5p and miR-21-5p (Tolnai *et al.*, 2020). A research identified 23 miRNAs that were associated with invasive pulmonary aspergillosis (IPA), a severe opportunistic infection caused by *A. fumigatus* with high mortality in patients with compromised immunity (Chen *et al.*, 2019). IPA-related miRNAs encompassed upregulated mmu-miR-124-3p, mmu-let-7b-3p, mmu-miR-29c-5p, mmu-miR-21a-3p, mmu-miR-3473b and mmu-miR-3473e, and downregulated mmu-miR-150-3p and mmu-miR29c-5p (Chen *et al.*, 2019) (Tab. 3). As per miRNA target prediction, all IPA-associated miRNAs possibly involve a cooperative regulation of main elements in the NF-κB signaling pathway.

Boomiraj *et al.* (2015) investigated the miRNA expression profiles and their immune regulatory roles in fungal keratitis caused by *A. flavus*. They collected the corneas from normal donors and 11 post-transplant patients suffering from fungal keratitis, and evaluated and identified the miRNAs/mRNA expression levels with their targets and regulatory roles by applying real-time quantitative PCR (RT-qPCR) followed by bioinformatics analysis. They showed that 43 miRNAs were found to be up-regulated (miR-21-5p, -146b-5p, -143-3p, -204-5p and miR-184 were highly expressed) and 32 miRNAs were down-regulated (miR-142-3p, -155-5p, -511-5p, and miR-451a were the most down-regulated) (Tab. 3).

It was predicted that miR-451a as a potential factor in would healing via regulating macrophage migration inhibitory factor (MIF) gene, and suppressing inflammation by triggering TLR pathway (Gilliver *et al.*, 2010). Also, two novel miRNAs, miR-cornea-5p and miR-cornea-3p were suggested to play major roles in disease pathogenesis by *A. flavus*.

The interactions between immune responses and pulmonary miRNA, mRNA profiles and some prominent signaling pathways in mice were evaluated by Croston *et al.* (Croston *et al.*, 2016) after 24 and 48 h of exposure to different forms of inhaled *A. fumigatus* conidia, particularly viable and heat-inactivated conidia (HIC) (Tab. 3).

Approximately, 50% of all 415 identified miRNAs were controlled following viable and HIC forms of conidia. They observed that six miRNAs (miR-23b-3p, -29a-3p, -30c-5p, -677-3p, -2137 and miR-1947-3p) had prevalent fold change, and miR-29a-3p was down-regulated that may play significant roles in shaping innate responses via regulating TGF-β3, Clec7a and IFN-β genes. Also, miR-23b-3p was observed to be down-regulated and involved in fine-tuning of TGF-β by regulating SMAD2 signaling pathway, IL-13 and IL-33. On the other hand, miR-1947-3p and miR-2137 were involved in triggering chemokine or TCR signaling. Hence, they established that these down-regulated miRNAs played major roles in pulmonary inflammatory response to inhaled conidia.

Conclusion

Application of immunotherapy of fungal infections has recently been the foremost subject in treating invasive fungal infections (IFIs) through various methods, such as cytokine therapy including CSF and IFN-γ, monoclonal antibody therapy, vaccines, ligand therapy via pattern recognition receptor (PRR) agonists, and positioning DCs as critical modulators of immune tolerance. Immune regulation is considered one of the chief approaches in order to control IFIs, therefore, better understanding of interactions between miRNA and immune responses to fungal pathogens is required. This might lead to attain new methods in miRNA-mediated immunotherapeutic against fungal infections, especially pathogenic and ubiquitous fungus such as *Aspergillus*, and also facilitate their application as biomarkers of specific phases of infection establishment and progression.

According to the potential regulatory roles of miR-155, miR-132, miR-142-5p, miR-142-3p, miR-21-5p, miR-26b-5p, miR-21, let-7 family, and miR-451a on exposure to *Aspergillus* particles, they can be applied as therapeutics in order to manipulate the immune players to optimize the immune responses against *Aspergillus* infection. When compared with available datasets probing miRNA profiles in allergic and inflammatory models infected on exposure of *Aspergillus*, some common differentially expressed miRNAs were recognized. Among these the purpose of miR-132 is to uphold a normal hematopoietic output during an immune reaction and normalizes genes at the commencement of an immune response to recover homeostasis of the immune system.

Another miRNA such as miR-155 induces both Th1 and Th17 immune reactions and persuades classical activation of macrophages. The investigations directed towards miRNA biology have highlighted the curiosity of research community in scrutinizing the transformed genetic profiles in different disease models (Pakshir *et al.*, 2020). The functionality of miRNA in governing diverse gene expression makes miRNA an ideal candidate for therapeutic applications, however, there only a few studies available that have scrutinized miRNA profiles following fungal exposure especially *Aspergillus*. Also, few data examined that the miRNA expression is transformed in various human diseases and its discriminating modulation through antisense inhibition (Fabani *et al.*, 2010) or replacement (Bader *et al.*, 2010; Bader, 2012) could ominously distress the prognosis of a disease. Although, there are some major challenges ahead in investigating miRNAs profiles such as multiple roles and functions of miRNA molecule leads to no selective and specific target for miRNAs. Also, the efficiency of a miRNA molecule is dose-dependent that is the effect of a miRNA molecule depends on the target mRNA level and its final product. Herein, involvement of miRNAs in the various immunological responses, and their importance and efficiency in fine-tuning the immunity to *Aspergillus* were discussed. Despite being hot spots in governing the immune responses by miRNAs against fungal pathogens, little studies have been done in this regard. More understanding and exploration is necessary about miRNAs interactions with immune responses and their therapeutic potential as an immunotherapy. Further investigation of miRNA profiles is required to provide greater mechanistic vision into the immunological response to clinically and environmentally relevant fungal species, and establish a treatment approach by conducting further studies. With the growing research, miRNA will have a bright future and become an innovative therapeutic tool.

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