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Review Article

microRNA: An Advance Diagnostic Approach in Tuberculosis

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ABSTRACT

Tuberculosis is the worldwide lethal infectious disease at current days, which is caused by Mycobacterium tuberculosis. microRNA is a small non coding RNA molecule that plays a key role in regulating various biological process. Host microRNA themselves can be up-regulated or down-regulated during disease condition. Potential unique host microRNA might be used as a biomarker in tuberculosis diagnosis at an earlier stage. Therefore, potential host microRNA recognition must be useful in tuberculosis in term of diagnostic purpose. miRNA biomarker field requires more comprehensive work in tuberculosis disease. This review summarizes the biogenesis and biological function of microRNA and various previous and recent studies on recognition of potential biomarker for tuberculosis in case of latent and active tuberculosis. This review also summarizes the role of specific host microRNA in tuberculosis.

Keywords: *microRNA, Biogenesis, Tuberculosis, Biomarker.*

INTRODUCTION

Globally, tuberculosis is the main health problem. Mainly, Seven countries have been notified for 64% of new tuberculosis cases: India, China, Philippines, Nigeria, Pakistan, and South Africa. The new data suggest that 10.4 million people suffer from tuberculosis disease, in which 6.2 million men, 3.2 million women, the 1 million children and total 1.7 million peoples died of tuberculosis in 2016-2017 according the WHO report (WHO Tuberculosis global report 2017). On the basis of this report, tuberculosis is highly infectious disease with high mortality in the world.

Tuberculosis is caused by the bacteria *Mycobacterium tuberculosis,* an infectious disease which is transmitted from person to person by air. Tuberculosis mainly affect lungs in the human body, but it also affects the other part of the human body like stomach, brain, kidney which is known as extra-pulmonary tuberculosis (cdc.gov). In the human body, tuberculosis infection could be Latent and Active that depends on the immune system of the host body. In latent TB, person have no signs & symptoms related to tuberculosis.

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However, *Mycobacteria tuberculosis* may be present for many years, even a lifetime in latent tuberculosis patients, but not create any problem until the patient's immune system is strong. Mainly 90% people suffering from TB that have no symptoms throughout life, but only 10% people suffering from TB that will convert into active TB that means the host immune system plays important role in developing the disease. Active TB patients have some symptoms like feeling sick, unexplained weight loss, fever and coughing with blood for 3 weeks or longer and clinical symptom is skin and blood test result positive (Harapan et al., 2013), if TB infection is early diagnosed it may be prevented to develop progression of tuberculosis.

The best method for TB infection diagnosis is the culture process of TB bacteria, but this is not efficient because this method detection is low. Hence, molecular diagnostic test was introduced, but the outcome of this method are not sure due to the presence of contamination. So in current days, the early diagnosis test is not available for TB. So TB is the main worldwide health issue (Wagh et al., 2016). But microRNA may be act as another option in TB diagnostic process because microRNAs have a specific expression like upregulated or downregulated during the mycobacterial infection, this expression suggesting the specific role for miRNA in tuberculosis diagnostic field (Liu et al.,, 2011). But microRNA as a biomarker of the TB diagnostic process is under research at the current scenario.

Several microRNA is used as alternative biomarker for tuberculosis diagnosis, but still none of the potential microRNA used as biomarker for TB diagnosis yet (Wagh et al., 2016). microRNA is small noncoding RNA that plays important role in the gene expression level and other biological system (O' Connell et al., 2010). microRNA is important regulator that contain 21-23 nucleotide that play the important function in various biological process through the modulating process and inhibit the translation process or induction of mRNA degradation process (Mehta & Baltimore, 2016). Specific miRNA binding to the complementary sequences of mRNA that results transcript degradation and this target mRNA not further code for proteins and at this point, process is completely stopped and not form any protein and product (Sabir et al., 2018). miRNA bind to the complementary sequences of target protein coding mRNA in 3' untranslated region that result transcript degradation and also inhibit the translation (Maute et al., 2014).

Alteration of specific miRNA profile between the disease condition and healthy condition which indicates their use as a biomarker in tuberculosis and in other diseases (Miotto et al., 2013). More than 2000 miRNA encode in the human genome and more than one genes may be suppressed by each miRNA and one mRNA may be targeted by the more than one miRNA (Sabir et al., 2018). A recent study reports that miRNA associated with communicable and non- communicable disease and other previous studies suggest that in tuberculosis problem alteration in specific gene profile in specific cell like macrophages, natural killer cell between the latent and active tuberculosis condition. These all alteration conditions are controlled by miRNA. So the abnormal expression of miRNA is linked to various human diseases. This abnormal expression of miRNA may be useful in diagnostic purpose. In tuberculosis disease, main problem is accurate diagnostic approach is not available, so aberrant expression of miRNAs may be helpful for best accurate diagnostic approach.

Various miRNA have been identified to regulate the cellular process and other biological process. Hence, alteration of miRNA profile represents a new class of biomarker, use as diagnostic biomarker in TB (Sabir et al., 2018). Various studies have done on host miRNA with various diseases like microRNA-21 have a specific role in cancer and miR-208 in cardiac disease and miR-221 in carcinoma and other disease, but in case of tuberculosis more comprehensive work is remaining because any microRNA relation status is not clear with tuberculosis yet (Zhonghan Li et al., 2014). In this review, we will discuss miRNA biogenesis and function and immunological aspect of microRNA and highlight our understanding on the basis of growing research. We will also discuss role

miR-155, miR-21 and miR-147 with tuberculosis. We will also discuss microRNA would be used as a potential biomarker in tuberculosis.

BIOGENESIS AND FUNCTION OF microRNA

The first small RNA was discovered as *lin-4* by Ambros and Ruvkun group in 1993 via the genetic screening in nematodes. After this discovery, *lin-4* play regulatory function for the *lin-14* gene, this also discovered the process indicating the regulatory function of small RNA. Now *lin-4* accepted as the root of an ample class of regulatory RNAs which are known as microRNAs (Fazli et al., 2010). In animals, all microRNA are synthesized in the multistep process with the help of various enzymes and the occurrence of first step is in the cell nucleus and the final ending step is completed in cytoplasm. Mainly microRNA gene transcription occurred by the RNA polymerase II after transcription process product known as primary miRNA which can contain several hundred nucleotides and also contain local stem loop structure (O' Connell et al., 2010). The flow of biogenesis of microRNA is shown in fig.1. The next step is called the nuclear processing in which primary miRNA are cleaved at the hairpin stem structure and released the product that contained the 60-80nt product known as the precursor of miRNA (pre-miRNA) (Fazli et al., 2010). This process occurred with the help of RNase III-type enzyme Drosha, in which process required DiGeorge syndrome critical region work as a co-factor in gene 8 (DGCR8) in human. When Drosha interacts with DGCR8 the formation of large, complex takes place which is known as microprocessor complex. Hence in this process, pri-miRNA is converted into pre-miRNA with 2-3nt at 3'overhange and the whole process is completed in the cell nucleus (Sabir et al., 2018; Fazli et al., 2010).

After this step, pre-miRNA transported into the cytoplasm from the cell nucleus via the nuclear pore complex that complex present in the nuclear membrane. This transportation process occurred with the help of RanGTP-nuclear transport receptor exportin-5. When exportin-5 attached with pre-miRNA it then transport into cytoplasm and removes the GTP from pre-miRNA by GTP hydrolysis process (Fazli et al., 2010). After this step pre-miRNA are further processed by endonuclease cytoplasmic RNase III Dicer enzyme and form the imperfect mature miRNA that contain 22 nucleotides. Usually Dicer is specific protein that is already exists in most of the eukaryotic organisms, but in few cases multiple Dicer are found in single organisms, like *D.melanogaster* have the two types of Dicer: Dicer 1 and Dicer 2. Both types of Dicer have a specific role that is Dicer 1 is used for miRNA maturation process and Dicer 2 is needed for the siRNA maturation process (Fazli et al., 2010). In humans, Dicer binds with some other protein like protein kinase and trans-activation response RNA binding protein (Chendrimada et al., 2005; Haase et al., 2005). According to the previous study, generation of the mature miRNA duplex by removal of terminal loop in pre-miRNA with the help of a Dicer enzyme (O'Brien et al., 2018). In this duplex, one strand is called the guide strand and another strand is called the passenger strand (miRNA*). Hence this duplex is also known as a miRNA:miRNA*complex (Harapan et al., 2013; Fazli et al., 2010). After this processing this duplex integrated into the Argonaute (Ago) family of protein with the ATP dependent manner. Now this complex becomes an effector complex. In this complex passenger strand (miRNA*) is degraded by AGO2 with the help of cellular process and other strand (guide strand) bound to Ago protein. A recent study suggests that the strand selection process from 5p or 3p strand that process depends on thermodynamic stability at 5' end of miRNA duplex or 5'U at 1st nucleotide location. Usually one strand has less 5' stability or 5'Uracil as compared to other strand, more stable strand is loaded into AGO and forms a complex. This strand consider as guide strand (O'Brien et al., 2018; Broughton et al., 2016). After the loading process guide strand guides this complex to mRNA target and further process silenced the mRNA via degradation or translation repression process (Broughton et al., 2016).

Previous study suggests that extracellular body fluid contains the miRNA such as in plasma, serum, urine, seminal fluids, breast milk, saliva, seminal fluid, tears.

The various miRNAs are linked with a variety of diseases are used as a biomarker for diagnostic purpose such as Tuberculosis. Extracellular microRNA have the unique properties as compared to cellular RNA. Extracellular microRNA is more stable and that also have more resistance property against the degeneration at room temperature more than 5 days and other bio-chemical condition such as alteration in PH, boiling and freezing situation. According to previous studies shows that same community of miRNA identified in vesicles like micro-vesicles and exosomes but another type community are bound with some specific protein like AGO2 (O'Brien et al., 2018). Some studies show that most miRNA are linked with AGO2 but other some studies show that most of miRNA is linked to micro-vesicle but this association process is unclear yet (O'Brien et al., 2018).

In mammals miRNA play various roles in distinct process and function of miRNA are interpreted by genes target and its expression. In mammals miRNA repress the gene in cell via various process via direct and indirect mechanism. In the direct mechanism translation is blocked at initiation step or post initiation one. On the blockage of the translation initiation by obstructing with various steps like 40S small ribosomal subunit recruitment and preventing the formation of 80S ribosomal complex and include various events in a post initiation block like, during the elongation process prevent the joining of 40S and 60S ribosomes. In degradation of mRNA that's another way of translating repression is known as indirect mechanism. According to the previous study suggest that most of the miRNA bind with target mRNA molecule at the 3'untranslated region site. This binding process results mRNA translation inhibits and then this target mRNA degradation occur (Harapan et al., 2013; Fazli et al., 2010). According to the previous study suggest that *lin-4* and *lin-7* miRNA create a defect in larva development process in *C. elegans* due to the loss of function mutation (Fazli et al., 2010; Lee et al., 1993). In the *D. melanogaster* two miRNA were identified: *bantam* and *lin-14*, *bantam* inhibit the apoptosis due the overexpression (Fazli et al., 2010).

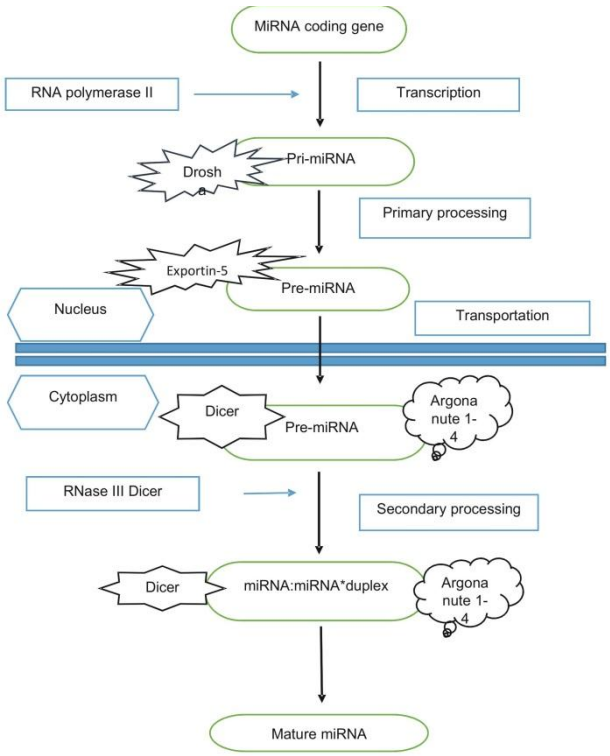

Fig. 1: This is the miRNA synthesis pathway. Firstly MicroRNA coding gene are transcribed then form the pri-miRNA by help of enzyme RNA polymerase II .Then pri miRNA converted into pre-miRNA due to the Drosha activity. The pre-miRNA contain 65-70 nucleotide. This all activities are occurred in cell nucleus then pri-miRNA are transport into the cytoplasm with the help of Exportin-5.After this step all process occurred in cytoplasm, formation of the miRNA:miRNA* duplex by the RNAIII dicer activity. Argonanute 1-4 and dicer are necessary for RISC (RNA –induced silencing complex).only one strand from duplex on argonanute and reaming strand is degraded. This line diagram show the miRNA synthesis in animal.

IMMUNOLOGICAL ANGLE OF TUBERCULOSIS

Macrophages plays the key role in host immunity and give a chance for the host human body to kill the mycobacteria and control the infection. Macrophages are unique phagocytic cells in the human body that fight various pathogens. Macrophages might not need the previous exposure to pathogens. Mainly macrophage receptor performs main role in the uptake mycobacteria process and complement system of the host human body are playing the key role in the phagocytosis process of bacteria. Recognition process increase by C3 protein from complement system so this way macrophages are first immunological angle in tuberculosis (Van et al., 2002). The first angle in tuberculosis immunology when *M.tuberculosis* infect human body, macrophage have toll like receptor (TLRs) that included in the recognization of *M. tuberculosis* primarily and this can release activation signal for nuclear factor k beta (NF-kβ), this process is responsible for release of pro-inflammatory cytokine. Usually pro-inflammatory cytokine, interferon-gamma (INF-γ) and tumor necrosis factor-alpha (TNF-α) used for protection in tuberculosis problem. In the macrophage inhibiting growth of *M. tuberculosis* by TNF-α and TNF-α also plays the critical role in establishing and retain of LTBI (Harapan et al., 2013). Another pro-inflammatory cytokine INF-γ play the key role in adaptive and innate immunity against the tuberculosis infection. On the basis of our growing understanding and research, pro-inflammatory cytokine is responsible for inhibit the growth of pathogen in the human body, but *mycobacterium tuberculosis* inhibit the production of pro-inflammatory cytokine so increases the growth of mycobacterium tuberculosis in the host body. Undeniably, previous research suggests that the INF-γ plays the critical role in tuberculosis infection in human and mouse model (Harapan et al., 2013; Schoenborn et al., 2007; North et al., 2004; Redford et al., 2010). A recent study shows that anti-microbial response is inhibited by interleukin-10. Hence, *M.tuberculosis* suppress the production of pro-inflammatory cytokines via various mechanisms (Redford et al., 2011; Fremond et al., 2007).

Another important immunological angle in tuberculosis is trehalose 6, 6'-dimycolate (TDM) produced by the MTB. TDM formed by single disaccharide, trehalose molecule that is attached to fatty acid chain. This is an insoluble complex and is highly responsible for virulence (Robert et al., 2016; Middlebrook et al., 1947; Indrigo et al., 2002; Indrigo et al., 2003) as it prevents the fusion of lysosome and phagosome which in turn inhibits the acidification of macrophages. This inhibition of formation of phagolysosome increases the survival ability of MTB and because of this, the mycobacterium survives in macrophages and escape host immune system (Robert et al., 2016; Indrigo et al., 2003). TDM also suppressed various other process during MTB function. TDM has capability to suppress the stimulation of macrophage surface antigen CD40, CD80, CD86, and MHCII and also prevent the stimulation of various cytokines like IL1β, IL-6, TNF-α and also play the important role to inhibit antigen presentation on the surface of MTB (Kan-Sutton C et al., 2009; Estrella et al., 2011).

The third immunological angle is autophagy, a biological process involving self-digestion and lysosomal degradation process. This is the very important intracellular process uses for immune response against the viral and bacterial infection in the human body. *Mycobacterium tuberculosis* have the special ability to inhibit the autophagy process (jin et al., 2017). When *mycobacterium tuberculosis* infection occur in the human body, bacterial DNA is recognized by cytosolic DNA sensors. This recognition process depends on the various autophagy related protein and autophagosomal membrane nucleation (VPS34, ATG14L) and lysosomal docking and fusion factor (UVRAG). All these components are playing the key role for activation of autophagy machinery and process. During the *Mycobacterium tuberculosis* infection, microRNA directly targets to the autophagy machinery components via the DNA damage regulated

autophagy modulator 2 (DRAM2).DRAM2 is directly linked with the UVRAG. This (UVRAG) is essential component for activation of autophagy machinery. microRNA decrease or inhibit the DRAM2, so finally inhibit the autophagy in human macrophages. On the basis of this research study, inhibition of autophagy process is playing the key role for increase survivability of *mycobacterium tuberculosis* in macrophages (Yang et al., 2018).

Another last important immunological angle is apoptosis. Apoptosis is an important biological process for controlling the bacterial infection. Apoptosis is programmed cell death during infection. During tuberculosis infection *mycobacterium* inhibits the apoptosis process through the FOXO3 protein in monocytes. microRNA modulates the expression of FOXO3 gene (which plays a key role in apoptosis) further inhibit the apoptosis process. This is an important way to increase the survivability of *Mycobacterium tuberculosis* in monocytes (Jian et al., 2015). These are the few immunological angles in tuberculosis on the basis of growing research. These angles provide the support for controlling the infection in human body.

ASPECT OF microRNA IN TUBERCULOSIS

Previous study suggests that microRNA plays the key role in gene expression in tuberculosis. In tuberculosis alteration gene expression in various important immune cells that also control the function of immune cell like NK cell and macrophages and T cell (Harapan et al., 2013). This alteration may be useful for the diagnostic purpose in various diseases. microRNA may be used as a biomarker for diagnostic purpose and as a therapeutic agent in the various diseases. In this review, we will discuss various miRNA in tuberculosis in case of molecular pathology and molecular function.

miRNA-155:

Previous study show that miRNA -155 participated in various biological process like immunity and infection that also plays a key role in regulation of T- cell reaction and that is also responsible for less production of IFN-γ. This process was studied and proved in the mouse model (Thai et al.,2007).Various previous studies shows that malfunction in miRNA-155 is involved in case of tuberculosis problem. A research study suggests that when *M.tuberculosis* infects a host then macrophages faced it's lipomannan which results in less production of TNF due to the downregulation of miRNA-155 by the TLR-MAPK pathway and further advanced analysis identified that *M.tuberculosis* inhibits the translation process at the initiation stage (Harapan et al., 2013). But other research studies show that if *M.tuberculosis* infection generated in murine macrophages results in upregulation expression of miRNA-155(Harapan et al., 2013). The different miRNA regulation profile in different cells creates a confusion that requires more comparative work to understand miRNA-155 regulation difference in cells like murine macrophage and human macrophages. Another study data result from Vishal Wagh et al., show that miRNA-155 use as a biomarker in tuberculosis. They measured expression level of miRNA-155 between the TB patient and healthy person with the help of qRT-PCR. They identified the levels of miRNA-155 was reduced in TB patients as compared than healthy persons (Wagh et al., 2016). A research study shows that miR-155 is directly contacted to the attenuation of expression of BTB and CNC homology 1 (Bach1) and SH2 containing inositol 5' phosphate (SHIP1) and this study also suggest the role of ESAT-6 in tuberculosis.ESAT-6 is a secretory protein produced by *mycobacterium tuberculosis*. According this study ESAT-6 is directly linked with the miR-155 induction and its results on a Bach1 and SHIP1 repression process. That conclude that the miR-155 induction process is helpful for the survival of *Mycobacterium tuberculosis* in host and another indication from this study miR-155 is responsible for the attenuate the host innate immunity (Ranjeet et al., 2012). Various studies have been done on miR-155 with tuberculosis, but actual condition is not clear. In the over all summary on miR-155 are correlated with TLR-AKT pathway and Bcl-2 pathway.Bcl-2 pathway are

responsible for apoptosis but *Mycobacterium* has special power to alter the Bcl-2 pathway to inhibit the apoptosis process. Another previous study shows the correlation between miR-155 and FOXO3. FOXO3 is a human protein encoded by FOXO3 gene. This protein is necessary for the apoptosis via the upregulation of gene. According this study, upregulation of miR-155 inhibit the apoptosis process during the *mycobacterium tuberculosis* infection in PBMC. This study's conclusion miR-155 combines with 3'UTRs region of FOXO3 gene and inhibit the expression of FOXO3 and inhibit the formation FOXO3 protein and finally decrease apoptosis in cell so *mycobacterium tuberculosis* bacteria easily survive in the host (Jian et al., 2015). The previous biological study suggests that apoptosis play the key role in innate defenses of macrophages during the *Mycobacterium tuberculosis* disease. So *Mycobacterium tuberculosis* are responsible for the death of macrophages and alter immune conditions in the host. But, till date miR-155 is not used as a biomarker in Tuberculosis disease. Although correlation of miR-155 is not clear with TB. This problem needs more excremental study with different-different models for understanding the miR-155 relation with TB. In overall summary miR-155 may be used as a potential host biomarker in tuberculosis disease. On the basis of research data and study miRNA-155 is not clear to use as a potential biomarker in tuberculosis yet. Few studies have been done on miR-155 profiling in response to TB treatment, like in un-treated patients miR-155 expression down regulated, but after the treatment miR -155 level upregulated so on the basis this result TB treated patients miR-155 expression is high as compared to untreated patients (Wagh et al., 2016). On the basis of differences in expression – different research studies suggest that miR-155 may be used as a biomarker in reference to TB treatment but comprehensive work need in this field.

miRNA-21:

miRNA-21 play the significant role in the suppression of pro-inflammatory cytokine expression like IFN-γ,IL-6 and TNF-α are necessary for controlling the MTB infection in human and miRNA-21 also enhance the production of IL-10 anti-inflammatory cytokine (Harapan et al., 2013). A recent study identified that miRNA-21 is upregulated in macrophages and dendritic cell (DC cell) when BCG infection was induced. This upregulation results in suppression of the cytokine IL-12 expression which directly impact on Th-1 response in host that's been inhibited. This study also suggests that DC apoptosis can be stimulated by miRNA 21 after BCG infection in the presence of targeting B-cell lymphoma (Bcl-2) (Wu et al., 2012). But over expression of miR-21 controlling Bcl2 mechanism is not clear yet. Various studies have done on miR-21 with various diseases like cancer. Previous study data suggest that miR-21 is mainly upregulated in tumour samples (Zhonghan Li et al., 2014).

miRNA-29:

On the basis of our growing research miR-29 is another important microRNA associated with TB. miR-29 is also playing a key role in controlling the immune response against the intracellular pathogen. miR-29 themselves can be up-regulated and down regulated during the intracellular infection**.** miR-29 mainly target the IFN-γ and alter the adaptive and innate immune response. miRNA-29 have the important role during the MTB infection that inhibited the immune response in IFN-γ producing natural killer cell and CD+ 4 cell by the downregulation of miRNA-29 against the tuberculosis infection, which inhibited the production of IFN-γ due to the targeting IFN-γ mRNA by miRNA-29 (Ma et al., 2011).miR-29 is also correlated with anti-apoptotic protein and other important protein like Bcl-2. When there is an increase in the expression level of miR-29, it inhibits the macrophage digestion process and also decrease the apoptosis in the host (Harapan et al., 2013). Previous study data shows that miRNA-29a is upregulated during the MTB infection in patient's sputum and serum.miR-29a was show upregulation in active pulmonary tuberculosis. On the basis of this evidence miR-29a may be used as a biomarker for

active tuberculosis pulmonary disease (Fu et al., 2011).miR-29 is directly and indirectly link with tuberculosis, but this is not clear yet. Various studies have been done on miRNA-29 but actual mechanism of miRNA-29 is still unknown. So more comprehensive study needed for miRNA-29 in case of tuberculosis.

miRNA-147:

miRNA-147 play important regulatory role in various biological process. On the basis of our research body microRNA -147 itself can be upregulated and downregulated. This expression may be used as a biomarker for diagnostic purpose in various diseases like tuberculosis, chronic myeloid leukemia and carcinoma. miR-147 alter the expression of pro-inflammatory cytokine like IL-6 and TNF-α .TNF-α play the key role in controlling the *M.tb* infection in macrophages. miR-147 act as negative regulator of immunity against the tuberculosis .microRNA-147 inhibit the innate immune response in the macrophages during mycobacterial infection (Liu et al., 2009; Santucci et al., 2011; Spinelli et al., 2013). On the basis of all evidence, miR-147 have anti-inflammatory properties. microRNA -147 relationship is not clear with tuberculosis till date and more experimental work need in this field.

microRNA WORKS AS A POTENTIAL BIOMARKER DIAGNOSTIC TOOL IN TUBERCULOSIS INFECTION

Tuberculosis is a lethal disease which can be controlled by detection at early stage. Nowadays rapid diagnosis of tuberculosis is not possible and all current tests are not capable for TB detection in early phase. Most of the test are based on pathogen detection in sample but this is not suitable for fast and rapid detection of TB problem. However, DNA based test is available, but this will not make us sure due to the presence of contamination and not able to discriminate between latent TBI and active TBI. Therefore biomarker will be useful for identification of infection in the human body at an early stage, but any potential biomarker is not found yet in case of tuberculosis problem. Previous study suggests that most of scientist are working on circulating miRNA like in sputum, serum, plasma. Lingma Lyu et al conducted an experiment on total 180 patient's serum from active TB patients and latent TB patients and healthy persons. They identified 3 miRNA expression (has-miR-140-3p, has-miR-3184-5p, has-miR-423-3p) upregulated as compare to others during the disease progressions. Hence these three miRNA may be used as a biomarker in tuberculosis (Lingna lyu et al., 2018). Another study by Wang et al reported that they identified four different miRNA (has-miR-223, has-miR-424, has-miRNA-451, has-miRNA-144) in active TB and latent TB and also up-regulated in PBMCs (Wang et al., 2011).

Recent study data suggest that two miRNA hsa-let-7b and hsa-miR-30b may be allied with TB disease development involving the target gene by TLR-NF –Kb signal pathway (Xin et al., 2016). Another previous study reported that Qi et al identified 97 different miRNA in pulmonary TB patients as compare than healthy persons with the help of TaqMan low-Density array. Then finally they identified three miRNA (miR-361-5P,miR-889,miR-576-3P) which shows different expression in pulmonary TB patients as compared than healthy patients with help of qRT-PCR and ROC analysis. Hence, these three miRNA might be used as a biomarker in tuberculosis (Qi et al., 2012). Previous study data suggest that miR-182, miR-197 are associated with TB and expression level show upregulated in TB patients as compare than healthy persons (Abd-El-Fattah et al., 2013). Other various miRNA that are involved in the alteration of immune response and inflammatory pathway in *M.tuberculosis* problem (Sabir et al., 2010). miRNA-155, miRNA-21,miRNA-29 controlled in innate immune cell activation process (Belver et al., 2011). Recent study data show that some miRNA expression upregulated but some miRNA expression is also downregulated like miRNA-29 in human macrophage. Cui et al screened the plasma microRNA between the cavity pulmonary tuberculosis and non-cavity pulmonary tuberculosis and healthy patients.

They identified miRNA-22, miRNA-769 and miRNA-320 that showed the unique pattern as compared than the other miRNA (Cui et al., 2017).

In another recent study they screened the serum microRNA in TB patients on the basis of 6 miRNA combination .they identified 92 miRNA from total 223 miRNA with different expression profile out of which 59 miRNA expression were upregulated and remaining 33 miRNA were expressed downregulated in TB patient's serum. miRNA-744, miRNA-218, miRNA-124, miRNA-191, miRNA-101, miRNA-93, miRNA-552, miRNA-382, miRNA-7, miRNA-379, miRNA-708 are some of the miRNA that were upregulated in TB patient's serum. miRNA-380, miRNA-765, miRNA-511, miRNA-206, miRNA-944, miRNA-3618, miRNA-3674, miRNA-3618. These all miRNA were identified as downregulated in TB serum (Zhang et al., 2013). Another previous study also focused on serum microRNA in TB, in this study they checked the miRNA expression level from TB and MDR TB patients .They identified expression level of two miRNA (miRNA-16 and miRNA-155) differ between MDR and TB patients (Wagh et al., 2016). These recent studies show that microRNA is the nucleus point for scientist community .This may be used as potential biomarker for circulating fluid like blood serum, plasma. But till date not any of these miRNA is consider as the potential biomarker in case of tuberculosis yet. At the current time, most of scientist are working on host microRNA in Tuberculosis but potential microRNA is not found for tuberculosis yet. This is a great opportunity for researchers to identify the unique potential miRNA use as a biomarker in various diseases like Brest cancer, Liver cancer, Tuberculosis, Asthma, Ulcer, carcinoma and heat diseases.

CONCLUSION AND FUTURE PERSPECTIVE:

Tuberculosis is one of the most infectious disease in the world and the control of the disease is difficult due to their specific survival capacity in macrophages and exact diagnosis is not available at early phases. Here we have concluded biogenesis and role of specific microRNA in Tuberculosis conditions. On the basis of previous and recent studies, microRNA may be used as a biomarker in Tuberculosis in earlier stage as a diagnostic tool. The future perspective of microRNA may be useful for treatment, but comprehensive work still remaining. But this is clearly shown in the latest studies that microRNAs are linked with various diseases and alteration in the expression of microRNA may be useful as an advance diagnostic approach in tuberculosis disease and other disease. If microRNA used as a biomarker for diagnostic purpose in the future, diagnostic approach may be more efficient and easily detect the infection in less time or at earlier stage of infection and another important advantage in term of cost, diagnostic cost may be decrease and also it decrease the mortality rate and thus can easily control the tuberculosis disease as compare than current scenario. microRNA may be also used as an indicator for response of treatment during the disease. Previous studies clearly showed that microRNA is the link between cancer and cardiovascular disease. Host biomarker is a positive diagnostic approach for tuberculosis and other lethal viral and bacterial disease. This might be used as a new diagnostic approach and controlling the tuberculosis infection. Based on the above conclusion, our perspective is that this unique host miRNA strategy may be used in early case detection and rapid treatment of MDR-TB.

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REFERENCES

Abd-El-Fattah, A.A., Sadik, N.A., Shaker, O.G., & Aboulftouh, M.L. (2013). Differential microRNAs expression in serum of patients with lung cancer, pulmonary tuberculosis, and pneumonia. *Cell Biochem Biophys 67*(3), 875-84.

Belver, L., Papavasiliou, F. N., & Ramiro, A. R. (2011). MicroRNA control of lymphocyte differentiation and function. *Current opinion in immunology 23*(3), 368-73.

Broughton, J.P., Lovci, M.T., Huang, J.L., Yeo, G.W., & Pasquinelli, A.E. (2016). Pairing beyond the Seed Supports MicroRNA Targeting Specificity. *Mol Cell* 64, 320–33.

Centers for disease control and prevention. https://www.cdc.gov/tb/topic/basics/default.htm.

Cui, J. Y., Liang, H. W., Pan, X. L., Li, D., Jiao, N., Liu, Y. H., Fu, J., He, X. Y., Sun, G. X., Zhang, C. L., Zhao, C. H., Li, D. H., Dai, E. Y., Zen, K., Zhang, F. M., Zhang, C. Y., Chen, X., & Ling, H. (2017). Characterization of a novel panel of plasma microRNAs that discriminates between Mycobacterium tuberculosis infection and healthy individuals. *PloS one 12*(9), e0184113.

Estrella, J.L., Kan-Sutton, C., Gong, X., Rajagopalan, M., Lewis, D.E., & Hunter, R.L. (2011). A novel in vitro human macrophage model to study the persistence of Mycobacterium tuberculosis using vitamin D(3) and retinoic acid activated THP-1 macrophages. *Front Microbiol 2*, 67.

Fazli Wahid, Adeep Shehzad, Taous Khan, & You Young Kim (2010). MicroRNAs: Synthesis, mechanism, function and recent clinical trail. *Biochim Biophys Acta 1803*(11), 1231-43.

Fremond, C.M., Togbe, D., Doz, E., Rose, S., Vasseur, V., Maillet, I., Jacobs, M., Ryffel, B., & Quesniaux, V.F. (2007). IL-1 receptor-mediated signal is an essential component of MyD88 dependent innate response to Mycobacterium tuberculosis infection. *J Immunol 179*, 1178e89.

Fu, Y., Yi, Z., Wu, X., Li, J., & Xu, F. (2011). Circulating microRNAs in patients with active pulmonary tuberculosis. *J Clin Microbiol 49*, 4246e51.

Haase, A.D., Jaskiewicz, L., Zhang, H., Laine, S., Sack, R., Gatignol, A., & Filipowicz, W. (2005). TRBP, a regulator of cellular PKR and HIV-1 virus expression, interacts with Dicer and functions in RNA silencing. *EMBO Rep; 6*, 961-967.

Harapan Harapan, Fitra Fitra, Ichsan Ichsan, Mulyadi Mulyadi, Paolo Miotto, Nabeeh A. Hasan, Marta Calado & Daniela, M. Cirillo (2013). The Role of microRNAs on tuberculosis infection: Meaning or Myth?. *Tuberculosis (Edinburgh) 93*, 596-605.

Indrigo, J., Hunter Jr, R.L., &Actor, J.K. (2002). Influence of trehalose 6,60 -dimycolate (TDM) during mycobacterial infection of bone marrow macrophages. *Microbiology 148*, 1991e8

Indrigo, J., Hunter Jr, R.L., Actor, J.K. (2003). Cord factor trehalose 6,60 -dimycolate (TDM) mediates trafficking events during mycobacterial infection of murine macrophages. *Microbiology 149*, 2049e59.

Jian Huang , Junhua Jiao , Weihua Xu , Huayang Zhao ,Chunxiao Zhang , Yan Shi, Zhijian Xiao (2015). miR-155 is upregulated in patients with active tuberculosis and inhibits apoptosis of monocytes by targeting FOXO3. Molecular medicine *12*(5), 7102-8.

Jin Kyung Kim ,Tae Sung Kim ,Joyoti Basu & Eun-Kyeong Jo (2017). MicroRNA in innate immunity and autophagy during mycobacterial infection. *Cellular Microbiology 19*, e12687.

Kan-Sutton, C, Jagannath, C., & Hunter Jr, R.L. (2009). Trehalose 6,60-dimycolate on the surface of Mycobacterium tuberculosis modulates surface marker expression for antigen presentation and costimulation in murine macrophages. *Microbes Infect 11*, 40e8.

Lingna, Lyu, Jinghui Wang, Hong-yan Jia, Liping Pan, Zi-hui Li, Feng-

jiao Du, Bo-ping Du, Qi Sun & Zong-de Zhang, (2018). MiRNA expression profiles of serum exosomes derived from individuals with latent and active tuberculosis. *bioRxiv* 1-26.

Liu, G., Friggeri, A., Yang, Y., Park, Y.J., Tsuruta ,Y., & Abraham, E. (2009). miR-147, a microRNA that is induced upon Toll-like receptor stimulation, regulates murine macrophage inflammatory responses. *Proc Natl Acad Sci* U S A *106*, 15819e24.

Liu, Y., Wang, X., Jiang, J., Cao, Z., Yang, B., & Cheng, X. (2011). Modulation of T cell cytokine production by miR-144* with elevated expression in patients with pulmonary tuberculosis. *Molecular Immunology 48*, 1084–1090.

Ma, F., Xu, S., Liu, X., Zhang, Q., Xu, X., Liu, M., Hua, M., Li, N., Yao, H., Cao, X. (2011). The microRNA miR-29 controls innate and adaptive immune responses to intracellular bacterial infection by targeting interferon-g. *Nat Immunol 12*, 861e9.

Maute, R. L., Dalla-Favera, R., & Basso, K. (2014). RNAs with multiple personalities. Wiley Interdiscip. Rev. RNA *5*, 1–13.

Mehta, A., & Baltimore, D. (2016). MicroRNAs as regulatory elements in immune system logic. Nature Reviews. *Immunology 16*, 279–294.

Middlebrook, G., Dubos, R.G., & Pierce, C. (1947). Virulence and morphological characteristics of mammalian tubercle bacilli. *J Exp Med 86*, 175e84.

Miotto, P., Mwangoka, G., Valente, I. C., Norbis, L., Sotgiu, G., & Bosu, R. (2013). MiRNA signatures in sera of patients with active pulmonary tuberculosis. *PLoS One 8*, e80149.

Naveed Sabir, Tariq Hussain, Syed Zahid Ali Shah, Antonio Peramo, Deming Zhao, Xiangmei Zhou. (2018). miRNAs in Tuberculosis: New Avenues for Diagnosis and Host-Directed Therapy. Frontiers in microbiology *9*, 602

North, R.J., & Jung , Y.J. (2004). Immunity to tuberculosis. *Annu Rev Immunol 22*, 599e623.

O'Connell, R.M., Rao, D.S., Chaudhuri, A.A., Baltimore, D. (2010). Physiological and pathological roles for microRNAs in the immune system. Nat Rev Immunol *10*, 111e22.

O'Brien, J., Hayder, H., Zayed, Y., & Peng, C. (2018). Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Frontiers in endocrinology *9*, 402.

Qi, Y., Cui, L., Ge, Y., Shi, Z., Zhao, K., Guo, X., Yang, D., Yu, H., Cui, L., Shan, Y., Zhou, M., Wang, H., & Lu, Z. (2012). Altered serum microRNAs as biomarkers for the early diagnosis of pulmonary tuberculosis infection. BMC infectious diseases12:384.

Lee, R.C., Feinbaum, R.L., & Ambros, V., (1993). The *C.* elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell 75*, 843-854.

Kumar, R., Halder, P., Sahu, S. K., Kumar, M., Kumari, M., Jana, K., Ghosh, Z., Sharma, P., Kundu, M., & Basu, J. (2012). Identification of a novel role of ESAT-6-dependent miR-155 induction during infection of macrophages with *Mycobacterium tuberculosis. Cell Microbiol.14*(10), 1620-31.

Redford, P.S., Boonstra, A., Read, S., Pitt, J., Graham, C., Stavropoulos, E., Bancroft, G.J., & O'Garra, (2010). A Enhanced protection to *Mycobacterium tuberculosis* infection in IL- 10-deficient mice is accompanied by early and enhanced Th1 responses in the lung. *Eur J Immunol 40*, 2200e10.

Redford, P.S., Murray, P.J., & O'Garra, A. (2011). The role of IL-10 in immune regulation during M. tuberculosis infection. *Mucosal Immunol* 4, 261e70.

Robert, L. Hunter, Shen-An Hwang, Chinnaswamy Jagannath, & Jeffrey K. Actor, (2016). Cord factor as an invisibility cloak? A hypothesis for asymptomatic TB persistence. Tuberculosis *101*, S2eS8

Santucci, N., D'Attilio, L., Kovalevski, L., Bozza, V., Besedovsky, H., del Rey, A., Bay, M.L., & Bottasso, O. (2011). A multifaceted analysis of immune-endocrine-metabolic alterations in patients with pulmonary tuberculosis. *PLoS One* ,(10), e26363.

Schoenborn, J.R., & Wilson, C.B. (2007). Regulation of interferon-g during innate and adaptive immune responses. *Adv Immunol 96*, 41e101.

Spinelli, S.V., Diaz, A., D'Attilio, L., Marchesini, M.M., Bogue, C., Bay, M.L., & Bottasso, O.A. (2013). Altered microRNA expression levels in mononuclear cells of patients with pulmonary and pleural tuberculosis and their relation with components of the immune response. *Mol Immunol 53*, 265e9.

Chendrimada, T.P., Gregory, R.I., Kumaraswamy, E., Norman, J., Cooch, N., Nishikura, K., & Shiekhattar, R. (2005). TRBP recruits the Dicer complex to Ago2 for microRNA processing and gene silencing. Nature *436*, 740-744.

Thai, T.H., Calado, D.P., Casola, S., Ansel, K.M., Xiao, C., Xue, Y., Murphy, A., Frendewey, D., Valenzuela, D., Kutok, J.L., Schmidt-Supprian, M., Rajewsky, N.,Yancopoulos, G., Rao, A., & Rajewsky, K. (2007). Regulation of the germinal center response by microRNA-155. *Science 316*, 604e8.

Van Crevel, R., Ottenhoff , T.H.M., & Van der Meer, J.W.M. (2002) Innate immunity to Mycobacterium tuberculosis. *Clin Microbiol 15*, 294–309.

Wagh, V., Urhekar A., & Modi, D. (2016). Level of microRNA miR-16 and miR-155 are altered in serum of patients with tuberculosis and associate with responses to therapy. *Tuberculosis 102*, 24-30.

Wang, C., Yang, S., Sun, G., Tang, X., & Lu, S. (2011). Comparative miRNA Expression Profiles in Individuals with Latent and Active Tuberculosis. *PLOS ONE* 6(10), e25832.

WHO. (2017). Tuberculosis global report.

Wu, Z., Lu, H., Sheng, J., Li, L., Wu, Z., Lu, H., Sheng, J., & Li, L. (2012). Inductive microRNA-21 impairs anti-mycobacterial responses by targeting IL-12 and Bcl-2. FEBS Lett 586:2459e67.

Xin, H., Yang, Y., Liu, J., Li, X., & Li, M. (2016). Association between tuberculosis and circulating microRNA hsa-let-7b and hsa-smiR-30b: A pilot study in chinese population. *Tuberculosis (Edinb) 99*, 63.

Yang, T., & Ge, B. (2018). miRNAs in immune responses to Mycobacterium tuberculosis infection. Cancer Letters *431*, 22–30.

Zhang, X., Guo, J., Fan, S., Li, Y., Wei, L., Yang, X., Jiang, T., Chen, Z., Wang, C., Liu, J., Ping, Z., Xu, D., Wang, J., Li, Z., Qiu, Y., & Li, J. C. (2013) Screening and identification of six serum microRNAs as novel potential combination biomarkers for pulmonary tuberculosis diagnosis. *PloS one 8*(12), e81076.

Zhonghan, Li., & Tariq, M. Rana, (2014). Therapeutic targeting of microRNAs: current status and future challenges. Nature Reviews Drug Discovery *13*, 622–638.