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Review Article,

Tuberculosis in Children: Circulating Mirna a New Diagnostic Method Approach

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Abstract:

Tuberculosis in children is still a challenge for world health problems, especially in establishing a diagnosis. Under diagnosis or over diagnosis can occur in some cases, so getting accurate data is still a challenging task. Clinical symptoms that are not typical in children add to the difficulty of diagnosis enforcement, especially in areas with a high incidence of TB infection. There has been much development of diagnostic TB methods in children, including genetic approach. Some studies report that miRNAs play an essential role in tuberculosis pathogenesis. MicroRNA as one of the diagnostic genetic methods can distinguish the incidence of latent and active infection in tuberculosis cases in children.

Key words: tuberculosis, children, diagnostic, miRNA.

Introduction:

Tuberculosis (TB) in children is still a significant problem globally. Pediatric TB is reported to cause about 230,000 deaths each year, of which 80% are < 5 year-olds. The burden of the disease begins at an early age; infants and toddlers are at high risk of infection until it continues to become a severe disease. Even children who are not immediately sick after infection have a risk throughout their life of significant reactivation (estimated in 10% of cases), most of which will occur in the first five years after infection.[1] It is estimated that there are about 5% of pediatric TB cases in *low TB burden* countries and 20-40% in countries with *high TB burden*. However, it has been challenging to get accurate data on the exact number of TB cases in children until now because diagnosing TB in children have considerable challenges due to germs that are paucibacillary and difficulty getting good quality sputum specimens and less specific clinical symptoms.[2]

Various diagnostic test methods began to be developed related to tuberculosis in children. Several approaches have been taken in the last ten years that have tried to find the best method of diagnosing TB in children. Microbiological examination using a culture that is still the gold standard in the diagnosis of child TB can only provide a sensitivity of 20-40% and take 8-12 weeks. Evaluations based on PCR and immunological tests that are quick diagnostic methods also show false positive and negative results, making them unreliable. Therefore, there is an increased need for new biomarkers or new diagnostic methods of TB diagnosis in children. [3,4] Currently, diagnostic approaches using biomarkers are being widely researched. These biomarkers are expected to identify M tuberculosis's immune characteristics or inflammatory responses. Biomarkers can be measured from blood samples tested ex vivo directly, or samples first stimulated with mycobacterial antigens to elicit a specific response to M. tuberculosis. Several examinations have begun to be developed and applied today, such as interferon-gamma and ELISPOT examinations. However, there are still weaknesses in determining diagnostics in pediatric TB because Interferon-gamma has not been able to distinguish between active infection, post-infection, or latent infection. While ELISPOT (Enzyme-linked enzyme-linked enzyme-Linked Immune Absorbent Spot), which targets cytokines T helper 1 such as interferon-gamma and

interleukin-2, detection of antibodies secreted by TB-specific plasma cells and flow cytometry-based tests, such as T cell activation markers (TAM)-TB assay also cannot be implemented in the field correctly. Tam-TB tests have shown good accuracy in small studies (83% sensitivity, specificity97%) of 113 children, 18 had culture-confirmed TB but currently have fairly complex procedures and are difficult to implement outside of the research setting. [5.6]

MicroRNAs (miRNAs) have been introduced as new diagnostic biomarkers widely involved in some cases such as cancer, heart disease, pregnancy, diabetes, psoriasis, and many infectious diseases. These small single-stranded RNA molecules can regulate gene expression and have led to an understanding of gene expression regulation. miRNA binds complementary sequences in 3′ untranslated messenger transcript (mRNA) regions and prevents translation. Each miRNA can inhibit some genes, and multiple miRNAs can target mRNA. Although studies on miRNAs are still relatively basic, it has been shown that miRNAs are crucial to gene expression, there are about 2558 human miRNAs, and these miRNAs are regulated to express 60% of protein-encoding genes. MiRNAs are the primary regulators of cell differentiation and cell function and modulators in most cellular functions, including the innate and acquired immune system. For example, in acquired immune response, B cell differentiation, antibody production, T cell development, and function are controlled by miRNA, and many studies describe the role of mammalian miRNAs in responding to bacterial infections. [3.7]

miRNA as a Marker of Tuberculosis:

M. tuberculosis is an ancient organism that has been coordinated with its human host, so it has adapted to macrophages in the host cell for survival. Until recently, the macrophage's immune response changed during tuberculosis infection by host miRNA, the first phagocyte immune response in the pulmonary microenvironment relative to M. tuberculosis were not clear. Regulation of miRNA expression by infection because pathogenic bacteria, as soon as infection occurs, is as essential a part of the host's response to infection and a new molecular strategy for regulating host cell pathways by bacteria. Macrophages are target cells for Mycobacterium infection but are not affected by miRNAs during infection. The tipping point of the innate and acquired immune response in dendritic cells can activate and polarize topical T cell responses, regulated by miRNAs. MiRNAs play an essential role in regulating the primary functions of macrophages, dendritic cells, and Natural Killer Cells (NPCs). Many studies show changes in gene expression in macrophages and NKCs, due to latent and active TB and in healthy individuals, compared to those with TB. miRNAs regulate changes in gene expression and variations in cellular composition. Some miRNAs regulate the differentiation of T cells and their function. Bin et al. showed that intrinsic macrophage activation pathways could change regulation through multiple miRNAs.[3.7]

M. tuberculosis modifies miR-26a, miR132, and other host miRNAs, weakening the immune response to ensure survival. They also showed that miR-132 and miR-29a typically act as negative regulators for macrophage function through interferon-gamma. In the case of pulmonary TB, the induction of these two miRNAs in alveolar macrophages limits the immune response and degenerates the alveolar space. Yuhua et al. showed for the first time that high levels of miR-361 were expressed in serum patients with TB, compared to healthy individuals, and it can be speculated that this reflects lung injury from TB infection, although the associated mechanisms are unclear (Table 1). [3]

Table 1.MiRNAs and their regulatory effects on genes involved in immunity against M. tuberculosis[3]

MiRNAs	The Role or miRNA
MiR-29	Inhibit og interferon gamma (IFN γ)
MiR-21	Reduced expression of IL-1B
	IL-12P3inhibition
	IL-10 increase inhibitory cytokine
MiR-99b	Target TNF-α mRNA transcript
MiR-125	Target TNF-α mRNA transcript
	Reduce inflammatory response
MiR-155	Target TNF-α mRNA transcript
	Inhibition of interferon gamma
MiR-144	Inhibition of interferon gamma and TNF-
MiR-223	α
MiR-26a	Inhibition of interleukin 6
	Polarization induction of anti inflammatory
	M2 macrophage phenotype

Several studies have described miRNA profiles after TB infection, and miR-155, miR-155, miR-200C, miR-193a-3p, miR-595, miR-432, and miR-9, miR-582-5p, miR-144, and miR-29b have been validated in other studies. Microarray data

from this study is mainly inconsistent with previous studies. For example, data from this study showed that miR-155 lowered late regulation in the TB group. However, Wu et al. showed that miR-155 was regulated in pure-cell mononuclear protein derivatives of peripheral blood challenging patients with active TB. Consistent with previous studies, miR-141, miR-32, and miR-29b were over expressed in the TB group of the study. The expression levels of miR-144 varied in previous studies. Wang et al. suggested miR-144 in up-regulation in TB patients, while Wu et al. observed down regulation. [9.11] In this study, no significant differences were observed in miRNA between a child suffering from TB and a healthy child.[12]
Furthermore, microarray data from recent studies state that differences in expression in several miRNAs have not been reported, including miR-31, miR-342-5p, miR-193a-3p, miR-10, and miR-33a. Zou et al., showing the results of the ROC curve show the diagnostic values of a single miRNA are as follows: miR-150>miR-146a>miR-125b>miR-31>miR-10a>miR-1 >miR-155>miR-29. However, a combination of eight miRNAs showed an increase in diagnostic value with an AUC of 0.996 (95% CI,0.914-1.0), sensitivity, and specificity were 95.8 and 100%, respectively. The combined identification of miR-1, miR-155, miR-31, miR-146a, miR-10a, miR-125b, miR-150, and miR-29 suggest may be new early diagnostic biomarkers.[12]miRNA research in child populations has also been conducted by Katrievel et al. The results of miRNAs have the following sequential sensitivities and specificities: miR-31> miR-155> miR-146a (Table 2). This result is slightly different from the results in adults. ROC analysis suggests that miRNAs such as miR-31, miR-146, and miR-155 may be suitable as potential biomarkers for early and effective diagnosis of children with active TB. [13]

Table2: Receiver operating characteristic (ROC) analysis of miRNA in pediatric TB.[13]

miRNAs	AUC	95% CI	Cutoff	Sensitivity	Specificity	*p* value
miR-31	0.978	0.945–1.000	0.73	93%	97%	**<0.0001**
miR-155	0.953	0.894–1.000	0.70	90%	90%	**<0.0001**
miR-146a	0.903	0.827–0.979	0.69	83.3%	86.7%	**<0.0001**

examinations through non-invasive techniques. They use sputum as a diagnostic sample. As expected, the results of miR-155 expression increased significantly in the phlegm of patients with active pulmonary TB. ROC analysis shows that the sensitivity of miR-155 in the sputum is 94.1%, and its specificity is 87.7%. Quantification of sputum miR-155 obtained good results in distinguishing cases of active TB with healthy people. However, the study was only conducted on one race and age group of the same age. No research has been done on children. [14]

Conclusion:

Diagnosis of TB in children is still a challenge to this day. There need to be other modalities that can be used as more efficient diagnostic biomarkers and have higher sensitivity and specificity than are available today. miRNA has a role in the pathogenesis of TB infection. Several genes can be indicators of active TB infection that have been studied. miR-31, miR-146, and miR-155 may be potential biomarkers in cases of active TB in children. The combination of several genes may also increase the sensitivity and specificity of the diagnosis in cases of child pulmonary TB.

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