



# The Brazilian Journal of INFECTIOUS DISEASES

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## Review article

# Genetic polymorphism and immune response to tuberculosis in indigenous populations: a brief review

Renata Maronna Praça Longhi<sup>a</sup>, Verônica Marques Zembrzusi<sup>b,c</sup>,  
Paulo Cesar Basta<sup>d</sup>, Julio Croda<sup>a,d,\*</sup>

<sup>a</sup> Faculty of Health Sciences, Universidade Federal da Grande Dourados (UFGD), Dourados, MS, Brazil

<sup>b</sup> Human Genetics Laboratory, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brazil

<sup>c</sup> Health Sciences School, Universidade do Grande Rio (UNIGRANRIO), Duque de Caxias, RJ, Brazil

<sup>d</sup> Escola Nacional de Saúde Pública, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brazil

## ARTICLE INFO

### Article history:

Received 18 June 2012

Accepted 1 November 2012

Available online 9 May 2013

### Keywords:

Tuberculosis

Immune response

Indigenous populations

Polymorphism

## ABSTRACT

We systematically reviewed studies of the immune response to tuberculosis and the genetic polymorphisms associated with Th1- or Th2-mediated cytokine expression in indigenous populations. A bibliographic search was performed on the Medline and ISI databases and included studies published between January 1980 and October 2011. The search terms were tuberculosis, American Indians, Amerindian, indigenous, Indians, native people, aboriginal, immun\*, host immune, immune response, cytokine\*, polymorphism\*, and gene. Regardless of their design, studies that evaluated immunoglobulin, cytokine levels and genetic polymorphisms that altered cytokine expression were included. Thirteen studies met the inclusion criteria. The majority of studies were performed in Latin America, and five investigated the Warao ethnic group of Venezuela. Most of the investigations indirectly evaluated the immune response. Higher anergy to the tuberculin skin test, higher IgG4 and IgM levels, higher IL-5 production and lower TNF- $\alpha$ , IL-12p40 and IFN- $\gamma$  production were found in the indigenous populations. The studies also reported a predominantly Th2-type response in these populations and a possibly higher susceptibility to tuberculosis. A better understanding of the relevant genetic polymorphisms and their role in immune regulation would help to clarify the immunogenetic mechanisms of TB infection in these populations. This information would be useful for identifying new treatments and preventing infection and progression to active disease.

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## Introduction

It is estimated that 2 billion people are infected by *Mycobacterium tuberculosis*, but only 5–10% of infected people develop

active disease.<sup>1</sup> Immune responses to infection and disease depend on complex interactions between the etiological agent, the environment and the host. The reasons why some people develop disease while others do not are yet to be fully elucidated.<sup>2</sup> The combined innate and adaptive immune

\* Corresponding author at: Faculdade de Ciências da Saúde, Universidade Federal da Grande Dourados, Rodovia Dourados, Itaúm, km 12, Dourados, MT 79804-970, Brazil.

E-mail addresses: [julicroda@ufgd.edu.br](mailto:julicroda@ufgd.edu.br), [julicroda@gmail.com](mailto:julicroda@gmail.com) (J. Croda).

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<http://dx.doi.org/10.1016/j.bjid.2012.11.001>

responses play an important role in host defenses against *M. tuberculosis* and can cause a broad spectrum of clinical manifestations.<sup>3,4</sup>

The course of infection is regulated immunologically by two distinct T lymphocyte populations that determine the magnitude and nature of the immune response. The cellular immune response is directly related to cytokine production and is determined by the balance between the T helper 1 (Th1) and T helper 2 (Th2) responses. The Th1-type response is linked to interleukin-12 (IL-12) and interferon-gamma (IFN- $\gamma$ ) production, whereas the Th2-type response is linked to the production of interleukin-4 (IL-4) and interleukin-5 (IL-5). Th2-type response, generally, induce a humoral (antibody) response critical in the defense against extracellular pathogens. If the Th1-type response predominates after infection, the host will usually be protected against *M. tuberculosis* and only develop a latent asymptomatic infection. If the Th2-type response prevails, there may be progression to active disease, with the more serious forms of the disease exhibiting exuberant symptomatology and high bacterial loads.<sup>3,4</sup> The production of interleukin-10 (IL-10) plays an important role in regulating the chronic or latent stages of the disease and may lead to the endogenous reactivation of *M. tuberculosis* and consequent host disease.<sup>5,6</sup>

Several polymorphisms have been described in genes associated with cytokine expression. These polymorphisms can induce a predominantly Th1 or Th2 immune response and direct the course of infection.<sup>7,8</sup>

Even after considering possible errors in case reporting into account, recent studies have suggested that the incidence of tuberculosis (TB) is significantly higher in indigenous than non-indigenous populations of Latin America.<sup>9-11</sup> Investigations conducted in Australia, Canada and the United States have also suggested a higher incidence in native populations than other ethnic groups.<sup>12-15</sup> The shortage of resources to manage TB in indigenous populations, associated to poverty, a lack of access to health facilities for diagnosis and treatment, a frequent alcohol use and unemployment may partly explain the observed discrepancies.<sup>16,17</sup> However, little is known about the immune mechanisms associated with TB in indigenous populations.

Recent studies conducted with different indigenous ethnic groups, have revealed that a large fraction of evaluated individuals did not react to the tuberculin skin test (TST), even in locations where the disease has a high prevalence and BCG vaccine coverage exceeds 80% of the population.<sup>18-21</sup> The objective of this investigation was to review studies of the immune response to TB and the genetic polymorphisms associated with the expression of cytokines involved in the Th1 or Th2 immune responses in indigenous populations.

## Methodology

We systematically reviewed primary scientific articles that analyzed the cellular or humoral immune responses to TB or the genetic polymorphisms associated with Th1- or Th2-mediated cytokine expression in indigenous populations. A bibliographical search was performed using the Medline and ISI Web of Knowledge databases and was limited to studies

published between January 1980 and October 2011. The search strategy began broadly and was gradually refined. It was based on combinations of the following terms: *tuberculosis*, *American Indians*, *Amerindian*, *indigenous*, *Indians*, *native people*, *aboriginal*, *immun\**, *host immune*, *immune response*, *cytokine\**, *polymorphism\**, and *gene*. A manual search was also used in reference lists for the identified articles.

All studies in English, French, Spanish and Portuguese that directly measured the immune response through immunoglobulin or cytokine levels were included, regardless of the design, as were studies of genetic polymorphisms that affect cytokine expression.

Studies that only used indirect methods to evaluate immunity to TB, such as the TST, were excluded. Studies were also excluded if they reported changes in immune response caused by other infectious diseases.

The filtered data were independently organized by the authors with the help of a standardized form. The names of the authors, publication year and place, language, ethnic group, sample size, participants' ages, immune tests and relevant genes were recorded.

## Results and discussion

The bibliographical search yielded 42 articles. Of these articles, 13 studies met the inclusion criteria. Seven studies investigated the immune response to TB, and six analyzed genetic polymorphisms associated with cytokine expression. Six of the immunological studies were written in English, and one was published in Spanish. All of the studies with a genetic focus were published in English.

Over 10 ethnic groups were investigated, and most of these groups were from Latin America. Five studies were conducted on the indigenous people of the Warao ethnicity, who live in the Amacuro Delta region in Venezuela. Native populations of Brazil, Canada, Iran, Mexico, Norway and Taiwan were also evaluated.

Most of the studies were based on small sample sizes. The studies that assessed the largest population samples were conducted on the Yanomami in 1997,<sup>18</sup> the Xavante in 2010,<sup>22</sup> and the Warao in 2008<sup>23-27</sup> (Table 1). Despite the small sample sizes, both adults and children were included in our analysis.

Only Giampietro et al.<sup>27</sup> evaluated the proliferative capacity of peripheral blood mononuclear cells (PBMC) after treatment with antigen and investigated the resulting cytokine levels (Table 1). Most studies analyzed the humoral immune response to TB<sup>18,23-27</sup> by measuring the concentration of immunoglobulins (IgG, IgG1, IgG2, IgG3, IgG4, IgM, IgA, saliva IgA and IgE) and complement fractions (C3 and C4). A large proportion of the studies used the TST as an indirect indicator of the cellular immune response, and two also tested the skin response to *Candida* as a control of the individual's ability to initiate a cellular response (Table 1).

Two studies analyzed immunoglobulin concentrations with the objective of evaluating their sensitivity and specificity for diagnostic use but not for measuring the strength of the immune response.<sup>24,26</sup>

In a case-control study, cells were stimulated and measured cytokines in 86 indigenous (Warao) and 34

**Table 1 – Characterization of the studies that examined the immune response to tuberculosis in indigenous populations.**

| Authors                  | Year of publication | Language | Ethnic groups/location | Design                    | Sample size                 | Immunoassay                          | TST           | Age (y)       |
|--------------------------|---------------------|----------|------------------------|---------------------------|-----------------------------|--------------------------------------|---------------|---------------|
| Sousa et al.             | 1997                | English  | Yanomami/Brazil        | Observational             | 589                         | Immunoglobulin levels                | Yes           | Not specified |
| Sanchez-Rodríguez et al. | 2002                | English  | Totonaca/Mexico        | Prospective observational | 55                          | IgG response to Ag85                 | Yes           | 17–70         |
| González et al.          | 2003                | Spanish  | Warao/Venezuela        | Survey                    | 107                         | Immunoglobulin and complement levels | Yes + candida | 0–15          |
| Araujo et al.            | 2004                | English  | Warao/Venezuela        | Survey                    | 80 (34 indigenous TB cases) | Immunoglobulin levels                | Yes + candida | 0–15          |
| Araujo et al.            | 2006                | English  | Warao/Venezuela        | Survey                    | 209                         | Immunoglobulin and complement levels | Yes           | 15–60         |
| Araujo et al.            | 2008                | English  | Warao/Venezuela        | Prospective Trial         | 295 (162 Warao)             | Immunoglobulin levels                | Yes           | 15–60         |
| Giampietro et al.        | 2010                | English  | Warao/Venezuela        | Survey                    | 86 (52 Warao)               | PBMC stimulation and cytokine levels | Yes           | 15–60         |

TST, tuberculin skin test.

non-indigenous (Creole) people with the objective of identifying differences in the immune responses of the two groups. In this study, cells were treated with IL-12p40, IL-4, IL-5, IFN- $\gamma$  and TNF- $\alpha$ . The indigenous group produced lower levels of IL-12p40, TNF- $\alpha$  and IFN- $\gamma$  and a higher level of IL-5, indicating that the Th2-type response predominated in this group. The production of IL-12p40 is decisive for IFN- $\gamma$  induction and control of the disease. All of the data indicate that the production of IL-12p40 is reduced in the Warao and that the differences in the immune responses of the two groups can partly explain the elevated prevalence of TB in the Warao.<sup>27</sup>

Sousa et al. have evaluated the prevalence of TB and TST responses among the Yanomami indigenous population near the Brazil-Venezuela border. In addition, the authors measured the concentrations of IgM and IgG antibodies and their subclasses in 589 serum samples. These data were compared to data collected from healthy military personnel living in the same region. The TST responses were lower in the indigenous population. The Yanomami exhibited higher IgM and IgG4 (IL-4 dependent) production and a negative correlation between TST response and IgM production, suggesting the predominance of the Th2-type response.<sup>18</sup>

Contrasting results were obtained by Araujo et al., who had analyzed the TST responses and concentrations of the immunoglobulins IgA (saliva), IgG,<sup>1-3</sup> IgM and IgE in groups of TB patients and non-patients from the Warao and the Creole populations of the Venezuelan Amacuro Delta region. The authors did not observe differences in the IgG subclass concentrations between the groups.<sup>26</sup>

González et al. have performed cutaneous sensitivity tests (TST and candida skin test) and measured the concentrations of complement fractions C3 and C4 and the immunoglobulins IgA, IgA saliva, IgE, IgG and IgM to analyze the immune response of Warao children younger than 15 years old. The study demonstrated that 80% of the children who were anergic to the TST were also anergic to the candida test. Complement levels were raised in all groups (with and without active TB), and IgA and IgG titers were higher in children with TB. These results suggest a possible defect in the group's nonspecific cellular immune response.<sup>23</sup>

Araujo et al. have evaluated the levels of the C3 and C4 complement components in a case-control study, comparing members of the adult Warao population to a Creole population in the region. The authors have observed lower complement levels in the indigenous people and concluded that the deficiency may relate to defects in opsonization and phagocytosis, thus explaining this population's greater susceptibility to TB.<sup>25</sup>

Araujo et al. have investigated immunoglobulin concentrations and cutaneous sensitivity test results (TST and candida skin test) among Warao children  $\leq 15$  years old to evaluate the diagnostic performance of these measurements. The authors have observed that 80% of the children did not respond to the TST or candida test,<sup>24</sup> an estimate similar to the one reported by González et al.<sup>23</sup> In addition, the patients with active TB who did not react to the TST exhibited elevated IgE concentrations, suggesting a predominantly Th2 immune response.<sup>24</sup>

Sanchez-Rodriguez et al. have conducted a study in Totonaca, Mexico to determine if the IgG concentrations observed after Ag85 stimulation could be useful for TB diagnosis. Of the 55 indigenous TB carriers evaluated, a third produced negative immunoblots. The authors have concluded that the population's genetic characteristics and nutritional deficits could be linked to the test's poor performance.<sup>28</sup>

Despite a distinct immune response to TB in the indigenous population, studies demonstrated that there are no differences regarding to severity and clinical forms of illness as compared with the non-indigenous population.<sup>29-31</sup> Only six studies that analyzed polymorphisms in cytokine genes in indigenous people were identified (Table 2). Most of these studies only compared genetic and/or genotype frequencies in distinct populations and did not investigate the factors associated with the immune response.

Larcombe et al. have analyzed the cytokine gene promoter regions of Canadian aborigines and found that polymorphisms related to the Th2-type immune response were common in this population.<sup>32</sup> In another study, the same research group had examined the frequency of these polymorphisms in an indigenous population with a high TB prevalence. Despite the small sample size, the results indicate that the populations, especially the Dené, may develop a less efficient Th1-type response, reinforcing their prior findings.<sup>33</sup>

**Table 2 – Characterization of the studies that investigated genetic polymorphisms associated with the expression of the cytokines involved in the immune response to TB in indigenous populations.**

| Authors           | Year of publication | Language | Ethnic groups/location           | Sample size                                   | Genes   | Age (y)             |
|-------------------|---------------------|----------|----------------------------------|---|---|---------------------|
| Trejaut et al.    | 2004                | English  | Ami, Tsou, Atayal and Tao/Taiwan | 50 (Ami, Tsou, and Atayal; each) and 40 (Tao) | IL1A, IL1B, IL1R, IL1RA, IL2, IL4, IL4RA, IL6, IL10, IL12, IFNG, TNFA, TGFB | Not specified       |
| Larcombe et al.   | 2005                | English  | Cree/Canada                      | 78  | IL6, IL10, TNFA, TGFB1, IFNG  | 18-60               |
| Torkildsen et al. | 2005                | English  | Sami/Norway                      | 200   | IL10  | Not specified       |
| Amirzargar et al. | 2006                | English  | Yazd/Iran                        | 121   | IFNG, TNFA, IL2, IL4, IL6, IL10   | Not specified       |
| Larcombe et al.   | 2008                | English  | Dené and Cree/Canada             | 61 (Dené) and 42 (Cree)                       | TNFA, INFG, IL6   | Mean 41 (Dené)      |
| Zembrzuski et al. | 2010                | English  | Xavante/Brazil                   | 481   | IL1B, IL12RB1, IFNGR1, TNFR1, IFNG, IL2, IL10, IL6, IL4, IL4R               | 0.3-91.7, mean 18.8 |

Zembrzuski et al. have investigated the Xavante population, which lives in Brazil's central region and has a high TB prevalence. The authors have examined potential associations between polymorphisms in cytokine genes and TST responses. The study revealed that the absence of a TST response (anergy) may be associated with a predominantly Th2 pattern, which may increase an individual's susceptibility to TB disease.<sup>22</sup>

Three other studies that analyzed native populations in Iran, Norway and Taiwan compared the frequencies of polymorphisms in cytokine genes between native groups and other populations (Caucasians, Afro-descendants and Asians). The studies found that the presence of specific polymorphisms in these populations specific polymorphisms were important predictors of disease susceptibility and clinical manifestations of disease. The differences observed may partly explain the disproportionate prevalence and risk of progression from infection to disease with some pathogens, particularly TB, in indigenous populations.<sup>7,34,35</sup>

## Conclusion

Although few scientific studies of indigenous populations' immune responses to TB have been published in the past three decades, the 13 studies analyzed here showed that Th2-type responses predominate in indigenous groups, indicating that these groups probably harbor an immunogenetic susceptibility to TB.

This review has shown that the immune response to TB in indigenous populations is different from the response in the general population. Adequate knowledge of genetic polymorphisms and their role in the immune regulation of indigenous populations could clarify the immunogenetic mechanisms involved in the response to TB. This information would be useful for improve the diagnosis methods, identify new treatments and prevent infection and progression to active disease in these populations.

## Conflicts of interest

The authors declare no conflicts of interest.

## Acknowledgements

We thank the Programa INOVA-ENSP from Escola Nacional de Saúde Pública (Fundação Oswaldo Cruz), the Fundação de Apoio ao Desenvolvimento do Ensino, Ciência e Tecnologia do Estado do Mato Grosso do Sul (09/2008 and 07/2009) and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (559094/2009-4) for financial support.

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