14

MHC Polymorphism and Tuberculosis Disease

Khalid Sadki, Youssef Bakri, M'Hamed Tijane and Saaid Amzazi
University Mohammed V-Agdal, Faculty of Sciences,
Laboratory of Biochemistry and Immunology
Morocco

1. Introduction

Mycobacterium tuberculosis (Mtb), the causal agent of tuberculosis (TB), remains a major public health throughout the world causing high mortality in humans. According to the report published by the World Health Organization in 2009, 9.3 million new cases of TB were declared in the world and 1.3 million HIV-negative people died by this infection (http://www.who.int/tb/publications/global_report/2010/en/index.html). One-third of the world's population is estimated to be infected with Mtb, but, only 1 in 10 subjects who become infected would develop clinical disease. Furthermore, until now it is not fully understood why this category of individuals develop different forms of TB, pulmonary and extra pulmonary TB. Several environmental factors principally malnutrition, HIV infection and a decrease of socio-economic level favours TB progression. Furthermore, it has been confirmed by numerous studies that the outcome of TB infection is under the influence of the host genetic background (Vannberg et al., 2011). In fact, twin studies have revealed the increased concordance of disease in monozygotic compared with dizygotic twins (Jepson et al., 2001; Maartens et al., 2007). In addition, numerous families and case-control studies have demonstrated the involvement of many genes in the control of immune response in the context of the susceptibility or resistance to TB. Among these genes Major Histocompatibility Complex (MHC) takes a substantial and central role in the control of TB infection (Kamath et al., 2004).

MHC is a genetic complex that encodes the antigen-presenting molecules and is involved in the recognition and cellular cooperation functions which the substratum is the T lymphocyte. Its principal function is to ensure the selection, the transport and the presentation of peptides generated in the antigen-presenting cells. MHC is characterized by an extensive polymorphism. There are currently 6810 HLA alleles described by the HLA nomenclature and integrated in the IMGT/HLA Database (http://www.ebi.ac.uk/imgt/hla/stats.html). This particularity allows to this genetic complex a strong impact in term of immune response efficiency. While some MHC variant genes play a role in the protection against TB others variants in contrast were considered as markers of susceptibility to TB. MHC is the first molecule tested for genetic associations with TB susceptibility. For more than four decades, several authors have described strong associations between some MHC specificities and several immunological disorder including infectious diseases such as TB infection (Yee, 2004; Hill, 2006). The tri-molecular complex of T cell receptor (TCR), antigenic peptide, and

MHC molecules represents the fundamental basis of the immune response. So, genetic variation that could occur in any genes which code one of these elements could have an impact on the functional levels. MHC system takes a great part of its responsibility in term of TB pathogenesis. For example, the impact of MHC class I alleles on the Mtb antigen-specific CD8+ T-cell response in patients with TB has been reported by several studies (weichold et al., 2007; Lewinsohn et al., 2007; Smith & Dockrell, 2000). In addition, according to the MHC class I specificity some important specific peptides selected from Mtb antigens as Ag85B and 19-kDa lipoprotein are identified to be recognized by CD8 positive T lymphocytes (Geluk et al., 2000; Lalvani et al., 1998; Mohagheghpour et al., 1998). These CD8 T cells subset has been suggested to control MTB infection.

The predictive value of MHC system takes a considerable importance concerning susceptibility or resistance to TB disease. Two situations are observed: First, certain MHC markers are positively associated with disease and thus they are considered as markers of susceptibility. Second, other MHC specificities are negatively associated and may have a role in the protection against TB.

In this context, MHC polymorphism has been also employed to identify the efficient peptide that can be used to improve sensitivity and specificity of diagnosis test of TB and vaccine development. On the basis of the prediction of Mtb antigen sequences that bind to MHC molecules, several authors have designed MHC-promiscuous T-cell multi-epitopic peptides (Seghrouchni et al., 2009; Zhang et al., 2010).

The present chapter will discuss the most important work relating, first the impact of MHC polymorphism in the outcome of TB infection, and in the second the improvement of diagnosis method of TB using reverse immunogenetic.

2. Major Histocompatibility Complex (MHC) Human Leukocyte Antigen (HLA)

Major Histocompatibility Complex (MHC) or Human Leukocyte Antigen (HLA) in human coding region is located on the short arm of chromosome 6 (6p21.3). It occupies a segment of about 4000 kb, containing over 220 identified genes (Robinson J et al., 2003). The strong proximity between HLA genes explains why we observe a low rate of genetic recombination within this region. Consequently, HLA genes are transmitted as haplotypes from parents to children. Each individual inherits two parental haplotypes which expression is codominant. The HLA system is divided into three regions (Figure 1)

- From the centromere, there is HLA class II region (about 900 kb) which includes at least 32 genes. The most functional histocompatibility genes are represented by HLA-DR, HLA-DQ and HLA-DP. Other genes as large multifunctional protease (LMP2 and LMP7) or Transporter associated with antigen processing (TAP1 and TAP2) are found in this region which play a crucial role, respectively, during antigen processing or in the active transport of peptides across the membrane of the endoplasmic reticulum.
- The intermediate region is HLA class III (about 1100 kb) and is composed of at least 39 genes. Among them there are tumor necrosis factor (TNF), complement components (C4A, C4B, BF, and C2), etc.
- The telomeric region covers HLA class I genes and spans 1600 kb. This area contains about 17 genes and is divided into two sub-classes:

HLA classical class I genes (class Ia) namely HLA-A, HLA-B and HLA-C and HLA non-classical class I (class Ib) namely HLA-E, HLA-F, HLA-G, Major Histocompatibility Complex class I chain-related A and B (MICA and MICB), etc. (Figure 1). In this region, there is others non histocompatibility genes as UNHCR (α-helix coiled coil rod homolog),and hemochromatosis gene (HEF).

HLA class I genes are composed of eight exons and seven introns. Exon 1 encodes the signal sequence, exons 2, 3, 4 respectively encode for the extracellular domain (α 1, α 2, α 3), exon 5 encodes the transmembrane portion and exons 6, 7, 8 encode the intra-cytoplasmic (Malissen et al., 1982). HLA class Ia genes are among the most polymorphic genes described in the human genome. According to the IMGT/HLA data base, 1698 alleles of HLA-A, 2271 alleles of HLA-B and 1213 alleles of HLA-Cw have been identified to date. This genetic characterization allows HLA molecule to bind a large repertoire of peptides, controlling T cell polarization and consequently the profile of the cytokines production. In contrast, this characteristic could subverted if the immune system is disturbed as observed in the auto-immune and also in some infectious diseases development (De Castro, 2009; Acharya et al., 2010).

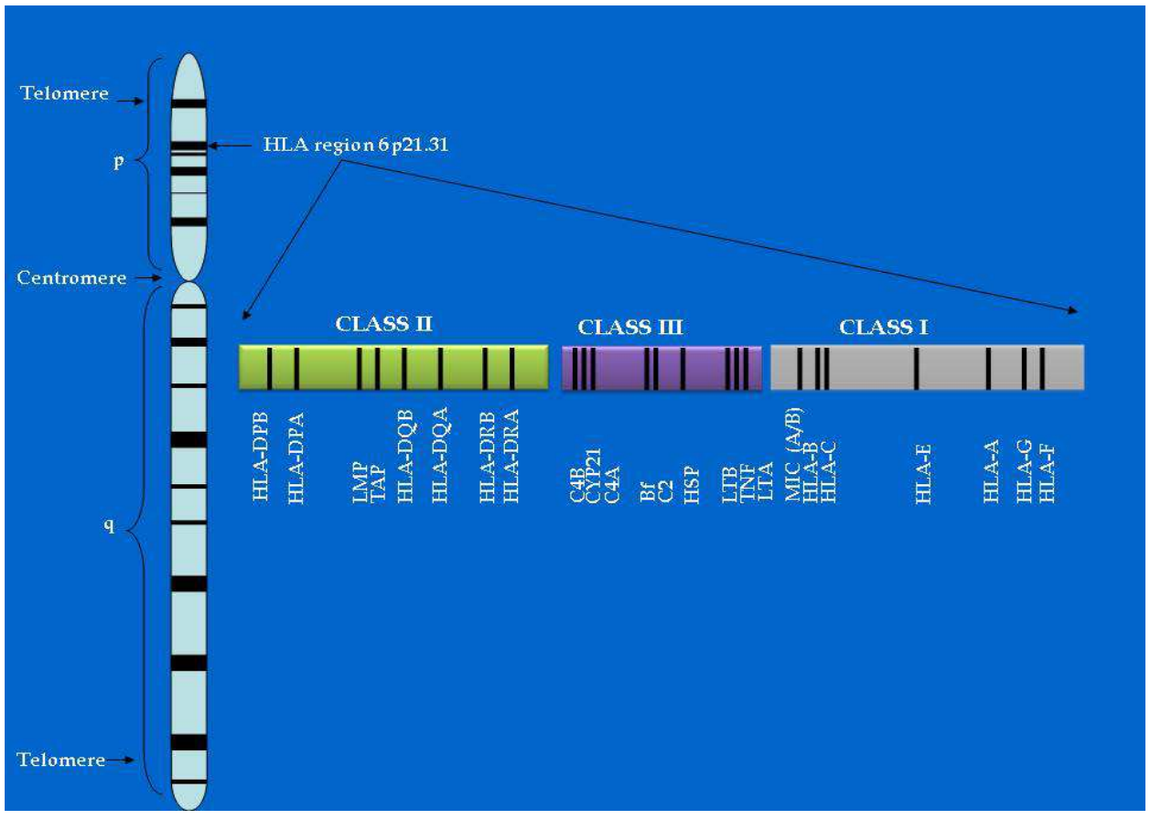

Fig. 1. Genomic organization of Major Histocompatibility Complex region.

At phenotypic level, HLA class I is represented by two chains: alpha heavy chain (α) and Beta 2-microglobulin (β2m) light chain, and the interaction between α1 and α2 domains generates a peptide binding cleft (figure 2). HLA class I molecule contains a series of six pockets, designated from A to F which can establish different interactions with antigenic

peptide residues (Bjorkman et al. 1987; Garrett et al., 1989). The conserved residues in pockets A and F are located at each side of the cavity and are responsible for the orientation of the binding peptide during antigen presentation step, while polymorphic residues located in the pockets B, C, D and E influence the specificity of peptide binding or site of peptide conformation within the cavity (Garrett et al., 1989; Madden et al., 1991; Matsumura et al., 1992).

Concerning HLA class II genes, HLA-DRB1 and HLA-DP1 encompass six exons whereas HLA-DQB1 includes five exons. HLA-DRB1 is the most polymorphic gene within HLA class II. HLA class II molecule consists of two polypeptides chains, alpha (α) and Beta chain (figure 2). Each chain includes two domains α1 and α2 for alpha chain, and β1 and β2 for β chain. The contact established between α1 and β1 domains creates the peptide binding site, which interact with TCR. These two domains play an important role during the presentation of antigenic peptide. Moreover, in this region where many genetics variations genetic variation are found, which characterize each HLA class II alleles thereby are influencing the outcome of the immune response.

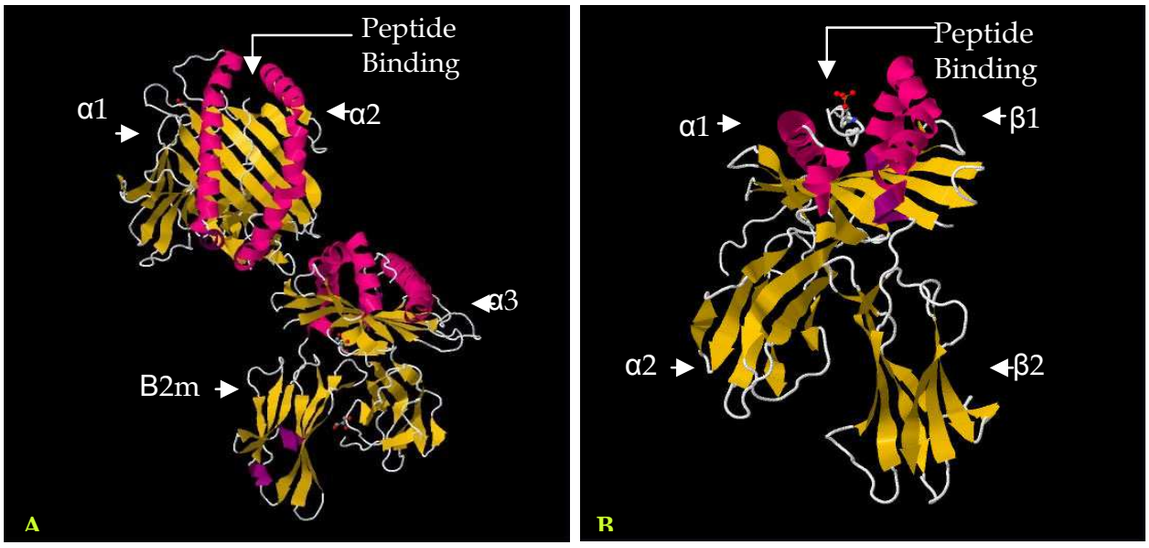

Fig. 2. Crystal structure of MHC class I (A) and class II (B) molecules in complex with antigenic peptide. (Accession numbers taking from Protein Data Bank are respectively 3PWJ and 3L6F) (Borbulevych et al., 2011; Li et al., 2010) **(A)** : HLA class I is comprised by two chains, alpha heavy chain (α) and Beta 2-microglobulin (β2m) light chain, with noncovalent interaction between them. The peptide binding groove shapes a short cleft by an interaction between α1 and α2 domains. **(B)**: HLA class II molecule consists of two polypeptides chains, alpha and Beta chain. Each chain includes two domains α1 and α2 for alpha chain and β1 and β2 for β chain. The interaction between α1 and β2 domains generates long peptide binding clefts which interact with TCR.

HLA molecules expression is different between the two classes. In fact, HLA class I molecules are expressed on most mononuclear cells, whereas class II molecules are expressed on antigen presenting cells (APCs): macrophages / monocytes, dendritic cells and B cells. Moreover, into the same class, different loci do not have the same level of tissue expression, such as HLA-C are naturally more weakly expressed than HLA-A or HLA-B.

3. MHC polymorphism and TB disease

One of the main roles of MHC is to regulate the immune response against all immunological abnormalities in normal physiological condition and during infection state. MHC is known as one of the important component of susceptibility and resistance to many infectious diseases and responsiveness to pathogens or vaccines. In the case of pulmonary TB (PTB) disease, case-control association studies have found significant associations between MHC genes polymorphism and this pathology (Kettaneh et al., 2006; Yim & Selvaraj, 2010). In fact, both genes encoding MHC class I and class II may play crucial roles in host susceptibility to PTB. table 1 summarizes the most important immunogenetic association studies related to MHC and PTB. Analysis of this table shows that first, the majors susceptibility locus are more within MHC class II region compared to those located in MHC class I section. Indeed, for MHC class I, almost all genetic association with TB are positive. In contrast, both negative and positive association are observed between TB and MHC class II polymorphism, suggesting a strong influence of MHC class II in the modulation of the immune response to MTB infection through cell-mediated immunity (Moss & Khanna, 1999; Kettaneh et al., 2006; Yim & Selvaraj , 2010).

However, the results are conflicting as reported by several studies. MHC polymorphism investigations have revealed, that the allele HLA-DRB1*04 is associated with TB in Syrian population (Harfouch-Hammoud & Daher, 2008), HLA-DRB1*07 and HLA-DQA1*0101 in Iranians (Amirzargar et al., 2004), HLA-DRB1*11 in Indonesians (Yuliwulandari et al., 2010), and HLA-DRB1*1302 in South Africans (Lombard et al., 2006). HLA-DRB1*0803 and HLA-DQB1*0601 were associated with PTB disease advancement in Koreans while a strong association with resistance to recurrent PTB is observed (Kim et al., 2005, Yuliwulandari et al., 2010) with HLA-DRB1*12 in Indonesians (Yuliwulandari et al., 2010). Finally, HLA-DR2 seems to be the main allele positively associated with PTB. This observation is replicated in populations with different genetic background, Indian (Brahmajothi et al., 1991, Ravikumar et al., 1999, Sriram et al., 2001), Chinese (Shi et al., 2011) and polish (Dubaniewicz et al., 2000). HLA-DR2 is divided into two subtypes, DRB1*15 and DRB*16. Except for the study reported by Dubaniewicz and his colleagues, DRB1*15, especially the DRB1*1501 allele, is strongly associated with PTB susceptibility (Dubaniewicz et al., 2000). This observation suggests that amino acids present in DR15 molecule but absent in DR16 could play an important role in the development of PTB. Certainly, this data does not exclude the involvement of other region parts of the protein and/or other immunoregulatory linked genes. The nucleotide sequence of the peptide presented by DRB1*15 are so different from those presented by DRB1*16 and may be recognized by $CD4^+$ T lymphocytes as inadequate form and consequently this situation could disturb the effective immune anti-TB response. At functional level, it has been suggested that HLA-DRB1*1501 and HLA-DRB1*1502 may be associated with down-regulation of perforin-positive cytotoxic cells (T-lymphocytes and natural killer) in PTB, supporting the potential role of theses alleles in the TB susceptibility (Rajeswari et al., 2007). On the other hand, HLA-DRB1*16 but not HLA-DRB1*15 are observed more frequently in Brazilian leprosy patients than in controls group (9.0% *vs.* 1.8%; P = 0.0016; OR = 5.81; CI = 2.05–16.46), underlying a difference in the impact of MHC polymorphism which may be related to the specificity of each pathology (Da silva et al., 2009).

Candidate allele	Genetic polymorphisms association			Population	P-value	OR	References
	Positive	Negative	Recurrent disease				
HLA class I							
A1		X		Indian	<0.001	ND	(Balamurugan et al., 2004)
B*1802			X	Indonesian	0,013	ND	(Yuliwulandari et al., 2010)
B*4001			X	Indonesian	0,015	ND	(Yuliwulandari et al., 2010)
B51	X			Indian	<0.0001	0.0	(Vijaya Lakshm et al., 2006)
B52		X		Indian	<0.0001	18.53	(Vijaya Lakshm et al., 2006)
Cw6		X		Indian	<0.001	ND	(Balamurugan et al., 2004)
Cw7	X			Indian	<0.001	ND	(Balamurugan et al., 2004)
HLA class II							
DR2	X			Indian	0,01	0.29	(Brahmajothi et al., 1991)
DRB1*1501	X			Indian	0.013	2.68	(Ravi kumar et al., 1999)
DRB1*15	X			Chinese	0,001	3.79	(Shi et al., 2011)
DRB1*16	X			Polish	<0.01	9.7	(Dubaniewicz et al., 2000)
DQB1*0301-*0304	x			South Africa	0,001	2.58	(Lombard et al., 2006)
DRB1*04	X			Syrian	0,01	1.77	(Harfouch-Hammoud & Daher, 2008)
DRB1*11		X		Syrian	0,003	0.51	(Harfouch-Hammoud & Daher, 2008)
DRB1*1101			X	Indonesia.	0,008	ND	(Yuliwulandari et al., 2010)
DRB1*1202			X	Indonesia.	0.0008	0.32	(Yuliwulandari et al., 2010)
DRB1*13		X		Polish	<0.001	0.04	(Dubaniewicz et al., 2000)
DRB1*1302	X			South Africa	<0,001	5.05	(Lombard et al., 2006)
DRB1*07	X			Iranian	0.025	2.7	(Amirzargar et al., 2004)
DRB1*0803			X	Korean	0.00009	5.31	(Kim et al., 2005)
DQA1*0301		X		Iranian	0.033	0.25	(Amirzargar et al., 2004)
DQA1*0601		X		Thailandaise	0.02	ND	(Vejbaesya et al., 2002)
DQB1*0301		X		Thailandaise	0.01	ND	(Vejbaesya et al., 2002)

Candidate allele	Genetic polymorphisms association			Population	P-value	OR	References
	Positive	Negative	Recurrent disease				
DQB1*0502	X			Thailandaise	0.01	2.06	(Vejbaesya et al., 2002)
DQB1*0601	X			Indian	0.008	2.32	(Ravi kumar et al., 1999)
			X	Korean	0.00003	5.45	(Kim et al., 2005)

Table 1. Genetic associations of important MHC gene variants with the susceptibility or resistance to tuberculosis and with disease recurrence. (OR: Odds ratio, ND: no Data)

Additionally, certain alleles like DRB1*11 and DRB1*13 are in contrast associated with protection against PTB (Harfouch-Hammoud & Daher 2008; Dubaniewicz et al., 2000). This conflicting results reported in theses studies could be due to the positive linkage disequilibrium (LD) observed between MHC class II alleles. DRB1*11-DQB1*03 haplotype was found in positive LD in controls polish patients (Dubaniewicz et al., 2005). In this case, DRB1*03 itself but not DRB1*11 may be linked to the resistance to TB. The hypothesis of the presence of other alleles in LD with DRB1*11-DQB1*03 haplotype is not excluded.

However, even if there are few studies reported in the literature concerning the impact of MHC class I polymorphism on the TB development, it seems likely that some MHC class I alleles are associated with PTB disease, as HLA-A1, HLA-B51, HLA-Cw6 and HLA-Cw7 in Indians (Balamurugan et al., 2004; Vijaya Lakshmi et al., 2006) and HLA-B*1802 and HLA-B*4001 in Indonesians (Yuliwulandari et al., 2010). Analysis of these results and others showed that HLA-B alleles may play the main role in PTB development comparing to the other alleles of MHC class I. HLA-B gene is the most polymorphic gene within the human MHC and the fundamental genetic variation occurs within exon 2 and exon 3, known by its determinant function during the presentation of antigenic peptide step. As cited above 2271 alleles of HLA-B are identified to date. In recent cellular immunological study, using IFN-g ELISPOT and following stimulation of T cell clones with specific Mtb synthetic peptide arrays, Lewinsohn and his colleagues have demonstrated that the immunodominant TB CD8 antigens was preferentially restricted by HLA-B (Lewinsohn et al., 2007). In the same way, it has been reported that the majority of epitope-specific CD8 T cells are HLA-B alleles restricted in patients with PTB and in addition these alleles found fast off-rates in peptide binding (Weichold et al., 2007).

4. Reverse Immunogenetic and TB diagnosis test development

For several years biologists used direct smear microscopy and culture for active TB diagnosis. But, until now the gold standard test remains the culture isolation of Mtb and it is the only test that confirms the diagnosis of TB disease. The control of the disease depends absolutely on early identification and treatment of active cases. However, direct microscopic examination as well as the culture doesn't have an adequate sensitivity and specificity, 20% and 80% for the first test and 60% and 99% for the second. For this reason, many teams interested in this topic have tried to improve these two parameters in bacteriological,

immunological and molecular biology techniques. At immunological levels, numerous studies have been reported on the cellular and humoral immunology field a significant improvement for the diagnosis of TB have been described (Seghrouchni et al., 2009; Panigada et al., 2002, Zhang et al., 2010). Unfortunately, none of the immunological methods reported in these studies was able to discriminate between active TB and latent TB infection. The use of Elispot technique and also the specific Mtb antigen have certainly played a good progress to resolve this problem. Among the panel of immunological technology used and the most relevant approach applied in this context is the reverse immunogenetic technique, based on in-silico identification peptide. This method allows the scientific community to better investigate the antigenic peptides that are presented by the relevant MHC molecules. Furthermore, this strategy offers the possibility to identify the specific T lymphocyte epitopes from living cells and provides a precious help for the development of vaccine candidates. This approach has been elegantly used to identify a specific T lymphocyte epitopes antigen in cancer (Liu et al., 2011; Imai et al., 2011) and in infectious disease (Kawashima et al., 2008; Hossain et al., 2003; Sobao et al., 2001; Seghrouchni et al., 2009; Wang et al., 2010). Various studies have been reported regarding the use of this strategy in TB disease. All immunological investigations are focused to produce a specific and synthetic peptide of Mtb in order to improve the sensitivity and the specificity of the diagnosis Kits. Several MTB-specific antigenic peptides demonstrated their potential application for TB diagnosis, (Ravn et al., 1999; Arend et al., 2002, Seghrouchni et al., 2009; Panigada et al., 2002, Zhang et al., 2010).

Both MHC class I and class II-restricted responses against Mtb are explored in this context with major importance for MHC class II. This importance takes its consideration regarding the roles played by CD4 T Lymphocytes in developing candidate vaccine for TB. In fact, Numerous Mtb specific antigens for CD4+ T lymphocytes have been identified and characterized up till now. We have previously identified Mtb specific peptide, selected from RD1 genomic region (Mahairas et al., 1996) and from proteins expressed during MTB growth in human macrophage (Cappelli et al., 2006; Mariani et al., 2000), and which are predicted to bind HLA–DR alleles (Seghrouchni et al., 2009. Baassi et al., 2009). IFN-γ ELISPOT after stimulation by Mtb selected peptide of peripheral blood mononuclear cells, extracted from TB patients and Healthy controls, have revealed an excellent result. In fact, using statistical algorithms we have identified a pool of specific Mtb immunodominant B and T cell epitopes, able to discriminate between active TB patients, tuberculin skin test positive (Mtb exposed subjects) and tuberculin skin test negative controls. A similar study has been reported recently using bioinformatic tools (chaitra et al., 2008). In fact, the authors of this work have designed some HLA class I binding epitopes of the PE (Pro-Glu) and PPE (Pro-Pro-Glu) proteins of Mtb, which are coded by Rv1818c, Rv3812 and Rv3018c genes, and have observed a significant difference in the responsiveness between healthy subjects and TB patients.

Likewise, other investigations have been reported concerning MHC class I and in-silico identification peptides. By means of appropriate bioinformatic tools several peptides are identified and could be used to improve both TB diagnosis and vaccine development. More recently, using HLA-peptide tetramers derived from Mtb peptides predicted to bind to HLA-A*0201, Tang and his colleagues have found a very interesting Mtb epitopes activating polyfunctional CD8+ T cells in human TB (Tang et al., 2011). Moreover, some specific

peptides to CD8 T Lymphocytes as HLA-B*35-restricted CD8(+) T-cell epitope in Mtb Rv2903c (Klein et al., 2002), HLA-A*0201-restricted T-cell epitope in the MPT51 protein (Aoshi et al., 2008) and HLA-B*35-restricted CD8 T cell epitopes in the antigen 85 (aa 204-212) WPTLIGLAM (Klein et al., 2001), were demonstrated to have a potential positive effect on Mtb -infected macrophages and produce significant level of gamma interferon and tumor necrosis factor alpha.

5. Conclusion

Taking all these data together reported in this review we can conclude that: MHC polymorphism and immunogenetic reverse studies offer a precious help at different level, in the identification of susceptibility/resistance genes or cluster of genes that are involved in the TB disease, and in the characterisation of a specific and relevant Mtb T lymphocyte epitopes for diagnosis improvement and vaccine development. The advancement of bioinformatic tools and immunological technologies could undoubtedly contribute to understand well the immunogenetic of TB, and consequently to improve the quality and the reliability (sensitivity/specificity) of immunological diagnosis Kits.

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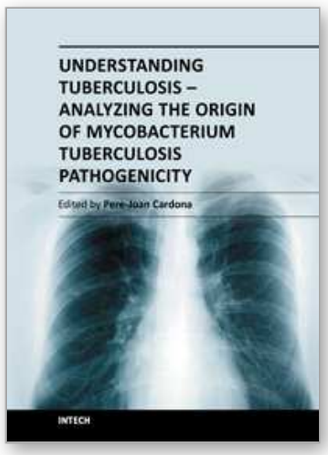

Understanding Tuberculosis - Analyzing the Origin of Mycobacterium Tuberculosis Pathogenicity

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Mycobacterium tuberculosis in an attempt to understand the extent to which the bacilli has adapted itself to the host and to its final target. On the other hand, there is a section in which other specialists discuss how to manipulate this immune response to obtain innovative prophylactic and therapeutic approaches to truncate the intimal co-evolution between Mycobacterium tuberculosis and the Homo sapiens.

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Slavka Krautzeka 83/A
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Phone: +385 (51) 770 447
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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