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Takayasu's Arteritis and Its Potential Pathogenic Association with *Mycobacterium tuberculosis*

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1. Introduction

Takayasu's arteritis is an idiopathic, inflammatory disease which involves large- and medium-sized arteries, specially the aorta, its major branches and the pulmonary arteries. In contrast to other vasculitides, Takayasu's arteritis is restricted to certain geographical areas. Initially thought to be confined to Japan and Korea, it has now been reported with increased frequency in Mexico, India, China, South America, South Africa, and the Mediterranean basin; while, the disease continues to be exceptionally described in individuals from the United States, North and Central Europe and other high-income regions.

The etiology of Takayasu's arteritis is unclear and attempts to clarify it are still limited. There are clinical and laboratory features suggesting an autoimmune basis, while others raise a question that aortitis may be the expression of delayed-type hypersensitivity reaction to tuberculin or other sensitizers. Finally, the occurrence of Takayasu's arteritis in homozygotic twins suggests a genetic background for predisposition.

A possible relationship between Takayasu's arteritis with both latent and active tuberculosis was suggested long time ago. Both diseases show similar chronic inflammatory lesions on histology, with occasional granuloma formation into the arterial walls. Delayed hypersensitivity to tuberculin is frequently found to be increased in patients with Takayasu's arteritis from almost all ethnicities. Isolated cases of Takayasu's arteritis coexisting with both latent and active tuberculosis, and improvement of arteritis after antituberculous treatment have been occasionally described. Finally, there are studies showing increased humoral and cellular immune responses directed toward mycobacterial 65 kDa heat shock protein (HSP) and its human homolog 60 kDa HSP. All these indirect evidences support that *Mycobacterium tuberculosis* and probably other mycobacteria may play a role in the immunopathogenesis of Takayasu's arteritis, possibly through molecular mimicry mechanisms; however, results of several recent studies are challenging this old but still valid etiopathogenic hypothesis of association. Analyzing this possible link is not futile because the potential risk of using anti-tumour necrosis factor (TNF) therapies in the treatment of patients with Takayasu's arteritis and the increasing use of Bacille Calmette-Guérin (BCG) for vaccination purposes around the world.

In this chapter we will discuss the main epidemiological, immunological and genetic evidence supporting and rejecting the existence of a pathogenic link between Takayasu's arteritis and *Mycobacterium tuberculosis*, to conclude hypothesizing on a novel, unifying pathogenic model that may explain the intricate relationship between tuberculosis and Takayasu's arteritis.

2. Overview on the history of Takayasu's arteritis

In 1830, Rokushu Yamamoto described a 45-year-old man with fever, pulselessness, loss of weight and breathlessness, who finally died after 11 years of follow-up and probably represents the first patient case reported in the literature. In 1905, Mikito Takayasu described a 21-year-old woman with ocular changes consisting of a peculiar capillary flush in the ocular fundi, a wreathlike arteriovenous anastomosis around the papillae, and blindness due to cataracts; even though, Professor Takayasu did not indicate if other arteries were involved. However, in the discussion of that case, Onishi and Kagoshima pointed out in two additional cases with similar ocular findings along the absence of the radial pulses. In 1948, Shimizu and Sano detailed the clinical features of the disorder, which was termed Takayasu's arteritis by first time in 1954 (Tann et al., 2008; Lupi-Herrera et al., 1977). Nowadays, both clinical manifestations and imaging findings typical of Takayasu's arteritis are adequately outlined, and different sets of classification criteria have been proposed and validated (Amezcua-Guerra & Pineda, 2007).

3. What is the Takayasu's arteritis?

Takayasu's arteritis is an idiopathic, chronic inflammatory disease which involves large- and medium-sized arteries, specially the aorta, its major branches and the pulmonary arteries, although virtually any arterial territory may be involved (Lupi et al., 1975; de Pablo et al., 2007; Pineda et al., 2003).

On the histological study, aortic sections reveal thickening of the adventitia, leukocyte infiltration of the tunica media and hyperplasia of the intimae. It has been postulated that *vasa vasorum* may act as the portal of entry for infiltrating inflammatory cells, which are mainly constituted by activated dendritic cells, several subsets of T lymphocytes, B lymphocytes, macrophages and multinucleated giant cells (Weyand & Goronzy, 2003). Hyperplasia of the intimae results from myofibroblast proliferation driven by growth factors such as the platelet-derived growth factor, which ultimately leads to fibrosis and to the development of arterial stenosis and occlusions typical of the late-stage disease. Occasionally, interstitial release of matrix metalloproteases and reactive oxygen species may induce arterial wall damage with formation of local aneurysms (Mason, 2010).

4. Influence of geography and ethnicity on the clinical expression of Takayasu's arteritis

In contrast to other vasculitides, Takayasu's arteritis is restricted to certain geographical areas around the world. Initially it was thought to be confined to Japan and Korea, but Takayasu's arteritis has been reported with increased frequency in Mexico, India, China, South America, South Africa, Israel, and the Mediterranean basin (specially in Iberian and

Italic Peninsulas); while, the disease continues to be exceptionally described in individuals from the United States, North and Central Europe and other high-income regions (Pantell & Goodman, 1981).

In essence, Takayasu's arteritis is a disease of childhood and early adulthood, with three quarters of patients initiating before the age of 20 years (Lupi-Herrera et al., 1977); nonetheless, there is a wide range of presenting age with anecdotal cases initiating as early as 2 years old (Ladhani et al., 2001). To date, Takayasu's arteritis is the third commonest vasculitis during childhood worldwide, and is responsible for more than half of cases with renovascular hypertension in young individuals (Tann et al., 2008; Kumar et al., 2003).

As regards to gender distribution, almost all available reports agree that the disease is more common in women, although the ratio varies by geographical affiliation of each population. While in Mexico it is reported that up to 84% of patients with Takayasu's arteritis are women (female/male ratio, 8.5 to 1) (Lupi-Herrera et al., 1977), the disease seems to occur almost equally in both genders (female/male ratio, 1.58 to 1) in patients from India (Chhetri et al., 1974).

Mortality rates associated with Takayasu's arteritis are high and also vary geographically. In Mexico, a retrospective analysis showed that 16 of the 107 cases died (overall mortality 14%) from causes directly related to arteritis (heart and renal failure, myocardial infarction, stroke, rupture of aneurysms) over 19-year follow-up period (Lupi-Herrera et al., 1977). Accordingly, 10-year survival is described to be around 85% in India (Subramanyan et al., 1989), with a similar figure reported from Korean patients (Park et al., 2005). In contrast, a clinical series including 75 patients from the United States showed 3% mortality by causes directly related with arteritis over 12-year follow-up period (Maksimowicz-McKinnon et al., 2007). The higher mortality rates observed in Mexican and Asian cohorts compared with North American patients may have several explanations, including differences in the treatment approaches as well as in the access to medical and surgical therapy in each country. This notion is supported by data from a Japanese cohort, which showed that 15-year survival rates have dramatically improved from 80% (1957 to 1975 period) to 96.5% (1976 to 1990 period), apparently in association with standardization of better health care protocols (Ishikawa & Maetani, 1994). However, these differences may also have been related to ethnic differences influencing both disease phenotypes and severity of disease expression (Maksimowicz-McKinnon et al., 2007). In this regard, there are severe manifestations of Takayasu's arteritis commonly found in Latin American and Asian patients whose presence has been barely reported in patients from the United States and Europe. A recent study focused on the renal microscopic changes in Takayasu's arteritis found that more than half of biopsy specimens from Mexican patients (14 of 25, 56%) showed high-grade inflammatory cell infiltrates in the glomerular microvasculature, diffuse mesangial proliferative glomerulonephritis and other associated glomerulopathies (de Pablo et al., 2007); similarly, it has been found that the patients with Mexican/mestizo ethnicity often develop uveitis and arteritis of the ophthalmic arteries (Pineda et al., 2003).

It is noteworthy that, in addition to geographical and ethnic differences, the prognosis of patients with Takayasu's arteritis is strongly affected by complications such as retinopathy, secondary hypertension, aortic regurgitation and arterial aneurysms. Data from an Indian cohort showed that, while five-year survival rate from diagnosis is 100% for patients with

not any complication this figure drops to 70 to 80% for those with one or more complications (Subramanyan et al., 1989).

5. Insights suggesting an association between Takayasu's arteritis and tuberculosis

Cumulative data support a central role for the immune system in the pathogenesis of Takayasu's arteritis, with both B and T lymphocytes as key culprits in mediation of aortitis; however, the primary cause of Takayasu's arteritis remains unclear and attempts to clarify it are still limited. As regards to etiology, there are clinical and laboratory data suggesting an autoimmune basis, while others suggest that aortitis may be an expression of delayed-type hypersensitivity reaction to tuberculin or other sensitizers. Moreover, the association of Takayasu's arteritis with specific human leukocyte antigen (HLA) haplotypes and the anecdotal occurrence of Takayasu's arteritis in identical twins suggest the existence of a genetic background for predisposition. Additionally, it is clear that exogenous factors such as environment and infectious agents are crucial to the development of Takayasu's arteritis.

A possible relationship between Takayasu's arteritis and both latent and active tuberculosis was first pointed out in 1948 by Shimizu and Sano (Shimizu & Sano, 1948). They suggested this hypothesis because the presence of Langhans giant-cell granulomas on arterial specimens from patients with Takayasu's arteritis, which morphologically resembled those found in tuberculous lesions. This was further supported by the finding of occlusive lesions in the arterial walls from patients with advanced pulmonary tuberculosis (Cicero & Celis, 1955). After that, several cases about the unquestionable coexistence of pulmonary and extra-pulmonary tuberculous foci in patients with Takayasu's arteritis have been published (Duzova et al., 2000, Kontogiannis et al., 2000; Lupi-Herrera et al., 1977). Moreover, there are anecdotal cases of patients with tuberculosis and concomitant Takayasu's arteritis showing complete symptomatic remission including return of pulses after successful antituberculous therapy (Baumgarten & Cantor, 1933; Owens & Bass, 1944; Pantell & Goodman, 1981). These inconclusive findings were pivotal for the exploration about a possibly causal, not coincidental association between tuberculosis and Takayasu's arteritis.

Epidemiological data show that past or present tuberculosis infection is over-represented in Takayasu's arteritis, with prevalence rates ranging from 21.8% to 70%. In a case series from India, patients with Takayasu's arteritis were 46.6 times as likely to have had active tuberculosis compared with general population (70% versus 1.5%) (Kinare, 1970). While, data from Mexico indicate that this ratio could be exceeded. From a clinical study including 107 cases with Takayasu's arteritis, 48% of patients were positive for a previous tuberculous infection such as pulmonary tuberculosis, tuberculous adenopathy, and Bazin's erythema induratum; in sharply contrast, the prevalence of active tuberculosis was reported to be 0.028% in the general population from Mexico (Lupi-Herrera et al., 1977).

6. Bacille Calmette-Guérin (BCG) vaccination and tuberculin skin tests in Takayasu's arteritis

Mantoux screening test is the main tuberculin reaction used in the world. It consists of an intradermal injection of a standard dose of 5 Tuberculin (purified protein derivative –PPD-) units; the reaction is assessed by measuring the diameter of induration after 48 to 72 hours. An individual who has been exposed to *Mycobacterium tuberculosis* is expected to mount an

immune response in the skin containing the mycobacterial proteins; however, positive results may be caused by non-tuberculous mycobacteria as well as previous administration of Bacille Calmette-Guérin (BCG) vaccine.

PPD skin test is found to be positive in 81% of Mexican patients with Takayasu's arteritis, as compared with 66% in the normal controls; interestingly, intradermal reactions with specific antigens of *Mycobacterium kansasii* (84%) and *Mycobacterium avium* (78%) are also more commonly positive in patients with Takayasu's arteritis than in average population with no arteritis (11 to 15% for both non-tuberculous mycobacteria) (Lupi et al., 1972). Of note, BCG vaccination is routinely administrated at birth in Mexico. Recently, it was showed that skin delayed hypersensitivity to PPD with induration over 10 mm may be as frequent (92.5% versus 89%) in Takayasu's arteritis as in patients with extra-pulmonary tuberculosis (Soto et al., 2007). Higher frequencies of positive tuberculin tests in Takayasu's patients than in general population also are described in series from Japan (85-92% versus 0.3%) and Korea (90% versus 4.2%) (Ueda et al., 1968 & Keun-Soo et al., 1967, as cited in Pantell & Goodman, 1981). Notably, the age of presentation does not appear to be a factor influencing sensitivity to intradermal reaction against mycobacterium; it has been showed that PPD test is positive in 73% of children with Takayasu's arteritis compared with 22% reported in healthy children (Morales et al., 1991).

In the context that BCG vaccine is routinely administrated at birth or during the infancy in almost all countries with high incidence of Takayasu's arteritis, a role for BCG vaccination as causative has been suggested (Kothari, 1995). However, the nearly worldwide coverage of BCG vaccination (including countries in which Takayasu's arteritis is exceptional) as well as the intricate relationship between mycobacterial infection and the immune system of the host maintains this provocative thesis as a merely speculative issue.

7. Loss of self tolerance to heat shock proteins

Heat shock proteins (HSP) are a family of phylogenetically conserved proteins found in a wide range of species extending from bacteria to humans. HSP form an ancient, primary system for intracellular self-defense with scavenger activities that are also involved in the correct folding of newly synthesized proteins. These molecules are known to be synthesized in response to a large variety of stimuli besides heat shock itself. Environmental stresses leading to the expression of HSP and other stress proteins include ultra-violet radiation, alcohol, heavy metal ions, oxidation/reduction cell imbalance, calcium influx inside the cell, overload of the endoplasmic reticulum, increased blood pressure, viral and bacterial infections, and unspecific inflammation (Quintana & Cohen, 2011).

Normal function of HSP is necessary for the homeostasis of the living cells, and becomes especially important in disease, when our cells have to cope with a stressful environment (Tiroli-Cepeda & Ramos, 2011). Of note, loss of self tolerance to diverse stress-induced cell proteins including human HSP and its consequent cross-reactivity against HSP from infectious agents is believed to be partially responsible for various rheumatic diseases such as rheumatoid arthritis and Behçet disease (Direskeneli & Saruhan-Direskeneli, 2003; Huang et al., 2010).

8. Role of humoral immune responses against heat shock proteins

Growing evidence points to a critical role of HSP in the pathogenesis of Takayasu's arteritis. In this regard, it is interesting that the main immunogenic component of BCG vaccine 65

kDa HSP is also a major immunoreactive protein antigen present in *Mycobacterium tuberculosis* and other mycobateria (Shinnick et al., 1987). Hernandez-Pando and colleagues have reported that Mexican patients with Takayasu's arteritis have an enhanced immune response against the mycobacterial antigens 65 kDa HSP and in a lesser extent, 38 kDa HSP (Hernandez-Pando et al., 1994). In this study, anti-65 kDa HSP IgG antibody titers were higher in patients with Takayasu's arteritis than in controls, and similar to those found in patients with pulmonary tuberculosis. Notably, serum antibody titers were higher in patients with active than in those with inactive arteritis. In contrast, Aggarwal and colleagues were unable to find differences in the positivity of anti-65 kDa HSP IgG antibodies between patients and healthy controls from India; however, they found a heightened immune response mediated by antibodies of IgM and IgA isotypes directed against the 65 kDa HSP (Aggarwal et al., 1996).

Recently, humoral immune responses against mycobacterial 65 kDa HSP and its human homologue 60 kDa HSP were investigated in 26 Indian patients with Takayasu's arteritis (Kumar Chauhan et al., 2004). Kumar Chauhan and colleagues found a significantly higher prevalence of IgG isotype reactive to both mycobacterial 65 kDa HSP (92% versus 11%, $P<0.0001$) and human 60 kDa HSP (84% versus 22%, $P<0.001$) in patients with Takayasu's arteritis compared with healthy controls. Moreover, a strongly positive correlation between anti-65 kDa HSP IgG and anti-60 kDa HSP IgG antibodies (r coefficient=0.814, $P<0.001$) was observed in patients with Takayasu's arteritis.

In support to an infection-induced autoimmunity through molecular mimicry mechanisms, 65 kDa HSP is over-expressed in the aortic tissue from patients with Takayasu's arteritis (Seko et al., 1994). However, this notion has been challenged by the finding of a similar increased cell expression of 65 kDa HSP in aortic tissue from patients with advanced atherosclerotic lesions; moreover, this expression is associated with elevated titers of circulating IgG antibodies against the 65 kDa HSP molecule (Xu et al., 1993).

9. Phenotypic analyses of infiltrating T cells in the arterial tissue with Takayasu's arteritis

Chronic inflammatory cell infiltration and its resulting injury to vessel wall suggest that diverse cell-mediated immunological mechanisms play an important pathogenic role in Takayasu's arteritis. A seminal report analyzing the phenotypes of infiltrating cells demonstrated a marked infiltration of T lymphocytes CD3+ CD8+, and absence of CD4+ T cells in aortic tissue from a single patient with Takayasu's arteritis (Scott et al., 1986). Subsequently, a more exhaustive study from Japan compared the immunological phenotypes of infiltrating cells among aortic specimens from patients with either Takayasu's arteritis or atherosclerotic aneurysms (Seko et al., 1994). In this study, it was found that infiltrating cells in Takayasu's arteritis consisted of CD4+ (14% of total cells) and CD8+ (15%) T lymphocytes displaying T-cell receptor αβ, CD14+ macrophages (13%), CD16+ natural killer cells (20%), and CD4- CD8- T lymphocytes displaying T-cell receptor γδ (31%). In contrast, aortic sections from atherosclerotic aneurysms showed infiltration by CD4+ αβ T lymphocytes (6%), CD8+αβ T lymphocytes (12%), macrophages (31%), natural killer cells (29%), and just few numbers of γδ T cells. As can be noted, the percentage of infiltrating macrophages and γδ T lymphocytes are quite different between diseases, with γδ T cells representing the main infiltrating lymphocytic phenotype in Takayasu's arteritis.

In addition to natural killer and cytotoxic CD8+ T cells, T lymphocytes bearing γδ T-cell receptor are recognized to play a critical role in cytolysis. These killer cells exert cytotoxicity through different two major pro-apoptotic pathways. One is the perforin-dependent colloid-osmotic lysis of target cell membrane; the other is Fas/Fas ligand (L)-mediated apoptosis signal induction. In support to a pathogenic role for cytotoxicity in the vascular damage seen in Takayasu's arteritis, Seko and colleagues found an increased expression of perforin in peripheral cytoplasmic granules of natural killer cells, CD8+ and γδ T lymphocytes, and demonstrated that numerous perforin molecules are released from these infiltrating cells directly onto the surface of aortic vascular cells (Seko et al., 1994). These authors also explore the expression of both Fas-L in infiltrating cells and Fas in aortic vascular cells from Takayasu's arteritis (Seko, 2000). They found that Fas was strongly expressed in vascular cells of *vasa vasorum*, while its ligand Fas-L was expressed in most of the infiltrating cells. However, aortic vascular cells seemed not to have undergone apoptosis, while some of the infiltrating cells underwent activation-induced cell death. These data suggest that perforin-mediated necrosis but not Fas/Fas-L apoptosis may play a major role in the mechanism of vascular injury in Takayasu's arteritis.

Perhaps the utmost demonstration for a main role for γδ T lymphocytes is the finding that infiltrating cells in Takayasu´s arteritis have restricted usage of T-cell receptor genes. In an elegant experiment, Seko and colleagues analyzed T-cell receptor Vγ and Vδ gene utilization by infiltrating γδ T lymphocytes in arterial specimens from a single patient with Takayasu's arteritis, and found that almost all T-cell receptor Vγ (Vγ1 to Vγ4) as well as Vδ (Vδ1 to Vδ5, with exception of Vδ4) genes were expressed in peripheral blood lymphocytes, whereas only Vγ3, Vγ4, and Vδ1 were preferentially rearranged and transcribed in infiltrating cells, indicating a tissue-specific oligoclonal accumulation of Vδ1+ T lymphocytes. Interestingly, this selective accumulation apparently is guided by over-expression of co-stimulatory molecules such as CD80, CD86, CD40, CD27L, and OX40L into the inflamed arterial tissue (Seko et al., 2000).

Studies focused on T lymphocytes displaying T-cell receptor αβ also have demonstrated that a limited number of Vα as well as Vβ genes are preferentially rearranged and transcribed in infiltrating cells from aortic tissue with Takayasu's arteritis. In contrast, almost all Vα as well as Vβ genes are expressed in peripheral blood lymphocytes from patients with Takayasu's arteritis as well as in aortic infiltrating cells from individuals with atherosclerotic aortic aneurysms (Seko et al., 1996; Swanson et al., 1994).

Restricted utilization of T-cell receptor Vα as well as Vβ genes or Vγ as well as Vδ genes by infiltrating T lymphocytes in Takayasu's arteritis indicate that at least one specific antigen located in the aortic tissue is targeted. Even when the exact nature of this antigen (or antigens) remains unknown, recently it was demonstrated that γδ T lymphocytes present in patients with Takayasu's arteritis are reactive to human 60 kDa HSP, and these T cells possess spontaneous cytotoxicity to aortic endothelial cells. Moreover, direct stimulation of these γδ T lymphocytes with 60 kDa HSP results in further enhancement of their cytotoxic potential. These cellular effects were found in γδ T lymphocytes from Takayasu's arteritis patients, while were absent in cells from patients with systemic lupus erythematosus and healthy controls (Chauhan et al., 2007).

Co-localization of 60 kDa and 65 kDa HSP over-expression and activated γδ T lymphocytes reactive to self-HSP into the arterial lesions as well as the restricted T-cell receptor gene usage of infiltrating αβ and γδ T cells in patients with Takayasu's arteritis suggest the

existence of a 60 kDa HSP driven expansion and infiltration of these cytotoxic cells in the arterial wall, which in turn may cause arterial damage mediated through both the perforin and Fas/Fas-L pathways.

10. Role of genetic factors in the immunopathology of Takayasu's arteritis

Both geographical incidence and occasional familiar occurrence suggest a role for genetic factors in the immunopathology of the disease. This autoimmune susceptibility arises from allelic variants or mutants in genes encoding a variety of relevant proteins of immune function. Several studies have proposed an association between Takayasu's arteritis and specific human leukocyte antigen (HLA) haplotypes.

As regards to major histocompatibility complex (MHC) it is described that susceptibility may be related with both class I and class II molecules. Specifically, alleles HLA-B52, DRB1*1502, DRB5*0102, DQA1*0103, DQB1*0601 as well as the extended haplotype HLA-Bw52-DRB1*1502-DRB5*0102-DQA1*0103-DQB1*0601 -DPA1*02-DPB1*0901 may confer susceptibility to Takayasu's arteritis in Japanese patients; whereas the combination HLA-Bw54-DRB1*0405-DRB4*0101-DQA1*0301-DQB1*0401 seems to confer resistance (Dong et al., 1992). While, studies based on Mexican cohorts show that Takayasu's arteritis is associated with higher frequencies of alleles HLA-B39, -B52, and –B39 class I molecules, as well as allele HLA-DRB1*1301 class II molecule (Girona et al., 1996; Soto et al., 2007; Vargas-Alarcón et al., 2008). In Indian patients, an association with alleles HLA-B5 and –B21 has been described (Rose et al., 1991).

Interestingly, some clinical forms of tuberculosis have been related with specific alleles of class II and class I molecules. An association with HLA-DR2 and particularly with its subtype DR15 in linkage disequilibrium with DQ5 has been found in patients with smear-positive pulmonary tuberculosis (Bellamy, 1998). This observation has been refined using DNA based HLA typing and it was confirmed a link with genes *DRB1*1501* and *DQB1*0502* (Meyer et al., 1998). Similarly, a higher frequency distribution of class I HLA-B60 antigen is seen in patients with smear-positive pulmonary tuberculosis than in non-infected, exposed controls (Bothamley, 1999).

Similar class I and class II MHC molecules have been described in association with Takayasu's arteritis and active tuberculosis, suggesting a possible genetic relationship between diseases. While, it may support a biological plausibility to PPD delayed-type hypersensitivity intradermal reactions commonly seen in both diseases. Unfortunately, available results from few studies focused on HLA-B alleles do not support this attractive thesis (Soto et al., 2007; Vargas-Alarcón et al., 2008).

Alternatively, there is a group of innate immune molecules whose genes are located near the HLA-B gene region; these molecules are termed MHC class I chain-related A (MIC-A) and may have a crucial role in the pathogenesis of Takayasu's arteritis. *MIC-A* genes are polymorphic and divergent from classical MHC class I genes. After different stimuli inducing cellular stress, *MIC-A* genes are rapidly over-expressed and their resulting proteins are deployed in membrane; then, MIC-A molecules may be recognized by NKG2D receptors expressed on the γδ T lymphocytes and natural killer cells. On cytotoxic cells, engagement of NKG2D receptors results in activation of cytolytic responses directed against targeted-cells expressing MIC-A (Bauer et al., 1999). In this regard, Kimura and colleagues have reported that *MIC-A-1.2* polymorphism is associated with Takayasu's arteritis in absence of *HLA-B52* gene, suggesting that a part of the HLA-linked genetic susceptibility to Takayasu's arteritis

may be mapped near the *MIC-A* gene region (Kimura et al., 1998). To further investigate the role of these cytotoxicity-mediated mechanisms, Seko and colleagues analyzed the expression of MIC-A and some co-stimulatory molecules in the aortic tissue as well as their counterpart ligands in the infiltrating cells from patients with Takayasu's arteritis. They found that MIC-A molecules are strongly expressed in the aortic tissue, along with over-expression of co-stimulatory molecules 4-1BBL and Fas; while, most of the infiltrating cells express NKG2D receptors as well as 4-1BB and FasL (Seko et al., 2004). These findings suggest that γδ T lymphocytes and other killer cells may recognize stressed aortic cells expressing MIC-A throughout NKG2D receptors. Over-expression of co-stimulatory molecules may facilitate further recognition and activation of cytotoxic cells, leading to an increase in the cellular stress of aorta and self-maintenance of chronic inflammation.

11. Absence of *Mycobacterium tuberculosis* in arterial tissue from Takayasu's arteritis

Despite clinical and laboratory studies supporting that *Mycobacterium tuberculosis* could be involved in the pathogenesis of Takayasu's arteritis, the pathogen has not been detected directly in the arterial tissue. Recently, Arnaud and colleagues looked for the presence of *Mycobacterium tuberculosis* by acid-fast and auramine-fluorochrome staining, mycobacterial cultures on Lowenstein-Jensen culture media, and nucleic acid -16S ribosomal RNA-amplification in arterial specimens (aorta and carotid arteries) from 10 patients with Takayasu's arteritis underwent surgery (Arnaud et al., 2009). Of note, no patient had evidence of active tuberculosis at the time of surgery and patients were Caucasians or North Africans; histological examination showed five active and five inactive arterial lesions. *Mycobacterium tuberculosis* was not detected in arterial specimens of either active or inactive Takayasu's arteritis by any of the methods used. Although these results almost exclude a direct arterial infection, do not exclude a latent, extra-arterial infection with anti-mycobacterial immune responses triggering a cross-reaction against antigens located in the arterial wall.

Diagnosis of latent infection by *Mycobacterium tuberculosis* has dramatically improved with the arrival of Quantiferon-TB Gold test. Quantiferon-TB Gold test identifies latent and active tuberculosis infection by measuring the *in vitro* interferon-γ release from T lymphocytes in response to three unique antigens highly specific for *Mycobacterium tuberculosis*, which are absent in almost all non-tuberculous mycobacteria including BCG vaccine. This test has been particularly helpful in countries in which the interpretation of PPD intradermal reaction is confounded because routinely early application of BCG vaccine (Lalvani, 2007). Recently, Karadag and colleagues assess the possibility of latent tuberculosis infection in ninety-four Turkish patients with Takayasu's arteritis using tuberculin test and Quantiferon-TB Gold test and compare it with healthy controls (Karadag et al., 2010). Even when tuberculin test positivity was higher in patients with Takayasu's arteritis than in controls (62.5% versus 41.4%; $P=0.008$), Quantiferon-TB Gold test positivity was equal between groups (22.3% versus 22.4%; $P>0.05$), suggesting that latent tuberculosis is similar in patients with Takayasu's arteritis and in healthy controls.

12. Proposal for a novel unifying model of pathogenesis

Previous model of pathogenesis has been supported on the premise that the arteritis results from delayed hypersensitivity to active or latent tuberculosis infection, through cross-

reactivity mechanisms against vascular peptides mimicking antigens constituents of *Mycobacterium tuberculosis* and other mycobacteria. This model has fascinated researchers and clinicians for more than a half century; however, recent studies showing absence of mycobacteria into the arterial tissue as well as absence of latent *Mycobacterium tuberculosis* infection by highly-specific *ex vivo* functional assays have knocked out this attractive hypothesis. Nevertheless, it is irrefutable the vast evidence showing indirect associations between Takayasu's arteritis and *Mycobacterium tuberculosis*; hence, we will hypothesize on a novel, unifying pathogenic model that may explain this relationship.

We speculate that, in a first step (non self-reactive phase), unspecific injuries such as infections, increased blood pressure, and other non-specific inflammatory stimuli may induce cellular stress in endothelial vascular cells, which in turn result in the production of large amounts of 60 kDa HSP and other stress-induced proteins. These "warning of danger" molecules may be sensed by innate cytotoxic cells through pattern-recognition receptors (PRR's) such as Toll-like (TLR) and Nucleotide-binding and oligomerisation domain (NOD)-like (NLR) receptors. After recognition, cytotoxic cells become activated and may promote apoptosis of vascular endothelial cells through perforin and Fas/Fas-L pathways, thus enhancing the stressed cellular environment.

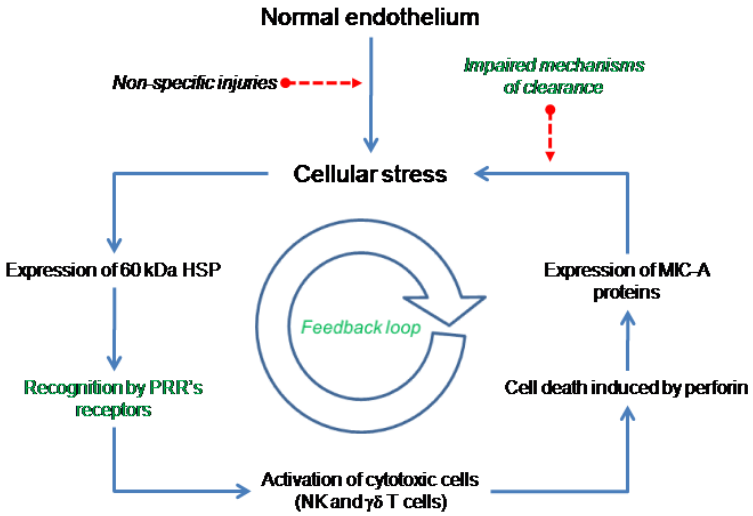

Fig. 1. A novel pathogenic model in Takayasu's arteritis. Non self-reactive phase. Unspecific damage factors induce stress in endothelial cells, which results in the expression of several stress-induced proteins, including 60 kDa heat shock protein (HSP). These stress-induced proteins are engaged by innate cytotoxic cells through pattern-recognition receptors (PPR's) and become activated, promoting apoptosis of vascular endothelial cells and enhancing the stressed cellular environment.

In a second step (self-reactive, innate immune phase), stressed vascular cells may rapidly activate *MIC-A* gene transcription (for instance, *MIC-A-1.2* polymorphism). Then, MIC-A molecules on endothelium may be recognized by NKG2D receptors on infiltrating Vδ1+ γδ T lymphocytes and natural killer cells, which in turn result in cytolytic responses against

endothelial targeted-cells expressing MIC-A. Vascular infiltration of oligoclonally expanded γδ T cells producing interferon-γ may amplify the expression of HLA class II and class I molecules (*i.e.* HLA-Bw52-DRB1*1502-DRB5*0102-DQA1*0103-DQB1*0601 -DPA1*02-DPB1*0901) and co-stimulatory molecules. Co-expression of MHC proteins and vascular antigens (muted or misfolded self-antigens?) may lead to massive aortic infiltration by oligoclonally expanded self-reactive αβ CD4+and CD8+ T lymphocytes.

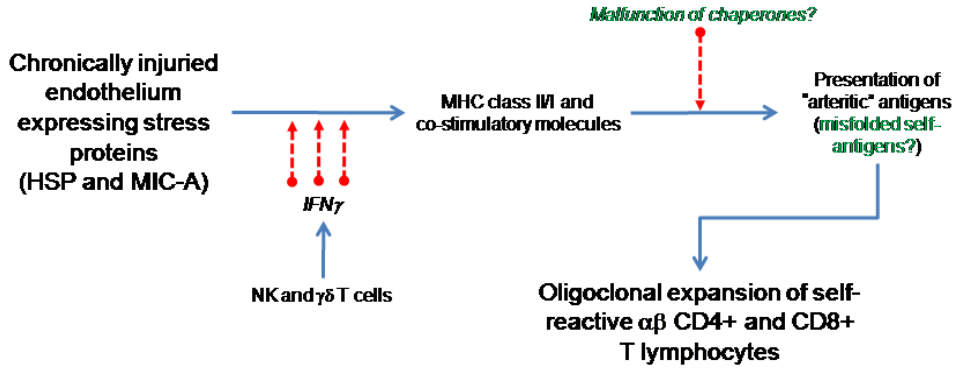

Fig. 2. A novel pathogenic model in Takayasu's arteritis. Self-reactive, innate immune phase. MIC-A molecules are over-expressed on vascular endothelial cells and may be recognized by infiltrating natural killer (NK) and γδ T cells, which amplify the interferon (IFN)γ-dependent expression of HLA class II and class I molecules and co-stimulatory molecules. Co-expression of MHC proteins and vascular antigens (muted or misfolded self-antigens?) lead to aortic infiltration by oligoclonally expanded self-reactive αβ CD4+and CD8+ T cells.

In a third phase (self-reactive, adaptive immune phase), self-reactive αβ CD4+ T lymphocytes may play central and multiple roles in the amplification and progression of the inflammatory response in Takayasu's arteritis. Different T cell subsets may provide help for B cell production of "arteritic" auto-antibodies such as anti-endothelial cells and anti-60 kDa HSP antibodies as well as antigen-driven T cell-dependent IgG isotype switching. T cells subsets also may modulate expansion and effector functions by infiltrating macrophages, directing their transformation into Langhans multinucleated giant cells and granuloma formation. Finally, infiltrating CD4+ and CD8+T cell subsets may promote the progression and maintenance of granuloma as well as the recruitment of fibroblasts; late in the process of tissue injury, massive deposition of collagen and matrix proteins may lead to fibrosis of arterial walls, which characterizes the pulseless stage of chronic Takayasu's arteritis.
In addition to better explain arterial tissue damage, this novel pathogenic model also may explain the common positive reaction to PPD (and other mycobacterial antigens) observed in patients with Takayasu's arteritis. Intradermal deposition of mycobacterial antigens may trigger both recruitment and activation of several subsets of T lymphocytes self-reactive against human 60 kDa HSP. These T cells may also mediate cross-reacting responses with the mycobacterial homologue 65 kDa HSP and, in a lesser extent, 38 kDa HSP, thus explaining the delayed hypersensitivity that underlies the Mantoux test as just an epiphenomenon.

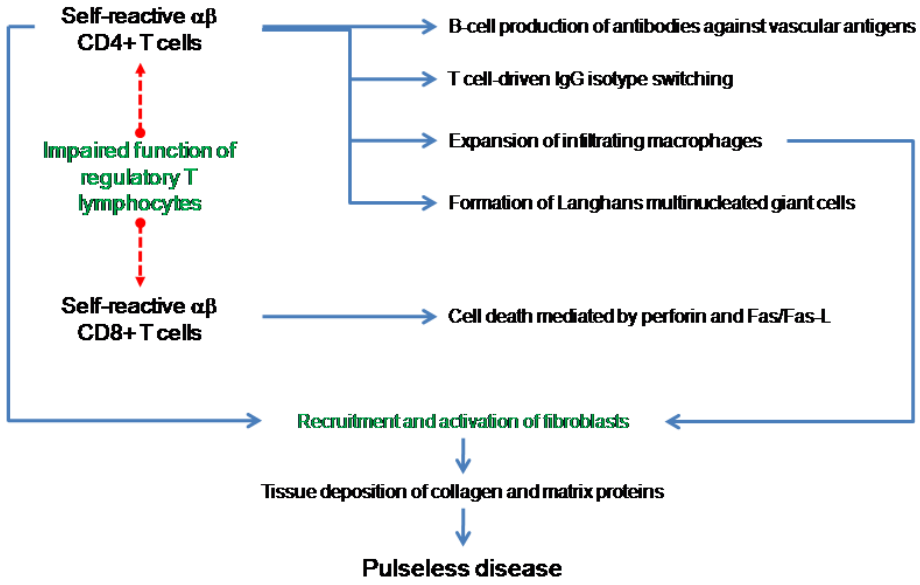

Fig. 3. A novel pathogenic model in Takayasu's arteritis. Self-reactive, adaptive immune phase. Self-reactive αβ CD4+ T lymphocytes play central roles in the inflammatory response seen in Takayasu's arteritis. Helper T cell subsets provide help for B cell production of antibodies against vascular antigens and IgG isotype switching. Helper T cell subsets also may modulate effector functions by infiltrating macrophages.

Finally, CD4+ and CD8+T cells may promote recruitment of fibroblasts and deposition of collagen and matrix proteins leading to fibrosis of arterial vessels (pulseless stage of Takayasu's arteritis).

13. Conclusion

A relationship between Takayasu's arteritis and both latent and active tuberculosis has been discussed for more than a half century. Indirect evidence had suggested that *Mycobacterium tuberculosis* and probably other mycobacteria could play a role in the immunopathogenesis of Takayasu's arteritis, possibly through molecular mimicry mechanisms. However, recent studies showing absence of mycobacteria directly into the arterial tissue as well as absence of latent *Mycobacterium tuberculosis* infection by highly-specific *ex vivo* functional assays have knocked out this attractive hypothesis.

Supported on currently available data, we speculate on a novel model of pathogenesis which may explain the intricate relationship between Takayasu's arteritis and *Mycobacterium tuberculosis*. This model is based in the loss of self-tolerance against stress-induced cellular molecules, with the innate immune system as key culprit in the initiation, amplification and progression of inflammatory response observed in Takayasu's arteritis.

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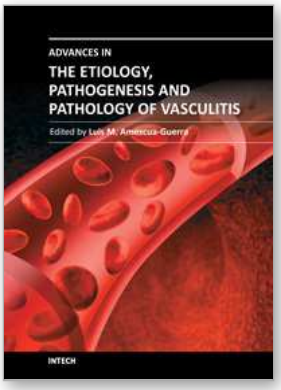

Advances in the Etiology, Pathogenesis and Pathology of Vasculitis

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This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to devote their work to this book by keeping both the text and the accompanying figures and tables lucid and memorable. Here, you will find an amalgam between evidence-based medicine to one based on eminence, through an exciting combination of original contributions, structured reviews, overviews, state-of the-art articles, and even the proposal of novel pathogenetic models of disease. The book contains contributions on the etiology and pathology of vasculitis, the potential role of endothelial cells and cytokines in vascular damage and repair as well as summaries of the latest information on several primary and secondary vasculitis syndromes. It also covers selected topics such as organ-specific vasculitic involvement and quality of life issues in vasculitis. The editor and each of the authors invite you to share this journey through one of the most exciting fields of the medicine, the world of Vasculitis.

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