Autoimmunity Reviews 11 (2011) 61–67

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Pathogenesis of Takayasu's arteritis: A 2011 update

Laurent Arnaud [a,b], Julien Haroche [a,b,c], Alexis Mathian [a,b,c], Guy Gorochov [b,c], Zahir Amoura [a,b,c,*]

[a] Department of Internal Medicine. French Reference Center for Rare Auto-immune diseases. Groupe hospitalier Pitié-Salpêtrière, AP-HP, 47–83 bd de l'hôpital, 75013, Paris, France
[b] Institut National de la Santé et de la Recherche Médicale, INSERM UMR-S 945, 75013 Paris, France
[c] Université Pierre et Marie Curie, UPMC Univ Paris 06, 75005 Paris, France

ARTICLE INFO

Article history:
Received 17 July 2011
Accepted 1 August 2011
Available online 9 August 2011

Keywords:
Takayasu arteritis
Vasculitis
Pathogenesis
Immunology
Review

ABSTRACT

While our knowledge of the pathogenesis of Takayasu's arteritis (TA) has considerably improved during the last decade, the exact pathogenic sequence remains to be elucidated. It is now hypothesised that an unknown stimulus triggers the expression of the 65 kDa Heat-shock protein in the aortic tissue which, in turn, induces the Major Histocompatibility Class I Chain-Related A (MICA) on vascular cells. The γδ T cells and NK cells expressing NKG2D receptors recognize MICA on vascular smooth muscle cells and release perforin, resulting in acute vascular inflammation. Pro-inflammatory cytokines are released and increase the recruitment of mononuclear cells within the vascular wall. T cells infiltrate and recognize one or a few antigens presented by a shared epitope, which is associated with specific major Histocompatibility Complex alleles on the dendritic cells, these latter being activated through Toll-like receptors. Th1 lymphocytes drive the formation of giant cells through the production of interferon-γ, and activate macrophages with release of VEGF resulting in increased neovascularisation and PDGF, resulting in smooth muscle migration and intimal proliferation. Th17 cells induced by the IL-23 microenvironnement also contribute to vascular lesions through activation of infiltrating neutrophils. Although still controversial, dendritic cells may cooperate with B lymphocytes and trigger the production of anti-endothelial cell auto-antibodies resulting in complement-dependent cytotoxicity against endothelial cells. In a near future, novel drugs specifically designed to target some of the pathogenic mechanisms described above could be expanding the physician's therapeutic arsenal in Takayasu's arteritis.

Contents

1. Introduction . . . 62
2. Patterns of vascular involvement in TA: from innate to adaptative immunity . . . 62
   2.1. Toll-like receptors in TA . . . 62
   2.2. Dendritic cells in TA . . . 62
   2.3. Natural killer cells, γδ T cells and pro-apoptotic pathways in TA . . . 62
   2.4. Molecular mimicry may drive innate immune responses in TA . . . 62
3. Cellular recruitment and infiltration in TA . . . 63
   3.1. Cellular recruitment in TA . . . 63
   3.2. Cell-mediated immunity in TA . . . 63
   3.3. Pro-inflammatory cytokine and mechanisms of lesions in TA . . . 64
4. The controversial role of B-cells in TA . . . 64
5. Conclusion . . . 65
Take-home messages . . . 65
References . . . 65

* Corresponding author at: Service de Médecine Interne 2., French reference center for auto-immune diseases, Groupe Hospitalier Pitié-Salpêtrière, 47–83 bd de l'Hôpital, 75013, Paris, France. Tel.: +33 1 42 17 80 40; fax: +33 1 42 17 80 44.
E-mail address: zahir.amoura@psl.aphp.fr (Z. Amoura).

1568-9972/$ – see front matter
doi:10.1016/j.autrev.2011.08.001

1. Introduction

Takayasu's arteritis (TA) is a rare primary and granulomatous large-vessel vasculitis of unknown origin predominantly affecting the aorta and its major division branches [1]. Although originally believed to be a disease mostly affecting young women of Asian descent since its original description in Japan by Takayasu, Kagoshima and Onishi at the beginning of the 20th century [2], TA is now well-recognized in both genders as well as in various ethnic groups worldwide [3,4]. Clinical manifestations of TA are strongly determined by the topography and type of vascular lesions [3,5], and whether vascular inflammation is persistent or not. Current therapeutic strategies are mostly based on the use of corticosteroids and of other immunosuppressive agents when the disease is refractory or if severe side-effects of steroids occur [6]. Additionally, a significant proportion of patients require surgical or endovascular revascularization procedures. The etiology of TA is still unknown but infectious agents [7], and genetic factors are known to play a significant role in the pathogenesis of this disease [8,9]. Over the last decades, cell-mediated autoimmunity has been strongly implicated in the pathogenesis of TA. Historically, immunohistochemical studies of infiltrating cells from the aortic tissue of patients with TA showed infiltration by macrophages, CD4+ T cells, CD8+ T cells, γδ T cells, natural killer (NK) cells and neutrophils [10], and this hypermetabolic infiltrate determines the 18F-Fluorodesoxyglucose uptake that may be seen when position emission tomographies are performed in TA [11,12]. The aim of this article is to review the most recently published data regarding the pathogenesis of TA and to draw ideas about promising therapeutic strategies that could be used in this rare disease.

2. Patterns of vascular involvement in TA: from innate to adaptative immunity

The natural history of vascular lesions is not well understood in TA [13]. However, it is well-known that vasculitides target certain portions of the vascular tree while sparing others. This suggests that there is a vessel-specific pattern in the response of the various arterial beds to inflammatory stimuli [14]. Because of the high frequency of left aortic arch branch involvement, Ishikawa hypothesized that TA lesions begin in the left subclavian artery and subsequently extend to other sites [15]. However, our recent cluster analysis of vascular involvement in TA has clearly shown that a given paired vascular bed clusters with its contralateral counterpart, suggesting that TA lesions mostly develop in a symmetric manner rather than in a contiguous way in paired vascular beds [16].

2.1. Toll-like receptors in TA

To further understand the patterns of vascular involvement in large-vessel vasculitides, Pryshchep et al. [14] have compared the expression profile of Toll-like receptors (TLR) 1 to 9, which are a type of receptors involved in innate immunity that recognize molecules broadly shared by pathogens, in human medium-sized and large arteries. This study revealed that each artery expresses a unique TLR profile with TLR2 and TLR4 ubiquitously present, TLR7 and TLR9 infrequent, and TLR1, TLR3, TLR5, TLR6, and TLR8 differentially expressed. Altogether, these data show that there is a specific pattern of vascular involvement in TA, and that TLR signatures are major determinants of this pattern. Interestingly, TLR modulators are being developed for auto-immune diseases, and could be valuable for improving the therapeutic management of vasculitides, in a near future [17,18].

2.2. Dendritic cells in TA

Pryshchep et al. also confirmed in organ culture and in a model of engraftment of human arteries in immunodeficient mice that pathogen-derived motifs are able to stimulate dendritic cells (DCs) embedded in the vessel wall [19] and thus provide a link between innate and adaptative immunity. Indeed, it is well established that the adventitia in TA contains T-cells co-localizing with DCs [20,21]. Immature DCs are widely distributed migratory cells that sample the antigenic environment. After activation, their chemokine receptor profile is modified and they migrate towards secondary lymphoid tissues where they express a mature chemokine-producing DCs profile and co-stimulatory molecules that can interact with antigen-specific T cells [22]. Immature dendritic cell have been found in temporal arteries of healthy subjects and are exclusively located near the media-adventitia border of the adventitia [22]. In giant cell arteritis (GCA), the other primary large vessel vasculitis [23], DCs are activated and produce the chemokines CCL18, CCL19, and CCL21 that bind the chemokine receptor CCR7 expressed on their cell surface, resulting in the trapping of these cells within the vascular wall [22]. Furthermore, DCs are frequently co-localized with T cells in inflamed aortic tissues from GCA patients and express the co-stimulatory molecule CD86, indicating that they are critical in maintaining T cell activation [20,21].

Some allelic variants of class II antigen-presenting HLA molecules constitute a genetic risk factor for TA [24]. Indeed, and despite a marked heterogeneity between the various studies performed, an increase frequency of HLA-B52 and HLA-DR4 alleles has been reported in ethnically different TA populations, providing an indirect clue for the role played by antigen stimulation of CD4+ T cells by DCs [25]. Some data have underscored the possible role of a specific epitope located on the peptide-binding site of the HLA-B molecule (63Glu and 67Ser) that appeared to be shared by several alleles associated with the disease [26,27]. This indirectly suggests that these shared residues may participate in the presentation of a limited number of antigen-derived peptides to the CD4+ T cells in TA.

2.3. Natural killer cells, γδ T cells and pro-apoptotic pathways in TA

The possible involvement of NK-cells, which are also involved in innate immunity, was investigated using the TUNEL (TdTmediated dUTP-biotin nick-end labelling) staining, which reveals apoptotic cells [28,29]. It showed apoptotic cells both in inflammatory areas and in non-inflammatory areas with vascular smooth muscle cell involvement. Seko et al. have shown that NK cells play a critical role in the vascular cell injury by expressing and releasing perforin directly onto the surface of arterial vascular cells [10]. Thus, other pro-apoptotic pathways such as 4-1BB/4-1BBL, Fas/FasL and MICA/NKG2D have also been investigated in TA [29]. 4-1BB is an inducible T cell surface receptor belonging to the tumor necrosis factor receptor superfamily which ligand (4-1BBL) is induced on activated antigen-presenting cells [30]. 4-1BB/4-1BBL interaction provides a costimulatory signal that enhances NK lymphocyte cytotoxic functions [31]. The engagement of death receptors like FAS on target cells by their ligands on NK cells results in caspase-dependent apoptosis [32] and NKG2D is an activating receptor expressed on most natural killer and γδ T cells [33], the ligand of which (Major Histocompatibility Class I Chain-Related A, MICA), is induced by cellular stress such as viral or bacterial infections. Engagement of NKG2D by MICA triggers cytotoxic responses of natural killer and γδ T cells against cells expressing MICA and costimulates antigen-specific effector T cells. Interestingly, 4-1BBL, Fas and MICA are induced in aortic samples from TA patients, and 4-1BB, FasL and NKG2D are expressed by infiltrating cells, which suggests a direct involvement of these pathways in vascular injury [29]. Up to now, these pathways have not been considered valuable therapeutic targets in vasculitides, probably because of their ubiquitous involvement in cellular homeostasis.

2.4. Molecular mimicry may drive innate immune responses in TA

While we have seen that NK cells and γδ T cells trigger apoptosis of vascular cells in TA, and that TLRs recognize molecules broadly shared