Takayasu Arteritis
Insights into Immunopathology
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SUMMARY

Takayasu arteritis is an acute and sometimes chronic form of vasculitis involving the aorta, its main branches and pulmonary arteries. Although its etiology is still unknown, immunopathologic analyses revealed that the infiltrating cells mainly consisted of \( \gamma \delta \) T-cells as well as \( \alpha \beta \) T-cells and NK cells. The infiltrating \( \gamma \delta \) T-cells, cytotoxic T-lymphocytes (CTLs), and natural killer (NK) cells directly injured the vascular cells by releasing a cytolytic factor, perforin. Expression of heat-shock protein (HSP)-65 as well as human leukocyte antigen (HLA) class I and II was enhanced in Takayasu arteritis lesions, supporting the pathogenic role of \( \gamma \delta \) T-cells and \( \alpha \beta \) T-cells. T-cell receptor (TCR) \( \alpha \beta \) gene usage by the infiltrating cells was restricted, strongly suggesting that a specific antigen was targeted. TCR \( \gamma \delta \) gene usage by the infiltrating cells was also restricted. Furthermore, it has been reported that a strong association with a specific haplotype of major histocompatibility complex (MHC) class I chain-related (MIC), MICA gene with Takayasu arteritis, suggesting that the HLA-linked gene susceptible to the disease is mapped near the MICA gene. This also supports a pathogenic role of \( \gamma \delta \) T-cells in Takayasu arteritis because \( \gamma \delta \) T-cells were shown to recognize MICA molecule, which can be stress-induced. These findings suggest that unknown stress, such as infection, may trigger the autoimmune process of inflammation involved in Takayasu arteritis. Jpn Heart J 2000; 41: 15-26

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Takayasu arteritis is a chronic form of vasculitis characteristic of stenotic and occasionally dilated lesions in the aorta, its main branches, pulmonary

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artery, and coronary artery. A young woman with peculiar anastomosis formation in the retinal vessels was first reported by Migito Takayasu in 1905. Since then, this disease (named Takayasu arteritis) has been mainly described as an acute inflammatory pulseless disease usually affecting young women. However, recently middle aged cases of Takayasu arteritis seem to be seen more often than before in Japan, in whom chronic vasculitis latently progresses without apparent inflammatory manifestations. This may be partly explained by the fact that the number of young, new cases decreased and former young cases have gotten older. Another possibility is the clinicopathological features of the disease may have changed in association with the changes in Japanese social and dietary life over the last several decades.

Histopathological analysis of the acute lesion revealed massive cell infiltration around the vasa vasorum and destruction of the media and adventitia, associated with intimal hyperplasia causing stenotic lesions. When destructive change of the media and adventitia predominates, it occasionally causes dilated lesions such as rupturing aneurysms. It seems that local inflammation sometimes persists even after acute inflammation apparently subsides, or local vasculitis may latently occur without apparent inflammatory manifestations, and causes chronic vascular cell damage, which may finally develop lesions with histological features resembling the atherosclerotic aortic aneurysm. Inflammatory cell infiltration and destruction of the vessel wall in Takayasu arteritis as well as atherosclerotic aortic aneurysm strongly suggest that a cell-mediated immunological mechanism plays an important role in the pathogenesis involved in these two diseases. Recently, Noris, et al. reported the close correlation of serum levels of inflammatory cytokines such as interleukin (IL) -6 and RANTES (regulated on activation, normal T cell expressed and secreted) with the disease activity. Evidence has accumulated that there is an association between Takayasu arteritis and specific human leukocyte antigen (HLA) haplotypes. These data also strongly support the involvement of a cell-mediated immunological mechanism in the pathogenesis of Takayasu arteritis. However, the precise mechanism of vascular cell injury as well as the primary cause which triggers the autoimmune process involved in Takayasu arteritis are still unknown and remain to be clarified. In this review, I discuss the investigations conducted so far on the immunological mechanism of the vascular injury in Takayasu arteritis. Because the cell-mediated immune response is induced by the interaction between immune effector cells (that is, infiltrating cells) and target cells or antigen-presenting cells (APCs) (that is, aortic vascular cells), the investigation was designed to analyze the characteristics of each side of the cells at the site of inflammation to examine how they can interact with each other. Furthermore, I mainly focus on two aspects of the cell-mediated immune mechanism. First, the mechanism of vascular cell injury by immune effector cells.
It is known that T-cells such as cytotoxic T-lymphocytes (CTLs) damage target cells through two major pathways. One is perforin-dependent direct lysis of the target cell membrane. The other is Fas/Fas ligand (L)-mediated apoptosis signal induction. Second, the mechanism of antigen-specific T-cell activation against the aortic vascular cells, which is mainly mediated by the main signal through T-cell receptors (TCR) as well as the costimulatory signals through costimulatory molecules belonging to the immunoglobulin superfamily and the tumor necrosis factor (TNF) receptor/ligand superfamily. Especially, the antigen-specificity of $\alpha\beta$ T-cells is thought to be determined by the diversity of combination of TCR and antigen-HLA complex.

Phenotypic Analysis of the Infiltrating Cells in the Aortic Tissue with Takayasu Arteritis

There have been only a few reports studying the phenotypes of the infiltrating cells in the lesion of Takayasu arteritis. Scott, et al.\textsuperscript{7} demonstrated the marked infiltration of CD3$^+$ CD8$^+$ (but not CD4$^+$) CTLs in aortic tissue of a patient with Takayasu arteritis, suggesting a role of CTLs in the immunopathology. Later, we analyzed the phenotypes of the infiltrating cells in the aortic tissue of 7 patients with Takayasu arteritis as well as 4 patients with atherosclerotic aortic aneurysm, and compared the immunological mechanism involved in these two diseases.\textsuperscript{8} We found that most of the infiltrating cells consisted of CD4$^+$ T-helper cells (Th-cells) (about 14% of total cells), CD8$^+$ CTLs (15%), CD14$^+$ macrophages (13%), CD16$^+$ natural killer (NK) cells (20%), and $\gamma\delta$ T-cells positive for TCR $\gamma\delta$ (31%). B-cells (CD20$^+$) were few in number or absent. On the other hand, the relative distribution of phenotypic markers among the infiltrating cells in the aortic tissue with atherosclerotic aortic aneurysm was Th-cells (6%), CTLs (12%), macrophages (31%), and NK cells (29%). There were only a few $\gamma\delta$ T-cells or B-cells. In general, most of the peripheral $\alpha\beta$ T-cells bearing TCR $\alpha\beta$ are CD4$^+$ CD8$^-$ (Th-cells) or CD4$^-$ CD8$^+$ (CTLs), and most of the peripheral $\gamma\delta$ T cells are CD4$^+$ CD8$^-$. Therefore, the infiltrating T-cells in Takayasu arteritis consisted of almost equal percentages of $\alpha\beta$ and $\gamma\delta$ T-cells. The percentages of the infiltrating macrophages and $\gamma\delta$ T-cells are quite different between the two diseases. Especially, the percentage of $\gamma\delta$ T-cells was almost the same as that of $\alpha\beta$ T-cells in Takayasu arteritis, whereas there were only a few infiltrating $\gamma\delta$ T-cells in atherosclerotic aortic aneurysm.

Mechanism of Vascular Cell Injury by Infiltrating Immune Effector Cells

Expression of a Cytolytic Factor, Perforin, in Infiltrating Cells: Killer cells such as
NK cells, CTLs and γδ T-cells, are known to play a pivotal role in cell-mediated cytotoxicity. These lymphocytes are thought to kill virus-infected cells or tumor cells with the effector molecules contained in their cytoplasmic granules, one of which is named pore-forming-protein or perforin. Evidence has accumulated that perforin is expressed in infiltrating lymphocytes in various diseases as well as lymphocytes under physiological conditions, and plays a critical role in cytolysis and can be a good marker for killer cells. It is thought that killer cells recognize and adhere to the target cells, and exocytotic discharge of perforin occurs in response to surface binding. After perforin monomers are released, they insert into the target bilayer cell membrane, then polymerize and assemble into transmembrane pores, which in turn cause colloid-osmotic injury to the target cells. Perforin pores and the membrane attack complex of complement (which consist of C5b, 6, 7, 8, and C9) have very similar microstructures. In addition, perforin and C9 have high molecular homology.

To analyze the pathogenic role these infiltrating cells might play (especially their cytotoxicity), we analyzed the expression of perforin in CTLs, NK cells, and γδ T-lymphocytes by double-immunostaining for surface markers and perforin. We found there was clear expression of perforin in the peripheral cytoplasmic granules of CTLs, NK cells, and γδ T-lymphocytes, indicating that these cells were activated killer cells. Furthermore, to investigate whether these killer cells really damage the aortic vascular cells and to confirm the mechanism, we examined the release of perforin molecules from the infiltrating cells by immunoelectron microscopy. We found that numerous perforin molecules were released from the surface of an infiltrating cell and directly onto the surface of an aortic vascular cell, which was in contact with the infiltrating cell. This represented the delivery of a lethal hit and indicated that perforin-mediated direct target cell damage had occurred. We found again that another infiltrating cell expressed perforin in the peripheral cytoplasm at the electron microscopic level. Perforin molecules seemed to be secreted from the infiltrating cell and pass across the narrow extracellular space (about 3 µm) to reach the surface of the vascular cell, strongly suggesting that perforin attacks target cells by passing through the extracellular space, followed by insertion and polymerization in the planar lipid bilayer of the target cell membrane.

We also examined the expression of perforin in infiltrating cells in the aortic tissue from atherosclerotic aortic aneurysm by double-immunostaining for perforin and surface markers CD8 and CD16. We found again that there was clear expression of perforin in the peripheral cytoplasmic granules of CTLs and NK cells. Immunelectron microscopic study also demonstrated that these infiltrating cells released massive amounts of perforin directly onto the surface of arterial vascular cells. Because there were only a few infiltrating γδ T-lymphocytes in
the aortic tissue, we did not study the expression of perforin in \( \gamma \delta \) T-lymphocytes. As for another example, we previously demonstrated by electron microscopy the formation of circular lesions with a diameter of about 15 to 20 nm (perforin-pores) on the surface of cardiac myocytes with viral myocarditis, indicating that perforin-mediated direct target cell injury really occurred.\(^{19}\) Although we did not confirm the presence of perforin-pores on the surface of vascular cells, these findings provide direct evidence that a significant proportion of the infiltrating cells in the aortic tissue consisted of killer cells, and strongly suggested that these killer cells played, at least in part, a critical role by releasing perforin molecules directly to the vascular cells in the development of vascular injury involved in atherosclerotic aortic aneurysm as well as Takayasu arteritis.

**Expression of Fas L in Infiltrating Cells and Fas in Vascular Cells:** Another known pathway of T-cell-dependent target cell injury is Fas / Fas L-mediated apoptosis signal induction. Therefore, we examined the expression of Fas L in infiltrating cells and Fas in vascular cells in aortic tissue with Takayasu arteritis. We found that Fas was strongly expressed in vascular (smooth muscle) cells in the vasa vasorum, and its ligand Fas L was expressed in most of the infiltrating cells, suggesting a possible interaction between them (Seko Y, unpublished observation). Next, to investigate whether apoptosis really occurred, we did TUNEL staining of the aortic tissue with Takayasu arteritis. However, aortic vascular cells such as smooth muscle cells seemed not to have undergone apoptosis. And, some of the infiltrating cells around the vasa vasorum were positive for TUNEL staining, suggesting that infiltrating cells partly underwent activation-induced cell death, that is apoptosis (Seko Y, unpublished observation).

Taken together, in my impression, perforin-mediated necrosis but not apoptosis may play a major role in the mechanism of vascular injury in Takayasu arteritis.

**Roles of \( \alpha \beta \) T-cells in the Immunopathology in Takayasu Arteritis**

**Analysis of TCR V\( \alpha \)-V\( \beta \) Gene Usage by Infiltrating Cells:** In general, foreign antigens such as viruses are digested and degraded into peptide fragments in the target cell cytoplasm, and then presented on the surface of the target cell membrane by major histocompatibility complex (MHC) antigens. T-cells specifically recognize processed antigens in conjunction with MHC molecules through their TCRs that consist mostly of \( \alpha \) and \( \beta \) chain heterodimers. The TCR \( \alpha \) chain consists of variable, joining, and constant regions, while the \( \beta \) chain consists of variable, diversity, joining, and constant regions. They are designated as V\( \beta \), D\( \beta \), J\( \beta \), and C\( \beta \), respectively. The antigen specificity of the TCR is defined by the V domains encoded by variable, diversity, and joining gene elements.
which are rearranged and joined during T-cell differentiation. Studies in autoimmune diseases,\textsuperscript{20-22} allograft rejection,\textsuperscript{23} and malignant tumors\textsuperscript{24} showed that T-cells involved in the local immune response used a limited range of TCR genes, indicating that these T-cells interact with a specific antigen and play an important role in the pathology. To investigate the roles of $\alpha\beta$ T-cells in the immunopathology in Takayasu arteritis, especially to determine whether $\alpha\beta$ T-cells specifically infiltrated the aortic tissue, we analyzed TCR V\textsubscript{\alpha} and V\textsubscript{\beta} gene usage in infiltrating cells in the aortic tissue with Takayasu arteritis as well as atherosclerotic aortic aneurysm by a reverse transcription-polymerase chain reaction (RT-PCR) method.\textsuperscript{25} We found that almost all TCR V\textsubscript{\alpha} as well as V\textsubscript{\beta} genes were expressed in peripheral blood lymphocytes with Takayasu arteritis and in infiltrating cells in the aortic tissue with atherosclerotic aortic aneurysm. In sharp contrast, only a few or limited number of V\textsubscript{\alpha} as well as V\textsubscript{\beta} genes were preferentially rearranged and transcribed in infiltrating cells in the aortic tissue with Takayasu arteritis. This indicates that distinct immunologic mechanisms are involved in the pathogenesis of these two diseases. The restricted usage of TCR V\textsubscript{\alpha} as well as V\textsubscript{\beta} genes by infiltrating cells in Takayasu arteritis indicated that a specific antigen in the aortic tissue was targeted. Whereas the polyclonal expression of TCR V\textsubscript{\alpha}-V\textsubscript{\beta} genes in atherosclerotic aortic aneurysm may indicate that non-specific T-cell recruitment by inflammatory cytokines occurred secondarily, Swanson, \textit{et al}.\textsuperscript{26} also reported polyclonal expression of TCR V\textsubscript{\beta} genes in human atheroma. However, we could not exclude the possibility that antigen-specific T-cells infiltrated the atherosclerotic tissue in a small population.

Furthermore, to investigate the TCR clonality in more detail, especially to examine whether there is a difference in TCR clonality within the same vascular lesion of Takayasu arteritis, we analyzed the TCR V\textsubscript{\beta} clonality in two separate parts (which are apart from each other) from the aortic tissue by RT-PCR, and then by a single strand conformation polymorphism (SSCP) method. We found that there were several clear bands of expressed TCR V\textsubscript{\beta} clones in a limited number of V\textsubscript{\beta} subfamily (Seko Y, unpublished observation), indicating that the expression of TCR V\textsubscript{\beta} clones was restricted, because polyclonal expression of TCR genes reveals a smear pattern. In addition, the patterns of the bands of expressed TCR V\textsubscript{\beta} clones in two separate parts within the same lesion were almost the same, strongly suggesting that the TCR V\textsubscript{\beta} clonality of the infiltrating cells in these two parts was almost the same (Seko Y, unpublished observation). This meant that TCR V\textsubscript{\beta} clonality within the lesion of Takayasu arteritis was consistent, and again strongly suggested that a specific antigen was targeted.

**Expression of HLA Class I, Class II, and Intercellular Adhesion Molecule-1 (ICAM-1) in the Aortic Tissue:** T-cells (especially $\alpha\beta$ T-cells) are known to recognize antigens by their receptors in association with syngeneic MHC
antigens, such as HLAs, on the surface of APCs. To become target cells for T-cells, the antigen-presenting cells must express MHC antigens. Furthermore, cell-cell interactions in the immune response are thought to be mediated by cell adhesion molecules expressed on both the immune cell and target cell. ICAM-1, which is a ligand for lymphocyte function-associated antigen-1 (LFA-1), is thought to be induced by cytokines on various target cells at the site of inflammation, and to play an important role in the recognition, adhesion, and cytotoxicity of killer lymphocytes. To clarify the interaction between infiltrating αβ T-cells and aortic vascular cells, we analyzed the expression of HLA class I, class II, and ICAM-1 in the aortic tissue. As compared with the expression in normal aortic tissue, the expression of these antigens (especially HLA class I) was moderately to strongly increased in the vasa vasorum with Takayasu arteritis. This indicated that vascular (smooth muscle) cells, at least in the vasa vasorum, could be the target cells for αβ T-cells (especially CTLs).

Expression of Costimulatory Molecules in Infiltrating Cells and Vascular Cells in the Aortic Tissue: It is necessary for T-cells to receive two signals from the APC for antigen-specific T-cell activation to occur. The first signal is provided by TCR engagement with an antigen/MHC complex, and the second signal, termed a costimulatory signal, is provided by costimulatory molecules on the APC. Among them, B7 family molecules B7-1 and B7-2, which belong to the immunoglobulin superfamily, are the most extensively characterized and appear to be the most critical. Other costimulatory molecules belonging to the TNF receptor/ligand superfamilies have been identified and characterized over the past several years. These include CD27/CD27 ligand (CD27L, CD70), CD30/CD30L (CD153), CD40/CD40L (CD154), OX40 (CD134)/OX40L, and 4-1BB (CD137)/4-1BBL. Evidence has accumulated that costimulatory molecules belonging to TNF receptor/ligand superfamilies play a pivotal role in T-cell-mediated immune responses, T-cell-dependent help for B-cells, and humoral immune responses. To clarify the T-cell-mediated immunological mechanism of vascular injury in Takayasu arteritis, we analyzed the expression of these costimulatory molecules in aortic tissue. We found that there was moderate to strong expression of B7-1, B7-2, CD40, CD27L, CD30L, and OX40L in the vascular (smooth muscle) cells and interstitial cells in the media. We also found that at least some of the infiltrating cells in the aortic lesion expressed their counterparts CD28, CD40L, CD27, CD30, and OX40, which are known to be expressed on the immune cells. Thus, expression of these costimulatory molecules in vascular cells as well as infiltrating cells at the site of inflammation again strongly supported the roles of T-cells in the immunopathology.
Roles of γδ T-cells in the Immunopathology in Takayasu Arteritis

Expression of Heat-Shock Protein (HSP)-65 in Aortic Tissue: Heat-shock proteins (HSPs) are known to be synthesized by various cells in response to environmental stresses, such as temperature changes, inflammation and viral infection. Evidence has accumulated that γδ T-cells can recognize autologous HSPs and may play an important role in autoimmunity.40,41) Because there was a significant increase in γδ T-cell infiltration, to clarify the mechanism of γδ T-cell infiltration, we examined the expression of HSP-65 in aortic tissue with Takayasu arteritis. HSP-65 was expressed weakly only in the media of aortic tissue from normal subjects, whereas the expression of HSP-65 was markedly increased in the media of aortic tissue with Takayasu arteritis. Some of the vasa vasorum also strongly expressed HSP-65.8) Markedly enhanced expression of HSP-65 in the media and vasa vasorum supported the participation of γδ T-cells in Takayasu arteritis. In contrast, there was only weak or slightly increased expression of HSP-65 in the media and vasa vasorum of aortic tissue with atherosclerotic aortic aneurysm, consistent with the absence of γδ T-cells. Xu, et al.42) reported that immunization with HSP-65 induced arteriosclerotic lesions in normocholesterolemic rabbits. The authors also reported that serum anti-HSP-65 antibodies were significantly increased in patients with carotid atherosclerosis.43) However, there was no evidence that the dominant population of the infiltrating T-cells was γδ T-cells and that HSP-65 was strongly induced in the arteriosclerotic lesions. It is uncertain that HSP-65-induced arteriosclerotic lesions can be a model for human atherosclerosis. Hohlfeld, et al.44) reported a case of polymyositis highly responsive to steroid therapy that was mainly mediated by γδ T-cells. The authors also demonstrated that all muscle fibers strongly expressed HSP-65 as well as HLA class I. This supports the critical role of γδ T-cells in the pathogenesis of Takayasu arteritis, because high-responsiveness to steroid therapy is generally seen in the acute stage of Takayasu arteritis. Aggarwal, et al.45) reported increased levels of serum antibodies against Mycobacterium tuberculosis antigens, especially its HSP-65, in patients with Takayasu arteritis. This also supports the pathogenic role of HSP-65 involved in Takayasu arteritis.

Analysis of TCR Vγ-Vδ Gene Usage by Infiltrating Cells: Because we found restricted usage of TCR Vα-Vβ genes by infiltrating cells in Takayasu arteritis, indicating that a specific antigen in the aortic tissue was targeted by the infiltrating αβ T-cells, to investigate in more detail the roles of γδ T-cells in the immunopathology, we analyzed TCR Vγ and Vδ gene usage by infiltrating γδ T-cells in arterial tissue from a patient with Takayasu arteritis. We found that almost all TCR Vγ (Vγ1 to Vγ4) as well as Vδ (Vδ1 to Vδ5, except for Vδ4) genes were expressed in peripheral blood lymphocytes, whereas only a limited
number of Vγ as well as Vδ genes (Vγ3, Vγ4, Vδ1) were preferentially rearranged and transcribed in infiltrating cells, indicating the oligoclonal accumulation of Vδ1+ cells at the site of inflammation.39) Clonal expansion of Vδ1+ cells at the site of inflammation was also reported in other autoimmune diseases such as multiple sclerosis,46) rheumatoid arthritis,47) and celiac disease,48) strongly suggesting the critical role of Vδ1+ cells in the pathogenesis involved.

Roles of Genetic Factors in the Immunopathology in Takayasu Arteritis

Genetic factors which determine susceptibility have been implicated in Takayasu arteritis. Also, evidence has accumulated that there is an association between Takayasu arteritis and specific HLA haplotypes such as HLA-B52 and -B39.49-53) Groh, et al.54) reported that intestinal epithelial γδ T-cells bearing Vδ1 TCRs recognize the MHC class I chain-related (MIC) molecules MICA and MICB, and that the expression and recognition of MICA/MICB can be stress-induced and may regulate protective responses by the Vδ1+ γδ T-cells. The MICA gene is polymorphic and highly divergent from classical HLA class I genes, and was found to be located near the HLA-B gene.55) MICA has been shown to be mainly expressed by fibroblasts, keratinocytes, endothelial cells, and monocytes, and not to be associated with β2-microglobulin.55,56) Up to now, at least 16 alleles of MICA have been identified.57) As for the polymorphism of the MICA gene (triplet repeat in the transmembrane region), a strong association of 6 GCT repetitions with Behcet disease was reported.58) For Takayasu arteritis, Kimura, et al.59) reported that MICA-1.2 (which has 6 GCT repetitions) strongly associated with the disease in the absence of HLA-B52, suggesting that HLA-linked gene susceptible to Takayasu arteritis is mapped near the MICA gene. Recently, Bauer, et al.60) reported that MICA was recognized by NKG2D receptor expressed on Vδ1+ γδ T-cells, CD8+ αβ T-cells (CTLs) and NK cells, and that engagement of NKG2D could activate cytolytic responses of these killer cells against transfectants and tumor cells expressing MICA. Although the amino acid sequence suggests that putative MICA chain folds similarly to HLA class I chains and may be able to bind peptide or other short ligands,55) the precise mechanism of antigen recognition between γδ T-cells expressing NKG2D as well as TCR γδ and APCs expressing MICA is unknown and needs further investigation.

Because anti-MICA antibody is not available at present, whether there was expression of MICA in the aortic tissue with Takayasu arteritis is unclear. At present, I speculate that the expression of MICA in the aortic tissue with Takayasu arteritis induced by stresses, such as infection, may trigger the infiltration by Vδ1+ γδ T-cells, which in turn enhances the expression of HLA class I and class II, and
ICAM-1 at the site of inflammation such as vasa vasorum by the release of cytokines, and then, infiltration by $\alpha\beta$ T-cells specific to some tissue-derived antigen (auto-antigen?) presented by HLAs may occur, as we previously reported. The expression of HSP-65 in vascular (smooth muscle) cells may play a role in the induction of MICA expression. It seems that $\gamma\delta$ T-cells (unlike $\alpha\beta$ T-cells) recognize small nonpeptidic antigens without antigen processing and presentation. Therefore, since the antigen recognized by infiltrating $\gamma\delta$ T-cells seems to be not always the same as that by infiltrating $\alpha\beta$ T-cells, identification of these antigens will facilitate the understanding of the pathological mechanism of Takayasu arteritis as well as the development of a specific treatment for Takayasu arteritis in the future.

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