Review

Pathogenesis of giant cell arteritis: new insight into the implication of CD161+ T cells

M. Samson[1-3], S. Audia[1-3], L. Martin[2-4], N. Janikashvili[2,3], B. Bonnotte[1-3]

[1]Service de Médecine Interne et Immunologie Clinique, CHU, Dijon, France;
[2]INSERM, UMR1098, Besançon, France;
[3]Faculté de Médecine, Université de Bourgogne, Dijon, France;
[4]Service d'Anatomie et Cytologie Pathologiques, CHU, Dijon, France.

Maxime Samson, MD
Sylvain Audia, MD, PhD
Laurent Martin, MD, PhD
Nona Janikashvili, PhD
Bernard Bonnotte, MD, PhD

Please address correspondence to:
Prof. Bernard Bonnotte,
Service de Médecine Interne et Immunologie Clinique,
CHU Dijon le Bocage,
2 Bd Mal de Lattre de Tassigny,
21000 Dijon, France.
E-mail: bernard.bonnotte@chu-dijon.fr

Received on January 28, 2013; accepted in revised form on February 19, 2013.

Clin Exp Rheumatol 2013; 31 (Suppl. 75): S65-S73.

Key words: giant cell arteritis, T cell, Th1 cells, Th17 cells, CD161, regulatory T cells, interleukin-6

Competing interests: none declared.

ABSTRACT

Giant cell arteritis (GCA) is a granulomatous large-vessel vasculitis that usually affects the aorta and/or its major branches, especially the branches of the carotid arteries. Histo-pathological lesions are observed in all layers of the artery leading to segmental and focal panarteritis with a polymorphic cell infiltrate that includes T cells, macrophages and multinucleated giant cells, a fragmented internal elastic lamina and intimal hyperplasia. The pathophysiology of GCA is complex and not fully understood. In this review, we discuss the immunological aspects of GCA pathogenesis with a particular emphasis on T cell responses. Upon dendritic cell activation in the adventitia, CD4 T cells co-expressing CD161 are recruited in the arterial wall and polarised into Th1 and Th17 cells that produce IFN-γ and IL-17, respectively. These cytokines activate macrophages, giant cells and vascular smooth muscle cells, thus inducing vascular remodelling which leads to the ischaemic manifestations of GCA. Macrophages infiltrating the adventitia produce IL-1β and IL-6, which are responsible for the general symptoms encountered in GCA.

Introduction

Giant cell arteritis (GCA) is a large-vessel vasculitis which usually affects the aorta and its major branches (1, 2). The term temporal arteritis is not a suitable alternative for GCA because temporal arteries are not always involved, and because other types of vasculitis can affect them. GCA is the most common vasculitis in adults over 50 years (3, 4). The peak incidence is observed between 70 and 80 years (3, 4). The prevalence of GCA depends on ethnic backgrounds. The disease seems to be very rare in African, Arabic, Hispanic and Asian countries (5-9). The highest prevalence is observed in Scandinavian countries and in Olmsted County, Minnesota, and reaches 18.8 cases per 100,000 people (10). This North to South incidence gradient and the highest frequency of GCA in Scandinavian ethnic groups suggest that GCA has a genetic background. A number of factors have been thought to increase the risk of GCA. These include haplotypes of human leukocyte antigen (HLA) class I and II (11), particularly the HLA-DRB1*0401, DRB1*0404 or DRB1*0408 haplotypes, expressed by 60% of patients affected by polymyalgia rheumatica (PMR) or GCA (12-14). Similarly to rheumatoid arthritis, a shared epitope exists in GCA: a conserved sequence of amino-acids between position 28 and 31 of the 2nd domain of the GCA associated HLA class-II β chain (HLA-DRB1*0401, HLA-DRB1*0404 and HLA-DRB1*0408) has been described (13). Other genes have been studied and polymorphisms of tumour necrosis factor-alpha (TNF-α) (14), interleukin-6 (IL-6) (15), corticotropin-releasing hormone (CRH) (16), intracellular adhesion molecule 1 (ICAM-1), NLRP1 rs8182352 polymorphism (17), regulated and normal T cell expressed and secreted (RANTES/CCL5) promoter, CCR5 or IL-1Ra (14) have been linked to an increased risk of developing GCA. Such associations underline the preponderant role of adaptive immunity in GCA pathogenesis. However, no pathognomonic genetic feature has been associated with GCA.

Some studies have also reported seasonal variations or a cyclic pattern, suggesting the involvement of a triggering environmental factor (3, 18). Several studies have investigated the potential role of viruses and/or bacteria

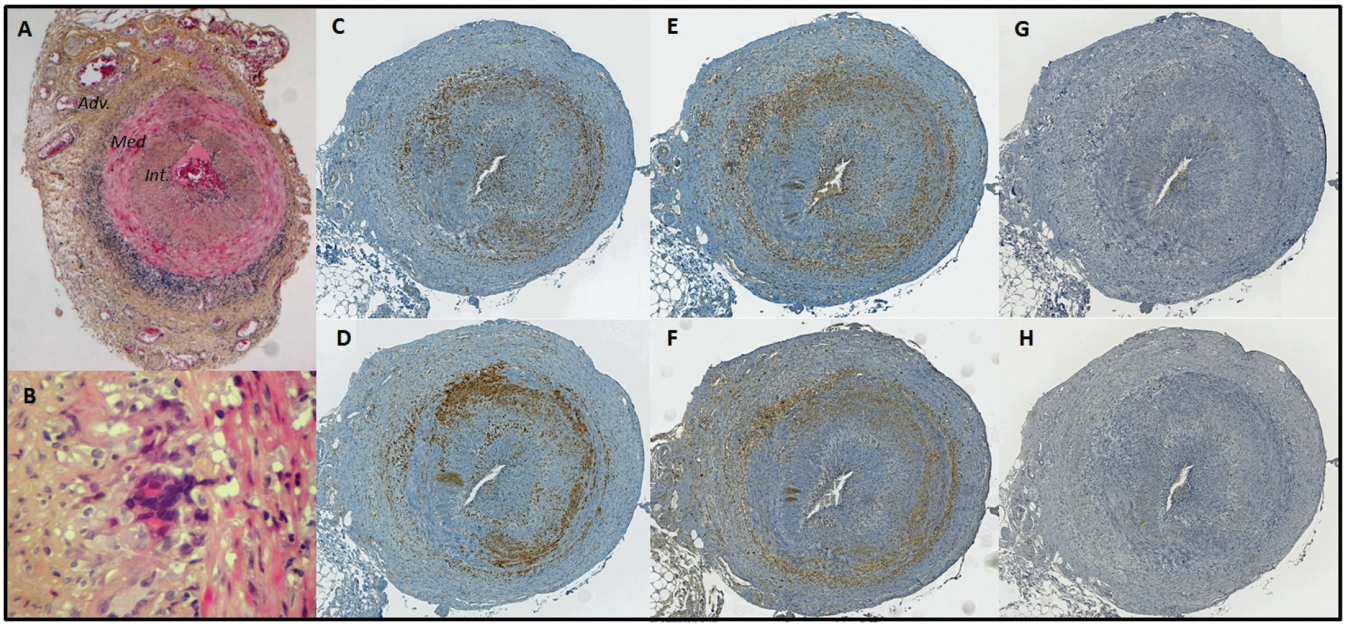

Fig. 1. Temporal artery biopsy affected by GCA. May Grünewald Giemsa staining (**A, B**) showing granulomatous inflammatory infiltration, fragmentation of the media and intimal hyperplasia leading to stenosis (**A**). Cellular infiltration is composed of mononuclear cells, especially at the media-adventitia junction where multinucleated giant-cells are observed (**B**). Immunohistochemistry analyses of a TAB from a patient affected by GCA (**C, D, E, F, G, H**). Positive cells appear in brown, showing an infiltration of the arterial wall by T cells (CD3 staining, [**C**]), macrophages (CD68 staining, [**D**]), Th1 cells (IFN-γ staining, [**E**]), Th17 cells (IL-17 staining, [**F**]). Very few Treg cells (Foxp3 staining, [**G**]) and no B cells (CD20 staining, [**H**]) are observed. Adv: adventitia, Med: media; Int: intima. Magnification x 40.

in the pathogenesis of GCA. Case-control studies have reported the detection of viral and/or bacterial DNA by PCR, immunohistochemistry or *in situ* hybridisation in temporal artery biopsies (TAB) from patients with GCA: cytomegalovirus, parvovirus B19, herpes simplex virus and *Chlamydia pneumoniae*, for example (19). However, these results have not been confirmed by larger studies. More recently, some authors reported evidence of the implication of a *Burkholderia*-like strain (*Burkholderia pseudomallei-like*): this attenuated newly-identified species of *Burkholderia* has been isolated from temporal arteries of GCA subjects, through 16S rRNA analysis followed by multilocus sequence typing. *Burkholderia* lipopolysacharide (LPS) has also been detected in TAB and serum of GCA patients. Culture of a GCA TAB was positive for Burkholderia *pseudomallei-like* species that were injected into mice and triggered inflammation of pulmonary blood vessels (20).

GCA is a focal and segmental panarteritis with non-necrotising granulomatous inflammation, affecting large vessels, especially the aorta, the external carotid and its branches such as the temporal artery. However, all large arteries can be affected (21). GCA classical histology is characterised by a granuloma associated with infiltration by T lymphocytes (mainly $CD4^+$ T cells) and macrophages, and the presence of multinucleated giant cells, which are usually located at the intima-media junction. B cells are usually absent in TAB from GCA patients (Fig. 1). However, only about 50% of routine biopsy samples show all these typical features. In the others, only a chronic inflammatory reaction, featuring lymphomononuclear cells but no giant cells is noticed. Fibrinoid necrosis in the temporal artery layers or in the wall of vasa vasorum is not usual in GCA lesions and should rule out the diagnosis.

Arterial topography of the inflammatory process accounts for ischaemic symptoms of the disease such as headache, jaw claudication, visual loss, scalp or tongue necrosis, central nervous system ischaemic complications. Systemic symptoms (fever, asthenia, anorexia and weight loss) are the consequence of chronic inflammation. In 27 to 56% of cases, GCA is associated with PMR, which has a common pathogenesis (22). The treatment of GCA is based on glucocorticoids that are very effective but difficult to stop. The mean duration of treatment is 18 months, which is responsible for a high level of morbidity and mortality in this elderly population (23). In this review, the pathogenesis of GCA is detailed, especially its immunopathology with emphasis on new therapeutic targets and the role of $CD4^+CD161^+$ T cells.

Pathophysiological model of GCA

GCA affects only large arteries such as the aorta and its major branches (before visceral arteries). These arteries have a prominent internal elastic membrane and vasa vasorum. The architecture of the artery plays a major role in the pathogenesis of the disease. When cervical arteries penetrate through the dura, they become thinner, have less elastic tissue and lose their vasa vasorum. Intracranial arteries are thus very rarely affected by GCA (24).

1. The three events in the pathogenesis of GCA

The pathogenesis of GCA can be divided into three phases (Fig. 2):

- Activation of vascular adventitial dendritic cells (DC) via TLR stimulation

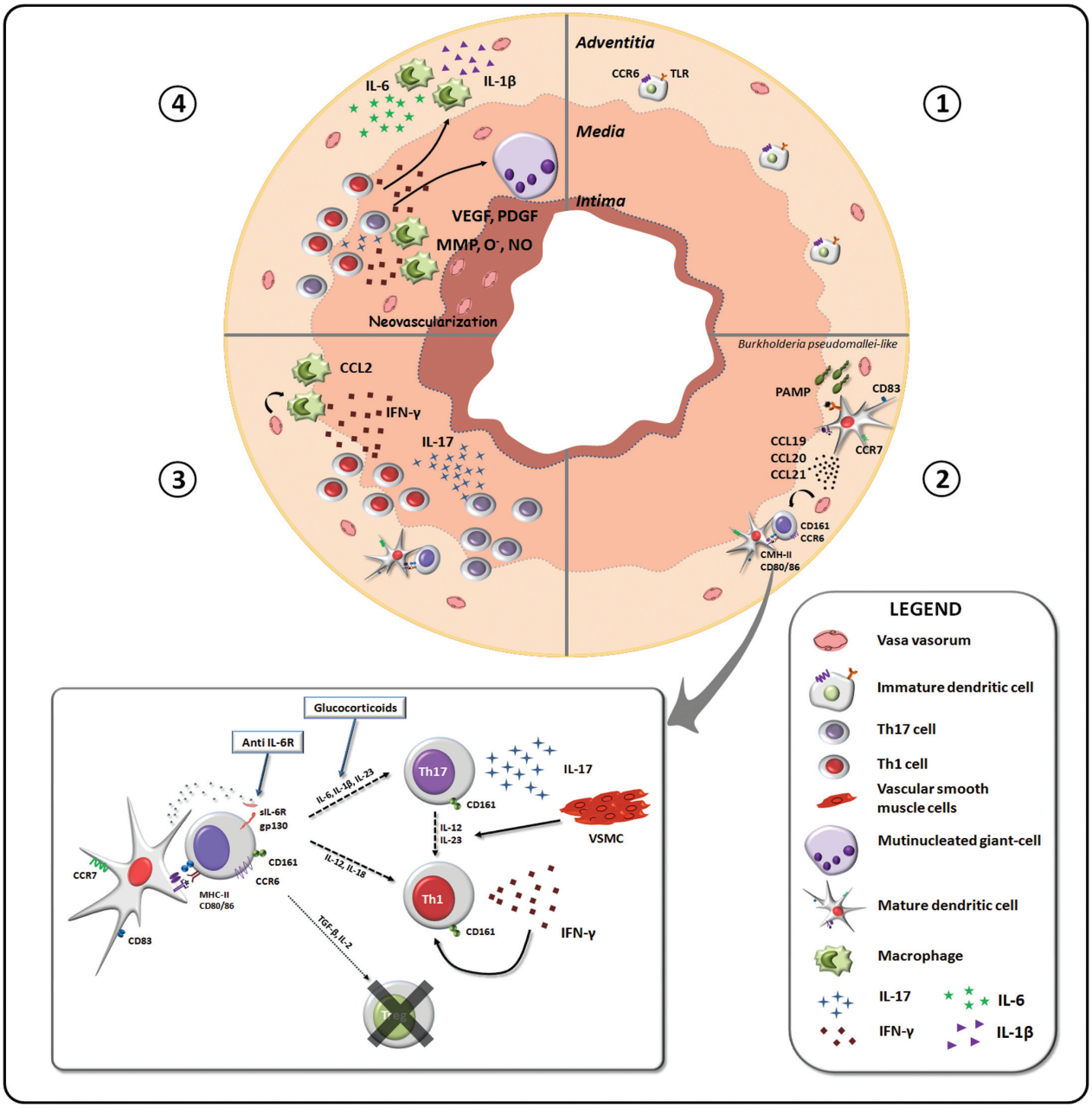

Fig. 2. Pathogenesis of GCA.

1. In healthy artery, dendritic cells (DC) of the adventitia are immature, express CCR6 and display particular TLR profiles, depending on the type of artery.

2. The detection of PAMPs (*pathogen associated molecular pattern*) or other danger signals by TLR induce DC activation. *Burkholderia pseudomallei-like* LPS could trigger DC activation. Activated DC modify their morphology, express high levels of MHC class-II, costimulatory molecules such as CD80 and CD86, CCR7 and produce cytokines and chemokines such as CCL19, CCL20 and CCL21 which recruit, activate and induce $CD4^+$ T cell differentiation. Recruited T cells mainly expressing CCR6 and CD161 are polarised into Th17 cells (in the presence of IL-6, IL-1β and IL-23) and/or Th1 cells (IL-12 and IL-18). These proinflammatory cytokines do not allow Treg generation, which leads to a chronic inflammatory response. Th17 cells produce IL-17, which triggers IL-23 and IL-12 production by resident cells, thus stabilising the Th17 lineage (IL-23) and increasing Th1 polarisation (IL-12). Glucocorticoids are able to decrease the production of Th17 cytokines but have no effect on Th1 cell polarisation. Anti-IL-6R (tocilizumab) can inhibit Th17 polarisation and increase Treg generation, correcting the Th17/Treg imbalance.

3. The arterial wall is infiltrated by oligoclonal Th1 and Th17 cells producing IFN-γ and IL-17, respectively. Thereafter, macrophages are recruited through CCL2 production. They are activated by cytokines secreted by T cells, especially IFN-γ.

4. Macrophages of the adventitia produce large amounts of IL-1β and IL-6 which are responsible for the general symptoms of GCA. IL-1β and IL-6 also initiate positive feedbacks that amplify local inflammation. In the media, macrophages produce growth factors: VEGF triggers neovascularisation, which increases immune-cell homing, while PDGF induces the migration and proliferation of vascular smooth muscle cells thus generating intimal hyperplasia. IFN-γ-activated macrophages also synthesise reactive oxygen species (O^-), nitric oxide (NO) and matrix metalloproteinases (MMP), which induce media destruction and internal elastic lamina digestion. Vascular remodelling is responsible for the ischaemic manifestations of GCA.

DC: dendritic cell; CCL: chemokines; CCR: chemokine receptor (CC family); CD: cluster of differentiation; MHC-II: major histocompatibility complex; IFN-γ: interferon-gamma; IL: interleukin; MMP: metalloproteinase; O^-: reactive oxygen species; PAMP: pathogen associated molecular pattern; PDGF: platelet-derived growth factor; TLR: toll like receptor; VEGF: vascular endothelial growth factor.

- Recruitment and activation of $CD4^+$ T cells
- Recruitment of macrophages (MP) and vascular remodelling

a. Activation of vascular adventitial dendritic cells (DC) via TLR stimulation

Immature myeloid DC, defined by a $S100^+CD11c^+CCR6^+CD83^-MHC\text{-}II^{low}$ phenotype are physiologically localised in the adventitia of arteries (25-28) and involved in immune surveillance. These cells play the role of immune sentinels and therefore, through the expression of toll-like receptor (TLR), have the ability to either sense danger signals and trigger adaptive immunity or to regulate localised and possibly systemic inflammatory responses in the absence of a danger signal (29). The detection of a danger signal via the TLR of adventitial DC induces their activation, followed by the phenotypic modifications ($S100^+CD11c^+CCR7^+CD83^+CD80/86^+MHC\text{-}II^{high}$) and the production of pro-inflammatory cytokines and chemokines responsible for the homing of $CD4^+$ T cells. Upon activated, DC express high levels of MHC class-II and co-stimulatory molecules responsible for T lymphocyte stimulation and their recruitment in the wall of the artery. In TAB from patients affected by PMR only, DC are activated but their presence is restricted only within the adventitia, whereas they infiltrate all the layers of the artery in GCA TAB, highlighting the pathological continuum between PMR and GCA (27, 28).

Using a humanised model of GCA, in which human temporal arteries are grafted into SCID mice, Weyand's team showed that the depletion of activated DC through an anti-CD83 antibody was able to reduce vasculitis, T cell infiltration and IFN-γ production, thus demonstrating the major role of adventitial DC in the pathogenesis of GCA (28). The danger signal in GCA has still not been identified but some data suggest on an infectious trigger recognised via TLR (3, 18, 19, 30). In healthy temporal arteries grafted into SCID mice, the injection of TLR ligands such as Freund complete adjuvant (TLR2 ligand) or LPS (TLR4 ligand) induced DC activation followed by vasculitis due to the activation of autologous T cells injected thereafter and recruited in the arterial wall (28). Among the different danger signals tested, LPS triggered the strongest activation of DC: CD83 expression, chemokine (CCL18, CCL19, CCL20) and cytokine (IL-18) production (28). The various locations of the artery lesions in GCA may be explained by the different profiles of TLR expression by adventitial DC. This hypothesis was confirmed by post-mortem TLR gene expression studies in large arteries from 37 patients (31). TLR were expressed almost exclusively by myeloid DC located at the adventitia-media junction. In all the arteries, most of the TLR (TLR1 to 9) were expressed: TLR2 and 4 ubiquitously, TLR7 and 9 infrequently, and TLR1, 3, 5, 6 and 8 were selectively expressed in some patterns, so that each vessel exhibited a distinct TLR profile. Notably, the temporal artery profile was different from that of other vessels: TLR2, 4 and 8 were highly expressed, whereas TLR1, 5 and 6 expression was low. The TLR expression profile in the aorta and carotid arteries was the most comparable to that in the temporal artery. These data can explain the tropism of GCA for the external carotid and its branches (31).

Unlike the classical immune response, activated DC do not migrate into lymph nodes in GCA. They produce CCL19 and CCL21 as well as their receptor (CCR7), and are thus trapped in the wall of the artery (27).

b. Recruitment, activation and polarisation of $CD4^+$ T cells

$CD4^+$ T cell depletion in the model of SCID mice engrafted with arteries from GCA patients led to a significant decrease in vasculitis lesions, while when there is no depletion the inflammatory process persists (32). These results highlight the essential role of $CD4^+$ T cells in the pathogenesis of GCA. Studies focusing on T-cell receptor (TCR) V genes in the arterial wall of GCA patients have shown a restricted oligoclonal repertoire, which strengthens the hypothesis of local proliferation and activation of $CD4^+$ T cells by mature DC (33-35). Furthermore, analyses of $CD4^+$ T cells recovered from right and left temporal arteries of the same GCA patient revealed identical TCR profiles, thus providing strong evidence of an antigen-driven immune response in GCA (35).

Notably, $CD4^+$ T cells are absent from the wall of healthy arteries; they are recruited after DC activation and maturation in response to the production of different chemokines: CCL18, CCL19, CCL20 and CCL21 (19, 26). $CD4^+$ T cells first infiltrate the adventitia through vasa vasorum, whose endothelial cells highly express adhesion molecules like intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (19, 26). It has been shown that the type of danger signal that activates adventitial DC determines the type of chemokines produced and consequently the subsets of $CD4^+$ T cells infiltrating the arterial wall. Activation of TLR4 by LPS triggers production of CCL20 leading to the recruitment of activated $CCR6^+CD4^+$ T cells that proliferate and trigger panarteritis (36). Interestingly, CCR6 is particularly expressed by Th17 cells, whereas Th1 cells do not express CCR6 but strongly upregulate CXCR3, the receptor for CXCL9, CXCL10 and CXCL11 (37). When DC are activated by a TLR5 ligand, only $CCR6^-CD4^+$ T cells are recruited in the arterial wall. These T cells are unable to infiltrate all the layers of the artery, thus triggering periarteritis that is different from GCA lesions (36).

Once recruited in the arterial wall, $CD4^+$ T cells are activated by DC that present a still unidentified antigen. The high concentrations of proinflammatory cytokines such as IL-12, IL-18, IL-23, IL-6 and IL-1β in the microenvironment, lead to Th1 and Th17 commitment of $CD4^+$ T cells. Th1 cells, generated in the presence of IL-12 and IL-18, produce IFN-γ, whereas Th17 cells, generated in the presence of IL-6, IL-1β and IL-23, produce IL-17. IL-17 is a potent proinflammatory cytokine that has recently been implicated in several autoimmune and autoinflammatory diseases such as multiple sclerosis, Crohn's disease or rheumatoid

arthritis (38, 39). The percentage of circulating Th17 cells in the blood of patients affected by GCA is increased in comparison with healthy controls (40-42). The arterial wall is also strongly infiltrated by Th1 and Th17 cells (figure 1). The response to glucocorticoids for these two populations of T cells seems to be different: after treatment Th17 decreased in both the blood and the arteries, whereas Th1 cells resist to glucocorticoids (40), even though data are sometimes contradictory (41). Indeed, corticosteroids trigger a decrease in Th17 cytokines (IL-1β, IL-6 and IL-23) but do not modify the production of Th1 cytokines (IL-12) by monocytes isolated from the blood or from TAB of GCA patients (40). IL-17 expression in TAB, measured by RT-PCR, has recently been shown to be a predictor of response to glucocorticoid treatment in GCA (43). These results may suggest the involvement of two distinct pathways in GCA pathogenesis (44). In the first pathway, DC produce IL-6, IL-23 and IL-1β triggering Th17 polarisation and IL-17 secretion, which activates endothelial cells, vascular smooth muscle cells (VSMC) and fibroblasts. This pathway is inhibited by glucocorticoids. In the second pathway, DC producing IL-12 and IL-18 lead to the generation of Th1 cells which secrete IFN-γ and activate macrophages, endothelial cells and cytotoxic cells. This pathway, which could be independent of the first one, is resistant to glucocorticoids and responsible for the chronic manifestations of GCA (40, 44). This hypothesis is probably not totally true since it is now admitted that polarised T cells, such as Th1, Th17 and regulatory T cells (Treg) are not stable. In fact, due to their plasticity, Th1, Th17 and Treg cells can differentiate into each other, depending on the cytokines produced in their environment (45-47). Rather than two independent pathways with two different types of DC and T cells, it is more likely that only one subset of DC triggers Th1 and Th17 polarisation from a common $CD4^+$ T cell precursor. Thereafter, under glucocorticoid therapy, Th17 cells decrease whereas Th1 lymphocytes are maintained due to the persistence of IL-12 producing DC (45). In a recent study using an IL-17-dependent colitis murine model, Th17 cells were able to induce IL-12 production by resident cells leading to the generation of Th1 cells producing IFN-γ (48). These results suggest that Th17 cells are able to induce their own polarisation into Th1 cells. Therefore, we cannot exclude the possibility that the extinction of Th17 cells and the persistence of Th1 cells might be the natural history of GCA.

Some results recently published by our team argue in favour of the former hypothesis. We have shown that $CD4^+CD161^+$ T cells, considered as precursors of Th17 cells in humans (49), were functionally modified in GCA. These $CD4^+CD161^+$ cells isolated from the blood of GCA patients produced higher levels of IL-17 than those from healthy controls (41). Furthermore, whereas they represent about 10 to 20% of circulating $CD4^+$ T cells, the great majority of T cells infiltrating the wall of the artery of GCA patients expressed CD161. Of note, $CD4^+CD161^+$ T cell recruitment in the artery is fostered by the expression of CCR6, more than 90% of these cells expressing CCR6 (41, 49). $CD4^+CD161^+$ T cells infiltrate all the layers of the artery during GCA and produce both IL-17 and IFN-γ (41).

However, these precursor cells need to be further characterised as different immune cells also express CD161. Actually, CD161 is the human homologue of the mouse NK1.1, expressed on NK cells and also some subsets of T cells defined as NKT cells (50, 51). In humans, NKT cells (type I) are α-galactosylceramide reactive and CD1d restricted, using invariant TCR α chain consisting of Vα24-Jα18 with Vβ11 (50, 51). The percentage of NKT cells among human circulating $CD4^+$ T cells is <1% (50, 51). Other human cell populations also express CD161 but are restricted to conventional MHC molecules, exhibit a polyclonal TCR repertoire and have been named NKT-like $CD4^+$ or $CD8^+$ T cells (50, 51). These $CD4^+CD161^+$ T cells represent about 10 to 20% of circulating $CD4^+$ T cells, express CCR6 and are characterised by a T-cell memory phenotype ($CD45RA^-$ $CD45RO^+$) (30, 50, 51). It is now clear that human Th17 cells differentiate from $CD161^+CD4^+$ T cells that are not CD1d restricted but dependent on MHC class II with a variant repertoire (49). CD161 is thus considered a specific marker of the Th17 lineage. Therefore, expression of CD161 by IFN-γ^+ T cells (Th1 cells) strongly supports the hypothesis that these Th1 lymphocytes are double positive (IL-17^+IFN-γ^+) or were polarised into Th1 from a Th17 state (41), due to the plasticity of T cell lineages (45, 46), as recently demonstrated in juvenile arthritis (52).

Regulatory T cells (Treg), defined by a $CD4^+CD25^{high}Foxp3^+$ phenotype are immunosuppressive cells that may also play a role in GCA pathogenesis (53). Actually, Treg are very rare in the arterial wall of arteries from GCA patients (figure 1) and the percentage of Treg in the peripheral blood of GCA patients is lower than that in healthy controls (41). However, their suppressive activity is not altered (41). This deficiency in the circulating Treg immune response in GCA is unable to control the strong Th1 and Th17 immune responses and thus, is probably involved in the sustained inflammation observed in GCA. Other types of immune dysregulation may also explain immune activation in the pathogenesis of GCA. It has recently been reported that the physiological expression of PD-L1 by endothelial cells of the vasa vasorum, which allows the inhibition of activated or cytotoxic T cells and have also been shown to trigger Treg generation (54), was strongly decreased, thus leading to a loss of the immune privilege that characterises the arterial wall. This hypothesis was confirmed by an accelerated vessel-wall inflammation (55) in human artery-SCID chimeras treated with a blocking PD-L1 fusion protein.

c. Vascular remodelling

Two different clinical signs of GCA are associated with two different processes: the inflammatory syndrome with systemic production of IL-6 and IL-1β is responsible for general symptoms, whereas vascular remodelling triggers ischaemic manifestations (56).

Infiltration of the arterial wall by T lymphocytes and their polarisation into

Th1 and Th17 cells leads to the secretion of high levels of IL-17 and IFN-γ. The exact role of IL-17 in vascular remodelling is still not completely defined (38). IFN-γ activates macrophages that are recruited in the arterial wall through CCL2 production (57, 58). Macrophage activation will lead to the genesis of giant cells that are one of the pathological GCA hallmark. CCL2 is produced by leukocytes in the arterial wall, but also by VSMC of the media (57). The involvement of CCL2 in the pathogenesis of GCA is supported by the positive correlation between the risk of relapse in the first year and the level of expression of CCL2 in the arterial wall (57). IFN-γ-stimulated macrophages of the adventitia produce IL-1β and IL-6 which amplify the local inflammatory response and are responsible for the general signs encountered in GCA: weakness, fever, weight loss, anorexia and acute phase response (19, 26, 30, 59-61). Upon activation by IFN-γ, macrophages in the media produce reactive oxygen species causing lipid peroxidation of phospholipids. Nitric oxide (NO) is produced by the induced NO-synthase and triggers nitration of endothelial proteins. Matrix metalloproteinase-9 (MMP-9), produced by VSMC and macrophages, is especially detected in granulomatous areas in arteries affected by GCA and is capable of destroying cellular matrix proteins including elastin and causing destruction of the media and digestion of the internal elastic lamina (19, 56). Macrophages activated by IFN-γ and giant cells produce also growth factors: platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) (62). PDGF triggers activation and proliferation of VSMC leading to vascular hyperplasia. VEGF is responsible for neoangiogenesis, which increases the recruitment of other immune cells (63).

VSMC of the media are major components of the arterial wall. They have contractile functions and are involved in the healing and repair of wall damage due to their ability to migrate, proliferate and produce matrix (36). During GCA, T cells and macrophages infiltrate the media so that VSMC are the direct target of their toxic mediators. VSMC are not only targets of the inflammatory process but are also implicated in its generation since they are able to migrate and proliferate in the intima and to produce MMP-2 and MMP-9 (36, 64). Neoangiogenesis and intimal hyperplasia are directly responsible for the ischaemic symptoms of GCA (63). Vasa vasorum are normally restricted to the adventitia. In GCA, they are also present in the media and the intima, which correlates with internal elastic lamina digestion and infiltration by giant cells.

Endothelial cells are the natural barrier between blood and tissues. They are involved in the regulation of vasomotion, hemostasis, angiogenesis and inflammation. Activated by the cytokines produced by macrophages and T cells, endothelial cells of the vasa vasorum and neovessels from TAB of patients affected by GCA express high levels of adhesion molecules such as ICAM-1, ICAM-2, P-selectin, E-selectin and VCAM-1 that are involved in the recruitment of immune cells (65).

2. Activation of the humoral immune response

The humoral immune response seems to be less involved in GCA pathogenesis than does the cellular immune response. A few B cells are sometimes detected in TAB of GCA patients, particularly in the adventitia (Fig. 1H) (41, 66, 67) where they are associated with plasma cells, especially in patients suffering from visual loss (68). Autoantibodies may be detected during GCA but their pathogenicity is not demonstrated. Anticardiolipin (aCL) antibodies are detected in 20% to 50% of GCA patients, but at a low level, without anti-β2glycoprotein I antibodies and without any correlation with an increase in the risk of ischaemic events (69-73). Anti-endothelial cell antibodies (AECA) have been detected in 33% of GCA patients (74). AECA are not specific to GCA, since they are also detected in healthy controls (75) and in other autoimmune diseases (76). However, it has been shown that AECA from GCA patients targeted specific antigens expressed by endothelial cells and VSMC, such as vinculine, lamin A/C, annexin V, voltage dependent anion-selective channel protein 2 (VDCA-2) and other proteins implicated in cellular energy metabolism (77). More recently, auto-antibodies directed against the heavy chain of human ferritin have been detected in 92% of GCA patients or PMR before treatment, but also in 29% of patients suffering from lupus and in only 1% of healthy donors (78).

3. Aging in GCA pathogenesis

Age is an essential factor in the onset of GCA. The aging process is associated with modifications of the immune response and vascular remodelling (79). Multiple types of cells are affected by aging: DC, T cells, endothelial cells and VSMC (79). Immune aging triggers a decrease in the number of naive T cells, an increase in memory and effector T cells, a decrease in the diversity of the T cell repertoire and an enrichment in $CD4^+CD28^-$ and $CD8^+CD28^-$ senescent T cells (80-83). DC are also affected by aging: TLR expression is maintained but DC activation and migration are impaired (84, 85). Elderly people are further exposed to infections, and latent viral or bacterial infections can be reactivated. Immune aging also alters the regulation of immune cells that can spontaneously produce cytokines: senescent DC, macrophages, endothelial cells and fibroblasts produce high levels of IL-1β, IL-6 and TNF-α (79, 86). This process might generate a chronic proinflammatory state leading to the development of auto-immune diseases and atherosclerosis. Aging also modifies arterial tissues: medial degeneration, calcium deposition, increased stiffness, wall thickening, elastic fiber fractures and biochemical modifications of matrix proteins (87-90). Combined with this proinflammatory state, these modifications could trigger immunisation against arterial auto-antigens and lead to GCA (79).

4. IL-6: a key cytokine and a promising therapeutic target in GCA

IL-6 has been shown to be highly implicated in GCA pathogenesis. Its concentration is increased in the serum of untreated GCA patients, is decreased

by glucocorticoid treatment and correlates with disease activity, erythrocyte sedimentation rate and C-reactive protein level (61). IL-6 is involved in the regulation of the Th17/Treg immune balance by triggering Th17 polarisation instead of Treg generation in the presence of TGF-β (91, 92). In GCA, the excess of IL-6 modifies the Th17/Treg immune balance in favour of Th17 cells (40-42). Glucocorticoids, the gold standard therapy for GCA, are able to decrease IL-6 concentration and impair Th17 polarisation (40, 41) but do not restore a normal Treg immune response, which might play a role in the occurrence of corticodependence or relapses when gluocorticoids are tapered. In rheumatoid arthritis, inhibition of the IL-6 pathway by tocilizumab, a humanised monoclonal antibody directed against IL-6 receptor (IL-6R), can correct the imbalance between Th17 and Treg cells by decreasing the percentage of Th17 cells and increasing the percentage of Treg (93). IL-6 pathway inhibition seems to be a promising therapeutic target in GCA. Several patients affected by GCA have already been treated with tocilizumab, either at diagnosis or in cases of refractory disease. A remission was rapidly obtained in almost all cases and no severe adverse events were observed after a relatively short follow-up period (5.1 to 8.3 months) (94-97).

Conclusion

The cause of GCA remains unknown but mechanisms involved in the disease are now better characterised. Particularly, IL-6, which is involved in the control of the Th17/Treg immune balance, has a critical role in the pathogenesis of GCA, thus allowing the development of new therapeutic targets in order to decrease the dose and the duration of steroid treatment.

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