Autoimmunity Reviews 16 (2017) 833–844

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

Recent advances in our understanding of giant cell arteritis pathogenesis☆,☆☆

Maxime Samson [a,b,c,*], Marc Corbera-Bellalta [c], Sylvain Audia [a,b], Ester Planas-Rigol [c], Laurent Martin [b,d], Maria Cinta Cid [c], Bernard Bonnotte [a,b]

[a] Department of Internal Medicine and Clinical Immunology, François Mitterrand Hospital, Dijon University Hospital, Dijon, France
[b] INSERM, UMR1098, University of Bourgogne Franche-Comté, FHU INCREASE, Dijon, France
[c] Vasculitis Research Unit, Department of Autoimmune Diseases, Hospital Clínic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[d] Laboratory of Pathology, François Mitterrand Hospital, Dijon University Hospital, Dijon, France

ARTICLE INFO

Article history:
Received 8 May 2017
Accepted 13 May 2017
Available online 28 May 2017

Keywords:
Giant cell arteritis
T cells
Interleukin-6
Interferon-gamma
Vascular remodeling

ABSTRACT

Giant cell arteritis (GCA) is a granulomatous vasculitis affecting large arteries, especially the aorta and the extra-cranial branches of the external carotid artery. Its exact pathogenesis is not fully understood but major progress has been made in recent years, leading to new therapeutic targets like inhibition of the interleukin-6 pathway or the modulation of immune checkpoints. The cause of GCA has not been clearly identified but it is thought that GCA occurs on a genetic background and is triggered by unknown environmental factors that could activate and lead to the maturation of dendritic cells localized in the adventitia of normal arteries. These activated dendritic cells then produce chemokines which trigger the recruitment of $CD4^+$ T cells, which in turn become activated, proliferate and polarize into Th1 and Th17 cells, which produce IFN-γ and IL-17, respectively. Exposed to IFN-γ, endothelial cells and vascular smooth muscle cells produce chemokines leading to the recruitment of further Th1 cells, $CD8^+$ T cells and monocytes. The latter differentiate into macrophages, which, when persistently exposed to IFN-γ, form giant cells, the histological hallmark of GCA. With the contribution of vascular smooth muscle cells, immune cells then trigger the destruction and remodeling of the arterial wall, thus leading to the formation of a neo-intima resulting in progressive occlusion of the arterial lumen, which is responsible for the ischemic symptoms of GCA. In this paper, we review recent progress in our understanding of GCA pathogenesis in the fields of genetics, epigenetics, infections, immunology and vascular remodeling.

Abbreviations: aCL, anti-cardiolipin antibodies; BCR, B-cell receptor; BDNF, brain-derived neurotrophic factor; CCLx, chemokine (CC family); CCR, chemokine receptor (CC family); CD, cluster of differentiation; CINC, cytokine-induced neutrophil chemoattractant; CRH, corticotropin-releasing hormone; CXCLx, chemokine (CXC family); CXCR, chemokine receptor (CXC family); DC, dendritic cell; DNA, deoxyribonucleic acid; DNMT1, DNA methyltransferase 1; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; GCA, giant cell arteritis; GWAS, genome-wide association study; HIF-1, hypoxia-inducible factor-1; HLA, human leukocyte antigen; ICAM-1, intracellular adhesion molecule-1; IFN-γ, interferon gamma; IL-x, interleukin-x; iNOS, induced NO-synthase; IRAK1, interleukin-1 receptor-associated kinase 1; LFA-1, lymphocyte function-associated antigen 1; LPS, lipopolysaccharide; LTA, gene of *lymphotoxin*-alpha (LT-α); LTB, gene of *lymphotoxin*-beta (LT-β); MECP2, methyl cpg binding protein 2; MHC, major histocompatibility complex; mIL-6R, membranous receptor of IL-6; MMP, metalloproteinase; NFAT, nuclear factor of activated T-cells; NGF, nerve growth factor; NLRP1, NLR family pyrin domain containing 1; NOS2, nitric oxide synthase 2; NOX2, NADPH oxidase 2; PAMP, pathogen associated molecular pattern; PD-1, programmed death-1; PDGF, platelet-derived growth factor; PD-L1, programmed death-ligand 1; PLG, gene of plasminogen; PMR, polymyalgia rheumatica; PPP3CC, gene of serine/threonine-protein phosphatase 2b catalytic subunit gamma isoform (PP2BC); PTPN22, protein tyrosine phosphatase, non-receptor type 22; RNA, ribonucleic acid; RT-PCR, reverse transcription polymerase chain reaction; RUNX3, RUNT-related transcription factor 3; SAA, serum amyloid A; SCID, severe combined-immunodeficiency; sIL-6R, soluble receptor of IL-6; SNPs, single nucleotide polymorphisms; STAT3, signal transducer and activator of transcription 3; TAB, temporal artery biopsy; TCR, T cell receptor; TFH, T follicular helper lymphocytes; TGF-β, transforming growth factor beta; Th, T helper; TLR, toll like receptor; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cells; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; VLA-4, very late antigen-*4*; VSMC, vascular smooth muscle cell; VZV, varicella zoster virus.

☆ Fundings: MS is funded by the French Vasculitis Study Group and the Foundation for the Development of Internal Medicine in Europe. Researches of MS, SA, LM and BB were supported by grants from the Groupement Interrégional de Recherche Clinique et d'Innovation Est (GIRCI), the University Hospital of Dijon, the Direction de la Recherche Clinique and the Conseil Régional de Bourgogne. MCB, EPR and MCC are supported by Ministerio de Economía y Competitividad (SAF 14/57708-R), Fundació la Marató de TV3 (201507), Instituto de Salud Carlos III (PIE13/00033) and Fondo Europeo de Desarrollo Regional (FEDER, una manera de hacer Europa).

☆☆ Disclosures: none.

* Corresponding author at: Service de Médecine Interne et Immunologie Clinique, Hôpital François Mitterrand, CHU de Dijon, 2, Bd Mal de Lattre de Tassigny, 21000 Dijon, France.
E-mail address: maxime.samson@chu-dijon.fr (M. Samson).

http://dx.doi.org/10.1016/j.autrev.2017.05.014
1568-9972/

Contents

1. Introduction

Giant cell arteritis (GCA) is a granulomatous large-vessel vasculitis usually affecting the aorta and its major branches, especially extracranial branches of the carotid artery [1–3].

The arterial topography of the inflammatory process accounts for symptoms of GCA, such as headache, jaw claudication, visual loss, scalp or tongue necrosis and central nervous system ischemic complications. Systemic symptoms (fever, asthenia, anorexia and weight loss) are the consequence of the acute-phase response related to chronic inflammation. In 27 to 56% of cases, GCA is associated with polymyalgia rheumatica (PMR), which shares pathological pathways with GCA [4]. The diagnosis of GCA is usually confirmed by a temporal artery biopsy (TAB) showing segmental and focal panarteritis with non-necrotizing granulomatous inflammation (Fig. 1). The arterial wall is infiltrated by T lymphocytes, macrophages, and multinucleated giant cells (the hallmark of GCA), the latter usually being located at the intima-media junction. However, only 50% of routine biopsy samples show all these typical features. In others, a chronic inflammatory reaction, featuring lymphomononuclear cells but no giant cells is noticed. By contrast with T cells, B cells are rarer in GCA lesions (Fig. 2).

GCA is the most common vasculitis after 50 years [5,6]. Women are affected two to three times more frequently than men. Its incidence increases progressively after 50 years with a peak occurring between 70 and 80 years [5,6]. The prevalence of GCA depends on ethnic backgrounds: GCA is very rare in African, Arabic and Asian countries [7–11], whereas the highest prevalence is observed in Scandinavian countries and in Olmsted County, Minnesota, where the population has a similar ethnic background and the overall annual incidence reaches 18.8 per 100,000 persons of 50 years of age or older [12]. This Nord to

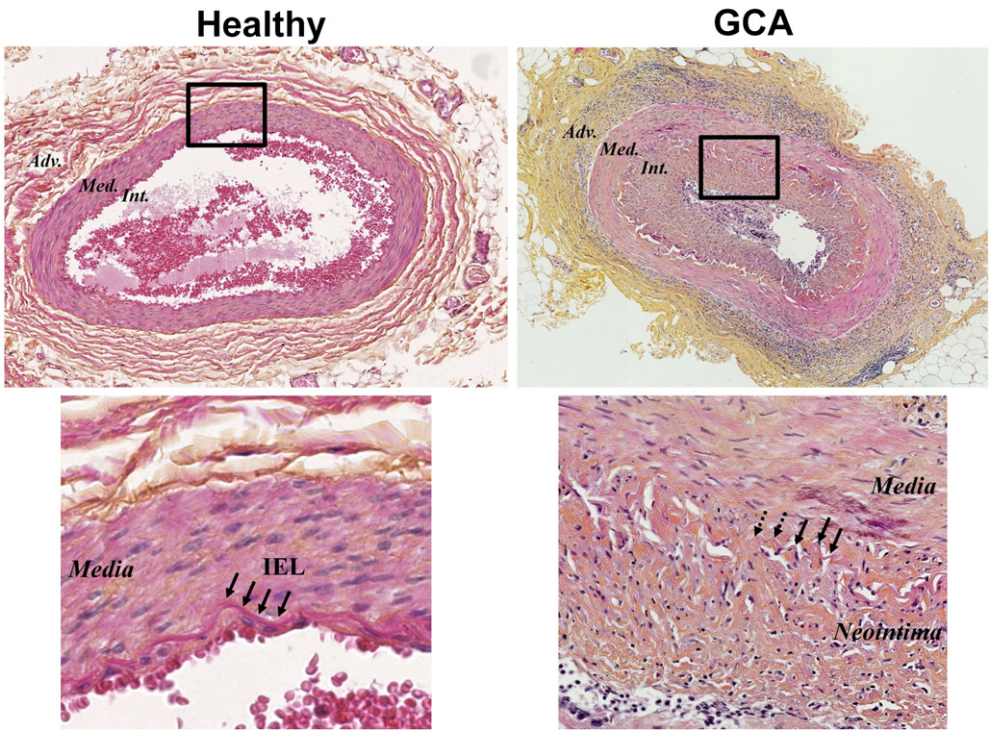

Fig. 1. Hematoxylin eosin safran staining of a healthy artery and of an artery affected by GCA. The healthy artery is characterized by a well-structured media and a thin intima separated by a preserved internal elastic lamina (IEL). In the healthy artery, the artery wall is free of inflammatory cells and its lumen is large. By contrast, many mononuclear inflammatory cells infiltrate the three layers of the artery affected by GCA (panarteritis). The media and the IEL are destroyed, thus allowing the migration and proliferation of vascular smooth muscle cells in the intima, leading to intimal hyperplasia and vascular occlusion. Magnification ×40. Adv: adventitia; IEL: internal elastic lumina; int: intima; med: media.