Autoimmunity Reviews 16 (2017) 774–786

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

The role of endothelial cells in the vasculopathy of systemic sclerosis: A systematic review

Y. Mostmans [a,h,*,1], M. Cutolo [b], C. Giddelo [a], S. Decuman [c], K. Melsens [c,d], H. Declercq [e], E. Vandecasteele [f], F. De Keyser [c,d], O. Distler [g], J. Gutermuth [a], V. Smith [c,d]

[a] Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Department of Dermatology, Laarbeeklaan 101, 1090 Brussels, Belgium
[b] Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy
[c] Ghent University, Department of Internal Medicine, Ghent, Belgium
[d] Ghent University Hospital, Department of Rheumatology, Ghent, Belgium
[e] Department of Basic Medical Sciences, Tissue Engineering and Biomaterials Group, Ghent University, Ghent, Belgium
[f] Department of Cardiology, Ghent University Hospital, Ghent, Belgium
[g] Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland
[h] Department of Immunology and Allergology (CIA) Centre Hospitalier Universitaire (CHU) Brugmann, Université Libre de Bruxelles (ULB), Van Gehuchtenplein 4, 1020 Brussels, Belgium

Abbreviations: Ab, antibodies; ACAs, anti-centromere antibodies; ACE, angiotensin converting enzyme; ADCC, antibody dependent cell mediated cytotoxicity; ADMA, asymmetric dimethylarginine; ADP, adenosine diphosphate; AECA, anti-endothelial cell antibodies; Ag, antigen; AIF-1, allograft inflammatory factor 1; Ang I, angiotensin I; Ang II, angiotensin II; Ang-1, angiopoietin 1; Ang-2, angiopoietin 2; Angptl3, angiopoietin-like protein 3; Anti-topo I, anti-topoisomerase; ATIII, antithrombin III; BALF, broncho-alveolar lavage fluid; BCGF, B cell growth factor; bFGF, basic fibroblast growth factor-2; BM, bone marrow; BM-MSCs, bone marrow mesenchymal stem cells; BMPRII, bone morphogenetic protein receptor II; CACs, circulating angiogenic cells; cAMP, cyclic adenosine monophosphate; CCL, chemokine ligand; CCN-1, cysteine-rich 61 matrix protein; CD, cluster of differentiation; CD44R, cluster of differentiation 44 receptor; CEC, circulating endothelial cells; CFU, colony-forming unit; cGMP, cyclic guanosine monophosphate; CIC, circulating immune complexes; CKO, knock out; CRP, C-reactive protein; CTSB, cathepsin B; CTSL, cathepsin L; CTSV, cathepsin V; CXCL, chemokine (C-X-C motif) ligand; CX_3CR1, fractalkine receptor; DAF, decay accelerating factor; dcSSc, diffuse cutaneous systemic sclerosis; DD, d-dimers; DLCO, diffusing capacity for carbon monoxide; DMVEC, dermal microvascular endothelial cells; DRC3f, complement C3f-des-arginine; DS, dermatansulphate; DU, digital ulcers; EC, endothelial cell; ECA, endothelial cytotoxic activity; ECs, endothelial cells; EGFL7, epidermal growth factor-like protein 7; EMP, endothelial cell-derived microparticles; ENA-78, epithelial-neutrophil activating peptide-78; EndoMT, endothelial-to-mesenchymal transition; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cells; ERK, extracellular signal-regulated kinase; EScSG, the European Scleroderma Study Group; ESR, erythrocyte sedimentation rate; EUSTAR, The European Scleroderma Trials and Research group; F-AnxV(−), Annexin V non-binding; FASSc, fibrosing alveolitis associated with systemic sclerosis; FEV, forced expiratory volume; FKN, fractalkine; FNG, fibrinogen; Fli1, friend leukemia integration factor 1; Fra-2, fos-related antigen-2; FVC, forced vital capacity; F2IP-M, tetranor-dicarboxylic acid metabolite of F2-isoprostanes; F1 + 2, prothrombin fragments 1 + 2; fVIII/vWF Ag, factor VIII/von Willebrand factor antigen; Gal3, galectin 3; GLUT-1, glucose transporter 1; GPA, granulomatosis with polyangiitis; GRO-α, growth-regulated oncogene-alpha; GVHD, graft-versus-host disease; HC, healthy controls; HDEC, human dermal endothelial cells; HMVEC, human microvascular endothelial cells; HGF, hepatocyte growth factor; HRC, hypertensive renal crisis; HUVEC, human umbilical vein endothelial cells; ICAM, intercellular adhesion molecule; IF, immunofluorescence; IFI16, gamma-interferon-inducible protein IFI-16; IFN-γ, interferon gamma; Ig, immunoglobulin; IL, interleukin; IP, interstitial pneumonia; iNOS, inducible NO synthase; JAM, junctional adhesion molecule; KDR, kinase insert domain receptor; KLK, human tissue kallikrein; LMP, leukocyte-derived microparticle; Lp(a), lipoprotein (a); MAC, membrane attack complex of complement; MC, mast cells; MCP, membrane cofactor protein; MDMP, monocyte-derived microparticle; Mesh, medical subject heading; MIF, macrophage migration inhibitory factor; MMP, matrix metalloproteinases; MMT, mesenchymal-to-mesenchymal transition; MPs, microparticles; mRNA, messenger ribonucleic acid; MRSS, modified Rodnan skin thickness score; MVD, microvessel density; MVEC, microvascular endothelial cells; Nb, number; NEP, neutral endopeptidase; NIH, national institute of health; NO, nitric oxide; NOS, nitric oxide synthase; NOx, total nitrate and nitrite; NVC, nail fold videocapillaroscopy; OA, osteoarthritis; OPG, osteoprotegerin; OSM, oncostatin M; PAI, plasminogen activator inhibitor; PAP, pulmonary artery pressure; PCs, pericytes; PDGF (−BB), platelet derived growth factor (−BB); PDMP, platelet-derived microparticle; PEDF, pigment epithelium-derived factor; PECAM, platelet endothelial cell adhesion molecule; PH, pulmonary hypertension; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PL, phospholipids; PlGF, placental growth factor; PRP, primary raynaud phenomenon; PS, phosphatidylserine; PSS, progressive systemic sclerosis; PTX3, pentraxin 3; RA, rheumatoid arthritis; RANTES, regulated on activation normally T cell expressed and secreted; RAS, renin-angiotensin system; RBP4, retinol binding protein-4; RF, rheumatoid factor; RhoA, GTPase Ras homolog gene family-member Ab; RNAse, ribonuclease; ROCKS, rho-associated creatine kinases; ROS, reactive oxygen species; RP, raynaud phenomenon; RT-PCR, reverse-transcriptase polymerase chain reaction; RVSP, right ventricular systolic pressure; sCD40L, soluble cluster of differentiation-40 ligand; SCF, stem cell factor; SDF-1, stromal cell-derived factor 1; sENG, soluble endoglin; sFKN, soluble fractalkine; sGP130, soluble glycoprotein 130; sIL, soluble interleukin; sIL-2R, soluble IL-2 receptor; sIL-6R, soluble IL-6 receptor; siRNA, small interfering RNA; SLE, systemic lupus erythematosus; α-SMA, alpha smooth muscle actin; SM22α, transgelin; SNAIL-1, transcriptional repressor zinc finger protein; SPARC, secreted protein, acidic and rich in cysteine; SRC, scleroderma renal crisis; SSc, systemic sclerosis; sTie1, soluble tyrosine kinase 1; sTie2, soluble tyrosine kinase 2; ST2, IL-1 receptor-related protein; sVEGF, soluble vascular endothelial growth factor; TAT, thrombin-antithrombin; TBARS, thiobarbituric acid reactive substances; β-TG, beta-thromboglobulin; TGF-β, tumor growth factor beta; TIMP, tissue inhibitor of metalloproteinases; TLR, toll-like receptors; TNF-α, tumor necrosis factor alpha; TM, thrombomodulin; tPA, tissue type plasminogen activator; TRAIL, tumor necrosis factor related apoptosis-inducing ligand; TSLP, thymic stromal lymphopoietin; TSP-1, thrombospondin 1; TXAR, thromboxane A2 receptor; uPAR, urokinase-type plasminogen activator receptor; U-II, urotensin-II; VA, alveolar volume; VC, vital capacity; VCAM, vascular cell adhesion molecule; VE-cadherin, vascular endothelial cadherin; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; VSMC, vascular smooth muscle cells; vWF, von willebrand factor.

* Corresponding author.
E-mail address: yora.mostmans@chu-brugmann.be (Y. Mostmans).
[1] Present address: Department of Immunology and Allergology (CIA) Centre Hospitalier Universitaire (CHU) Brugmann, Université Libre de Bruxelles (ULB), Van Gehuchtenplein 4, 1020 Brussels, Belgium.

http://dx.doi.org/10.1016/j.autrev.2017.05.024

ARTICLE INFO

Article history:
Received 8 April 2017
Accepted 13 April 2017
Available online 29 May 2017

Keywords:
Biomarker
Endothelial cells
Systemic sclerosis
Systematic review
Vasculopathy
EULAR study group on microcirculation in Rheumatic Diseases

ABSTRACT

Introduction: Systemic sclerosis (SSc) is an autoimmune connective tissue disorder characterized by fibroproliferative vasculopathy, immunological abnormalities and progressive fibrosis of multiple organs including the skin. In this study, all English speaking articles concerning the role of endothelial cells (ECs) in SSc vasculopathy and representing biomarkers are systematically reviewed and categorized according to endothelial cell (EC) (dys)function in SSc.

Methods: A sensitive search on behalf of the EULAR study group on microcirculation in Rheumatic Diseases was developed in Pubmed, The Cochrane Library and Web of Science to identify articles on SSc vasculopathy and the role of ECs using the following Mesh terms: (systemic sclerosis OR scleroderma) AND pathogenesis AND (endothelial cells OR marker). All selected papers were read and discussed by two independent reviewers. The selection process was based on title, abstract and full text level. Additionally, both reviewers further searched the reference lists of the articles selected for reading on full text level for supplementary papers. These additional articles went through the same selection process.

Results: In total 193 resulting articles were selected and the identified biomarkers were categorized according to description of EC (dys)function in SSc. The most representing and reliable biomarkers described by the selected articles were adhesion molecules for EC activation, anti-endothelial cell antibodies for EC apoptosis, vascular endothelial growth factor (VEGF), its receptor VEGFR-2 and endostatin for disturbed angiogenesis, endothelial progenitors cells for defective vasculogenesis, endothelin-1 for disturbed vascular tone control, Von Willebrand factor for coagulopathy and interleukin (IL)-33 for EC-immune system communication. Emerging, relatively new discovered biomarkers described in the selected articles, are $VEGF_{165}b$, IL-17A and the adipocytokines. Finally, myofibroblasts involved in tissue fibrosis in SSc can derive from ECs or epithelial cells through a process known as endothelial-to-mesenchymal transition.

Conclusion: This systematic review emphasizes the growing evidence that SSc is primarily a vascular disease where EC dysfunction is present and prominent in different aspects of cell survival (activation and apoptosis), angiogenesis and vasculogenesis and where disturbed interactions between ECs and various other cells contribute to SSc vasculopathy.

Contents

1. Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder characterized by fibroproliferative vasculopathy, immunological abnormalities and progressive fibrosis of multiple organs such as skin and lung [1]. Dysregulation of endothelial cell (EC) function within the vascular wall plays an important role in vascular remodeling associated with the fibroproliferative vasculopathy observed in SSc. Endothelial cell injury is proposed as a crucial initiating event leading to vascular remodeling with intimal proliferation of arterioles and capillary breakdown and finally, blood vessel occlusion [2–4]. Ongoing research continues to focus on the role of endothelial cells (ECs) in SSc vasculopathy and on identification of related biomarkers. This study, performed on behalf of the EULAR study group on microcirculation in Rheumatic Diseases, gives an overview on the large body of data of current research in this domain, obtained after systematically reviewing the literature.

2. Methods

2.1. Search strategy

A structured search on Pubmed, The Cochrane Library and Web of Science was performed without limitation on publication date to