Autoimmunity Reviews 15 (2016) 719–725

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

"Kill" the messenger: Targeting of cell-derived microparticles in lupus nephritis

Christoffer T. Nielsen [a], Niclas S. Rasmussen [a], Niels H.H. Heegaard [b,c], Søren Jacobsen [a,*]

[a] Copenhagen Lupus and Vasculitis Clinic, Centre for Rheumatology and Spine Diseases, Rigshospitalet, Copenhagen University Hospital, Denmark
[b] Department of Autoimmunology and Biomarkers, Statens Serum Institut, Copenhagen, Denmark
[c] Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark

ARTICLE INFO

Article history:
Received 26 February 2016
Accepted 2 March 2016
Available online 9 March 2016

Keywords:
Lupus nephritis
Apoptosis
Microparticles
Immune complexes
Electron dense deposits
Galectin-3-binding protein

ABSTRACT

Immune complex (IC) deposition in the glomerular basement membrane (GBM) is a key early pathogenic event in lupus nephritis (LN). The clarification of the mechanisms behind IC deposition will enable targeted therapy in the future. Circulating cell-derived microparticles (MPs) have been proposed as major sources of extracellular autoantigens and ICs and triggers of autoimmunity in LN. The overabundance of galectin-3-binding protein (G3BP) along with immunoglobulins and a few other proteins specifically distinguish circulating MPs in patients with systemic lupus erythematosus (SLE), and this is most pronounced in patients with active LN. G3BP co-localizes with deposited ICs in renal biopsies from LN patients supporting a significant presence of MPs in the IC deposits. G3BP binds strongly to glomerular basement membrane proteins and integrins. Accordingly, MP surface proteins, especially G3BP, may be essential for the deposition of ICs in kidneys and thus for the ensuing formation of MP-derived electron dense structures in the GBM, and immune activation in LN. This review focuses on the notion of targeting surface molecules on MPs as an entirely novel treatment strategy in LN. By targeting MPs, a double hit may be achieved by attenuating both the autoantigenic fueling of immune complexes and the triggering of the adaptive immune system. Thereby, early pathogenic events may be blocked in contrast to current treatment strategies that primarily target and modulate later events in the cellular and humoral immune response.
© 2016 Elsevier B.V. All rights reserved.

Contents

Abbreviations: ANA, antinuclear antibodies; CCP, cyclic citrullinated peptides; CRP, C-reactive protein; dsDNA, double-stranded DNA; EDS, electron dense deposits; G3BP, galectin-3-binding protein; GBM, glomerular basement membrane; HMBG-1, high mobility group box-1; IC, immune complex; IFN, interferon; ISN/RPS, International Society of Nephrology/Renal Pathology Society; LN, lupus nephritis; MP, microparticles; MBL, mannose-binding lectin; NETs, neutrophil extracellular traps; PAD, peptidylarginine deiminase; pDC, plasmacytoid dendritic cell; RA, rheumatoid arthritis; ROS, reactive oxygen species; RIP-3, receptor-interacting protein kinase-3; SLE, systemic lupus nephritis; TLR, Toll-like receptors; WHO, World Health Organization.

* Corresponding author at: Copenhagen Lupus and Vasculitis Clinic, Centre for Rheumatology and Spine Diseases, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, Copenhagen Ø DK-2100, Denmark. Tel.: +45 35 45 05 45 (mobile).
E-mail address: soeren.jacobsen.01@regionh.dk (S. Jacobsen).

http://dx.doi.org/10.1016/j.autrev.2016.03.009
1568-9972/© 2016 Elsevier B.V. All rights reserved.

1. Introduction

1.1. Lupus nephritis

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease with a heterogeneous disease presentation that may affect most organ systems. Some of the common manifestations include non-erosive polyarthritis, malar rash, hypersensitivity to sunlight, serositis, hematological abnormalities, central nervous system involvement, vasculitis, autoimmune thrombosis, and glomerulonephritis [1]. A common pathogenic denominator is the development of antinuclear autoimmunity, and more than ninety-five percent of SLE patients exhibit the serological hallmark of SLE, antinuclear antibodies (ANA) directed against chromatin-components such as double-stranded DNA (dsDNA) and nucleosomes, and ribonucleoproteins [2].

SLE primarily affects women in the fertile age with a female to male ratio of 9 to 1 [2]. Kidney disease in SLE, termed lupus nephritis (LN), is a frequent (30–40%) and severe manifestation [3]. LN often presents within the first years of disease and is an independent predictor of poor prognosis [3–5]. LN is linked to significant disease and treatment related morbidity and mortality and may lead to end-stage renal disease and renal transplantation [3,5]. Aggressive immunosuppressive treatment regimens are employed for the more severe, proliferative forms of LN, and these typically include prednisolone in combination with mycophenolate mofetil, cyclophosphamide, or azathioprine [6–9]. The response to induction treatment is often slow and unpredictable, and refractory disease is strongly associated with a poor renal outcome [6,8–10]. Twenty to sixty percent obtain complete or partial renal response within the first 6 to 12 months of induction therapy [6–8,11]. During subsequent maintenance therapy, 10–20% of the patients experience renal flares, progression to end-stage renal disease, and death [12,13]. Further, these immunosuppressive treatments are significant determinants of major infections in SLE patients [14]. Thus, there is a need for more efficient and less toxic treatment regimens. Major efforts are currently undertaken exploring new treatment strategies that primarily target IFN-α signalling, T- and B-cells, cytokines and chemokines, or their receptors [15,16]. These strategies primarily target the cellular and humoral arms of the immune system and not the sources of autoantigens that trigger the cellular and humoral immune system to a sustained state of autoimmunity.

2. Origin of immune complex deposits in lupus nephritis

In SLE, ICs are found in the basement membrane of most organs, particular in the skin and the glomerular basement membrane (GBM) in the kidney. These ICs are found in the mesangium or the subendothelial and the subepithelial spaces and can be identified as electron dense structures (EDS) in the GBM by electron microscopy in LN biopsies (Fig. 1) [15,17,18]. While the occurrence of ICs and EDS is recognized as early important pathogenic events, the mechanisms behind their occurrence are still elusive as well as the events leading to the progression from mesangial to the membrano-proliferative lesions. Histopathologically, LN is classified based on the glomerular pathology as minimal mesangial (class I), mesangial proliferative (class II), focal proliferative (class III), diffuse proliferative (class IV), membranous (class V), and advanced sclerotic (class VI) according to the classification criteria by the World Health Organization (WHO) and International Society of Nephrology/Renal Pathology Society (ISN/RPS) [15,19]. Early in LN pathogenesis, ICs deposit in the mesangial matrix and activate the complement system and engage with Fc-receptors and Toll-like receptors (TLRs) on/in mesangial cells triggering the release of cytokines and chemokines that recruit infiltrating immune cells that further promote inflammation, endothelial activation, cellular proliferation and tissue damage [15,16,18]. Supposedly, ICs deposit from the circulation and/or form *in situ* as a result from binding of autoantibodies to locally formed autoantigens in the kidney (Fig. 1, II) [18,20,21]. Past data favor that nuclear antigens, including chromatin, become accessible *via* apoptosis and delivery by the bloodstream, rather than *via* local apoptotic processes in the glomeruli [18,21,22]. The degree of local apoptotic activity in the kidney is minimal, and chromatin without autoantibodies has not been detected, supporting that the autoantigens are more likely to derive from the circulation (as part of ICs) than from local apoptotic cells in the kidney (Fig. 1, II-C) [20,21]. Also, previous notions of unspecific binding of chromatin to GBM through interactions with GBM proteins or based on electrostatic binding through DNA have been more or less abandoned [21]. Altogether, the available data suggest that the majority of ICs in the EDS in LN kidneys originate from circulating ICs. The extracellular autoantigens fueling these pathogenetic processes may become available in subcellular particles (microparticles, MPs) derived from apoptotic cells or from activated/dying neutrophils (neutrophil extracellular traps, NETs). These particles carry many bioactive molecules, and the presentation of autoantigens in particles modulates the interaction with other cells, other particles, and the extracellular matrix and, thus, is highly likely to influence the IC deposition and immune cell triggering in LN. Accordingly, it is important to clarify the origin and composition, in particular, the surface characteristics and functional capabilities of the particles, to identify new candidate drug targets in LN [23].

3. Dying cells as sources of extracellular autoantigens in SLE

A characteristic feature of SLE is the loss of immunological tolerance against self and the occurrence of autoantibodies against nuclear components, antinuclear antibodies [2]. It is believed that an increased production of type I interferons (IFNs) prime and promote the triggering of autoreactive T- and B-cells by autoantigens from improperly cleared apoptotic cells and activated neutrophils and hence the formation of autoantibodies and ICs [24]. The linking of the development of SLE with defective clearance of dying cells and the exposure of nuclear autoantigens on apoptotic cell surface blebs (MPs and apoptotic bodies) fostered the notion that dying cells could be major endogenous sources of autoantigens triggering antinuclear autoimmunity in SLE [25–27]. It is now recognized that, besides apoptosis, other types of cell death, NETosis, necrosis, and necroptosis may also serve as sources of extracellular autoantigens [25,27–30]. Convincing evidence linking apoptosis and SLE have thus accumulated over the years, while the connection between the release of neutrophil extracellular traps (NETs) and SLE is still being uncovered.

In SLE patients, several different innate clearance deficiencies have been identified, both in opsonising molecules such as C1q, mannose-binding lectin (MBL), and C-reactive protein (CRP), in extracellular DNA degradation (DNase1), and in professional phagocytes [25,27,31–33]. Several of these deficiencies have been replicated in murine lupus models, e.g., monozygotic C1q deficiency [31,32]. Normally, an apoptotic cell is opsonized and phagocytosed rapidly and in an immunologically silent manner [34]. However, if clearance is compromised, apoptosis is allowed to progress into later stages of apoptosis and secondary necrosis, which incites inflammation [35,36]. The highly active enzymatic processes during apoptosis drive the cell dismantlement [34]. If clearance is delayed, this enzymatic milieu in apoptosis (caspases, reactive oxygen species (ROS), peptidylarginine deiminase (PAD), and more) is a powerful generator of neo-antigens by a myriad of autoimmunogenic post-translational protein modifications [37–39]. During this, the chromatin is fragmented and relocated into small surface blebs (here collectively termed microparticles) and bodies together with other co-stimulatory proteins from the nucleus (e.g., high mobility group box-1 (HMBG1)) and the endoplasmic reticulum [40–44]. Ultimately, the particles are released to the extracellular environment [40,42,44,45]. Several *in vitro* studies demonstrate that lupus autoantigens are displayed on the surface of apoptotic-derived MPs and that anti-dsDNA and anti-histone antibodies from SLE sera bind to these, and that this binding can be reduced by DNase and RNase treatment [29,35,42,46,47]. The notion that such excess

Download English Version:

https://daneshyari.com/en/article/3341349

Download Persian Version:

https://daneshyari.com/article/3341349

Daneshyari.com