THE SIGNIFICANCE OF ENDOTHELIAL DYSFUNCTION IN HEMORRHAGIC VASCULITIS

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Abstract

Immunoglobulin A (IgA) vasculitis (IgAV), also known as Henoch-Schönlein purpura, is the most common form of childhood vasculitis. It is characterized by cutaneous hemorrhage, resulting from red blood cell leakage into the skin or mucosae, possibly caused by damage to small blood vessels. These acute symptoms usually disappear without treatment. Endothelial cells are distributed on the inner surfaces of blood vessels and lymphatic vessels, and have important functions in metabolism and endocrine function, as well as being the primary targets of external stimuli and endogenous immune activity. Injury to endothelial cells is a feature of IgA vasculitis. Endothelial cell damage may be related to the deposition of immune complexes, the activation of complement, inflammatory factors, and chemokines, oxidative stress, hemodynamics, and coagulation factors. Both epigenetic mechanisms and genetic diversity provide a genetic background for endothelial cell injury. Here, research on the role of endothelial cells in allergic IgA vasculitis is reviewed.

Key words: endothelial cells, vasculitis, inner surfaces, hemodynamicshemodynamics, system of complement, vascular endothelial injury, metabolomics markers, gene polymorphisms, immunoglobulin A vasculitis.

Immunoglobulin A (IgA) vasculitis (IgAV) is a systemic disease typified by leukocyte burst vasculitis, involving the deposition of capillaries and IgA immune complexes (Pillebout and Sunderkötter, 2021). Over 90% of IgAV patients are below the age of 10 (Gardner-Medwin et al., 2002; Yang et al., 2005; Leung et al., 2020). Epidemiological studies have shown that the incidence of IgAV is higher in Asians than in Caucasians and Africans (Gardner-Medwin et al., 2002). Renal injury, known as IgA vasculitis with nephritis (IgAVN), is a major manifestation in IgAV, with potentially fatal outcomes. During the first 4–6 weeks of IgAV onset, about 40% of children with IgAV may develop IgAVN (Saulsbury, 2010), and persistent purpura, severe abdominal symptoms, and older age are three risk factors for IgAVN (Buscatti et al., 2018). It is important to consider IgAV in clinical diagnosis, differential diagnosis, and treatment. Understanding the pathogenetic mechanism of IgAV is necessary for the provision of suitable treatment and medication, and this involves investigation of the association between vascular endothelial injury and IgAV.

Endothelial cells (ECs) are flat cells that form a highly differentiated monolayer on the inner surfaces of blood and lymphatic vessels. ECs have vital metabolic and endocrine functions in the human body. They are responsible for maintaining vascular permeability, stability of circulation, and anticoagulation, and are also the primary targets of attack by external stimuli and immune complexes (Yang et al., 2002; Cardinal et al., 2018). Injury to ECs is the first step in the development of a variety of vascular conditions, such as atherosclerosis (Kim et al., 2021), diabetic nephropathy (Mahdy et al., 2010), and hypertension (Li et al., 2021). Recent evidence has linked EC injury to the pathogenesis of IgAV, together with the development of proteinuria. This can lead to glomerular sclerosis, renal interstitial fibrosis, and damaged renal function. Matrix deposition is a pathological outcome and contributes to the formation of vascular lesions; this includes the deposition of immune complexes, metabolites, and enzymes such as oxidases and proteases, and is closely related to immune vascular damage. Matrix deposition is coordinated by the complement system, inflammation, the immune response, and metabolic abnormalities, in association with genetic polymorphism, and leads to the replacement of normal tissue. This replacement leads to abnormal cellular respiration and renal vascular hypoxia, with an increase in reactive acidic products, promoting the contraction of vascular endothelial cells and the widening of the inter-cellular spaces, leading to hematuria and renal fibrosis in a vicious circle that eventually results in kidney failure. In this review, we discuss EC injury in terms of complement activation, the formation of IgA1 immune complexes, chemotactic and inflammatory cytokines (Heineke et al., 2017), coagulation factors, epigenetics, and genetic polymorphisms, amongst other factors, in the pathogenesis of IgAV.

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Immunoglobulin A-Containing Immune Complexes

In IgAV, galactose-deficient IgA1 (Gd-IgA1) can be detected not only in the serum but also in the skin and kidney tissue (Neufeld et al., 2019; Oni and Sampath, 2019; Zhang et al., 2020), and IgA1-containing immune complexes, especially IgA1 accumulation in vessel walls, promote the development of IgAV. A multi-hit hypothesis is generally considered to illustrate the role of Gd-IgA1 in the pathogenesis of IgAV. IgA is a major class of immunoglobulins present in mucosal secretions where they are closely involved with mucosal immunity. There are two IgA subclasses, IgA1 and IgA2, with approximately 90% of circulating IgA monomers belonging to IgA1. The hinge region of the IgA1 molecule contains three to six O-glycosylation sites allowing the addition of Gal-GalNAc disaccharides. These glycosylated Gd-IgA1 proteins auto-aggregate or bind to IgG molecules that recognize galactose-deficient IgA. These immunoglobulin complexes may be too large to access the space of Disse in the liver and are, therefore, able to avoid coming into contact with hepatic receptors

and can thus avoid degradation by hepatic cells. The IgA1 complexes thus accumulate in the circulation where they bind and activate FcαR1 transmembrane receptors on ECs, forming a soluble IgA1-sCD89 complex (van Zandbergen et al., 1999). This induces a widespread pro-inflammatory reaction involving the recruitment of neutrophils, activation of downstream signaling pathways, the release of neutrophil extracellular traps (NETs) resulting in the induction of NETosis and elevation of the levels of reactive oxygen species (ROS). Antibody-mediated cytotoxicity may also occur, together with cytokine and chemokine secretion, leading to EC injury (Aleyd et al., 2014; Heineke et al., 2017; Takeuchi et al., 2021). Furthermore, the activation of FcaR1s triggers the release of leukotriene B4 (LTB4), which activates and attracts neutrophil migration, forming a feedback loop (van der Steen et al., 2009). The pro-inflammatory cytokine, tumor necrosis factor-alpha (TNF-α), which is released by neutrophils, can activate ECs, inducing them to expose the hidden β2-glycoprotein I antigen (β2GP I) (Kim et al., 2021). Recognition of anti-endothelial cell antibodies (AECA) in combination with β2GP I activates the MEK/REK signaling pathway, along with the release of IL-8 and chemokines that attract polymorphonuclear leukocytes and monocytes (Yang et al., 2006, 2012). Pathogens, such as bacteria or viruses, induce similar IgA activities that are able to crosslink with ECs to propagate downstream signals. IgA1 complexes also stimulate mesangial cells through the transferrin receptor CD71 to trigger both proliferation and matrix production, leading to the release of angiotensin II, nitric oxide synthase, and cytokines, which appear to play key roles as direct or indirect effectors of EC damage by triggering acute and chronic inflammatory reactions (Chen et al., 1994; Novak et al., 2012).

It has been found that the sera of patients with active IgAV can induce the production of the chemokines CCL5, CXCL16, and CXCL1, as well as promote migration in dermal microvascular ECs and the human HL-60 leukemic and THP-1 monocytic cell lines (Chen et al., 2011a). It has also been found that patients' sera promoted the translocation of nuclear factor-κB (NF-κB) p65 to the nucleus and stimulated phosphorylation of the extracellular signal-regulated kinase ERK1/2 protein. These findings indicate that sera from patients with active IgAV may damage ECs and stimulate chemokine secretion through the NF-κB and ERK1/2 pathways (Figure 1). Yuan et al. (2014) observed upregulation of the pro-apoptotic protein Bax and downregulation of the anti-apoptotic protein Bcl-2 in ECs cultured with IgA1 isolated from IgAV patients. This suggests that IgA1 can induce EC apoptosis, which may be linked to the vascular endothelial injury seen in IgAV. This IgA1-induced apoptosis of ECs may occur through the activation of apoptotic cell protease activator-1 and pro-proteogen-9, forming apoptotic bodies and reducing the downstream effectors, cysteine proteases 3, 6, and 7 (Steinberg et al., 2007). In summary, IgA1-containing immune complexes can induce inflammatory reactions by activating

inflammatory signaling pathways and recruiting neutrophils, together with regulating the expression of apoptosis-related proteins, all of which could ultimately result in EC injury and promote the development of IgAV.

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