activation of dendritic cells. They also decrease IL-2 production and IL-2 receptor expression in activated T cells; induce regulatory T cells; and suppress the activation, proliferation, chemotaxis, and antibody production of B cells.9 These immunosuppressive actions of BMSC can be further understood; however, some speculate that secreted, soluble factors suppress inflammation and mediate the beneficial actions in tissue repair.

What are the cellular targets of this conditioned medium? Presumably they are renal stem cells or progenitor cells. Kidney stem cells have been described in the renal papilla,10,11 Bowman’s capsule,12 and the S3 segment of the proximal tubule.13–15 CD133+ stem cells in or near Bowman’s capsule can differentiate into epithelial and endothelial cells. Oct4-, Pax-2+, and CD90-expressing cells in the proximal tubules differentiate into tubular cells.15 Multipotent renal progenitor cells expressing Pax-2, Sca-1, and Musashi-1 have been isolated from microdissected S3 segments.14 Taking advantage of the slow cycling of stem cells, a population of proximal tubular epithelial cells have also been isolated in important experiments.15

Further studies, of course are necessary to identify the beneficial effects of soluble factors in the condition medium of BMSC on kidney repair, and confirmatory experiments are needed in other models of acute kidney injury and experimental glomerulonephritis. For the future, more vertical research on mechanisms of kidney regeneration is needed, and a high priority should be placed on the identification of the therapeutic factors and target cells in and around the nephron.

DISCLOSURES

None.

REFERENCES


See the related article, “Stromal Cells Protect against Acute Tubular Injury via an Endocrine Effect,” on pages 2486–2496.

Anti–Endothelial Cell Antibodies in Vasculitis

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Anti–endothelial cell antibodies have been described in association with small vessel systemic vasculitides since the late 1980s. Opinions have waxed and waned about their importance. An early study from this group suggested they were present in 59% of 168 samples from patients with Wegener’s granulomatosis or microscopic polyangiitis, while a contemporaneous study by Varagunam using a similar patient cohort.
(43 microscopic polyangiitis, 27 Wegener’s) suggested that anti–endothelial cell antibodies were not a major antibody system, being present in 2% of patients with polyangiitis and 19% with Wegener’s; both studies relied on ELISA with human umbilical vein endothelial cells (HUVEC) as a detection system. Other groups have contributed to this debate, some demonstrating a relationship with clinical disease activity. A recent study employing 173 serum samples from patients with active Wegener’s suggested a 20% incidence, similar to the Varagnam study. Techniques and cell source have been variously suggested as the reason for the lack of consensus, although macrovascular HUVEC have been the main cellular source underpinning detection assays. It has been suggested that cyttofluorimetry is a more physiological technique for testing anti–endothelial cell antibodies binding to endothelial cells than ELISA.

The study by Holmen and colleagues in this issue of JASN cuts across this divide by using human kidney microvascular endothelial cells (HKMEC). This group reported previously that samples from 28 Wegener’s patients (18 active disease; 4 renal limited disease) contained a high incidence of anti–endothelial cell antibodies reactive with HKMEC (71%), pulmonary microvascular endothelial cells (25%), and nasal endothelial cells (61%), compared to only 7% detected with HUVEC. For the present study, 13 of these samples were selected for further analysis after depletion of anti-neutrophil cytoplasm antibodies by adsorption with immobilized proteinase-3. Binding of anti–endothelial cell antibodies to HKMEC elicited a calcium flux, secretion of the chemokines MCP-1 and GCP-2 (but not IL-8 or GRO-α), and upregulation of the ligands MHC-class I related antigen A (MICA) and vascular adhesion protein-1 (VAP-1). Signal transduction via the SAPK/JNK pathway appeared to be important in increased expression of MCP-1, GCP-2, and MICA, but not VAP-1, because specific inhibition of SAPK/JNK inhibited these effects, as well as inhibiting the phosphorylation of the downstream transcription factors c-Jun and ATF-2. In contrast to the current study, Yazici found that signalling induced by anti–endothelial cell antibodies was not related to JNK activation. Both groups found that anti–endothelial cell antibodies also activated NFκB.

Functionality has been attributed to anti–endothelial cell antibodies with earlier studies showing upregulation of E-selectin, VCAM-1, and ICAM-1, possibly via mechanisms involving release of IL-1 from endothelial cells and an autocrine activation loop. IL-6 secretion may also increase after anti–endothelial cell antibody stimulation. The Holmen study does not rule out the possibility of an autocrine loop being responsible for initiation of the signal that leads to NFκB activity. Additionally it is known that IgG purified from patients may be contaminated by cytokines if high levels had originally been present in serum and such contaminating cytokines can lead to similar intracellular signals.

The Holmen study takes a fresh look at functionality by focusing on MICA and VAP-1, which are shown to be upregulated in kidney glomerular and tubulointerstitial microvasculature. However, the study stopped short of demonstrating unequivocal links to endothelial cell damage, although the potential was acknowledged for engagement of cytotoxic T cells or natural killer cells via MICA, and production of hydrogen peroxide, aldehydes, and ammonium through the enzymatic activities of VAP-1. Others have suggested injurious effects of anti–endothelial cell antibodies via complement-mediated lysis or antibody-dependent cellular cytotoxicity and, while such mechanisms can be demonstrated in vitro, their relevance in vivo to a pauci-immune condition such as small vessel systemic vasculitis is questionable. More intriguing are demonstrations of ability of anti–endothelial cell antibodies, for example those with putative recognition of Hsp60, to induce endothelial cell apoptosis and it would be interesting to know whether the anti–endothelial cell antibodies isolated from Wegener’s patients by Holmen et al. have this capability, because these investigators provided evidence of increased levels of circulating endothelial cells in serum of patients with vasculitis.

So, are anti–endothelial cell antibodies directed against microvascular endothelial cells, particularly within the kidney, a cause of vasculitis? Certainly, fascinating functional activities appear to have been demonstrated by the Holmen study, with the tantalizing possibility that at least some of the antibodies are directed against predominantly microvascular-expressed antigens and the molecular weights, but not the identities, of three antigens expressed by HKMEC were defined. Nevertheless, some words of caution are needed. First, the observations have been based on a relatively small number of Wegener’s samples, so to generalize is difficult at this stage. Second, the HKMEC used to detect binding of anti–endothelial cell antibodies were likely from a mixture of glomerular and peritubular sites, were from a limited number of donor organs (three), and no allowance was made for potential alloantigens. That alloantigens can activate endothelial cells is well recognized within transplantation where HLA-specific antibodies can activate endothelial cell NFκB.

The possibility that anti–endothelial cell antibodies contribute to amplification of endothelial injury may still be relevant, even if such antibodies do arise as a secondary event to endothelial injury. Initial endothelial injury may result from pathogenic processes that may be unleashed during development of the vasculitic process itself, for example, by proteolytic enzymes released from neutrophils after their inappropriate activation by anti-neutrophil cytoplasm antibodies. It is also likely that sequestered viral infections, such as cytomegalovirus that can replicate within endothelial cells, may become relatively more activated during the development of an autoimmune response and particularly after introduction of immunosuppression. That cytomegalovirus can induce anti–endothelial cell antibodies is recognized. Once present, anti–endothelial cell antibodies have the potential to inhibit potent anti-inflammatory mechanisms. Nara et al. showed antibody binding to endothelial-expressed thrombomodu-
lin and postulated that this inhibited protein C activity. The further activation of NFkB in this system could suppress the expression of the thrombomodulin gene and further decrease anti-inflammatory mechanisms.¹⁵

DISCLOSURES

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REFERENCES


See the related article,”Anti–Endothelial Cell Autoantibodies Selectively Activate SAPK/JNK Signalling in Wegener’s Granulomatosis,” on pages 2497–2508.

Fabry Nephropathy and the Case for Adjunctive Renal Therapy

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Proteinuria in advanced Fabry nephropathy does not respond to enzyme replacement therapy (ERT) alone using recombinant agalsidase-α or -β. In this issue of JASN, Tahir et al.¹ describe a series of patients who had Fabry nephropathy and achieved sustained reductions in proteinuria and stabilization of kidney function after treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) combined with ERT. Because proteinuria has emerged as an important risk factor for progression of kidney disease and ACEI/ARB therapy is effective in lowering proteinuria in other renal diseases, the result by Tahir et al. is important, incremental news for this group of patients.

Replacement of a deficient enzyme with recombinant protein has been a turning point for the clinical management of lysosomal storage disease. Gaucher disease in the 1990s was the first lysosomal storage disease for which ERT provided exceptional clinical results, and only after a few treatments over a