VLA-4 and its ligands: relevance to kidney diseases

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Summary. Alterations in cellular immunity have been implicated in many kidney diseases. The role of the adhesion molecule VLA-4 and its known ligands VCAM-1 and CS-1 have just begun to be evaluated in association with kidney diseases. VCAM-1 in human kidney is normally expressed in the Bowman’s capsule, in the proximal renal tubule, and in the vascular endothelium. Up-regulation of VCAM-1 expression is seen in many different forms of glomerulonephritis as well as in a mouse model of lupus nephritis. Up-regulation of VCAM-1 expression is observed in the renal allograft with acute cellular rejection, and correlates with areas of leukocyte infiltration and vascular inflammation. CS-1 may also be up-regulated in the rejecting kidney. Animal studies on cardiac transplantation demonstrate that blockade of VLA-4 or VCAM-1 can attenuate transplant rejection. Hemodialysis patients, known to have a cellular immunodeficiency, have increased levels of soluble VCAM-1 in their serum. There is increasing evidence that there are alterations in VLA-4, VCAM-1 and CS-1 in association with kidney diseases. Further studies will be required to delineate the role of these molecules in the immunopathogenesis of select kidney diseases and the possibility of intervening in these adhesion pathways to ameliorate clinical syndromes.
Introduction

Acute and chronic kidney diseases contribute significantly to morbidity and mortality. In the USA alone, there are 200,000 individuals with end-stage renal disease (ESRD), and the cost of their care is over 7 billion dollars per year [47]. Renal transplant recipients constitute about 25% of this population [47]. These figures do not even take into account the human and economic cost of acute renal failure (found in up to 5% of all hospitalized patients), and chronic kidney diseases that have yet to lead to total renal shut-down [24]. Progress in the understanding and treatment of kidney diseases will substantially benefit many patients as well as lessen the burden on the health care system. Although the etiology of most renal conditions is unknown, it is well established that perturbations in immunity contribute to the pathogenesis of many renal diseases, as well as continuing to affect patients with ESRD on dialysis or with transplants. The rapid emergence of information implicating leukocyte adhesion in many aspects of the immune response has recently generated considerable interest in exploring the role of leukocyte adhesion molecules in kidney diseases. There has been an explosion in the knowledge base and the number of adhesion molecules that have been discovered. In this brief review, we will attempt to focus on the VLA-4 adhesion molecule and its ligands in relationship to the kidney in health and disease. The reader is advised to refer to recent reviews that discuss other adhesion molecules in association with the kidney [5, 11, 37]. Due to the surge of literature in this field, we apologize in advance for possibly overlooking relevant publications.

VLA-4, VCAM-1, and CS-1

Prior to embarking on the relationships of VLA-4 with the kidney, a brief review of the biology of VLA-4 and its known ligands will help an uninitiated reader. VLA-4 is a beta (β)1 integrin, a member of the integrin superfamily of receptors which are heterodimeric transmembrane molecules that mediate cell-cell and cell-substratum adhesion [27]. The β1 integrin family members have been coined VLA proteins because of the "very late" appearance of these antigens on lymphocytes observed in early studies [22]. The alpha (α)4 subunit which combines with the β1 subunit to form α4β1, or VLA-4, was initially shown to be involved in lymphocyte homing to endothelial cells in Peyer's patches of the intestine [23]. The VLA-4 protein is found on lymphocytes, basophils, eosinophils and monocytes, but is notably absent on neutrophils [15]. The α4 subunit can also associate with an β7 subunit, a "promiscuity" between an α subunit of one family with a β subunit of another that is being increasingly recognized among integrins [43]. In addition to the role of VLA-4 in cell adhesion and migration, it has been shown to be involved in cell signaling, evidenced by a co-stimulatory role with the T cell receptor leading to T cell activation [45]. Although most of the evidence has been obtained in vitro, signal transduction through VLA-4 has been suspected to mediate an in vivo model of allergic asthma [40]. This is based on evidence that monoclonal antibodies (mAb) to VLA-4 significantly attenuated the early and late airway hyper-reactivity to antigen challenge in rats, despite having minimal effects on leukocyte migration into the airways.

The vascular cell adhesion molecule-1 (VCAM-1), the best established ligand for VLA-4, is a cytokine-inducible molecule on endothelium and is a member of the immunoglobulin supergene family [15]. VCAM-1 has subsequently been shown