VLA Integrin Expression in Normal and Diseased Human Kidney: How Should We Interpret Immunohistochemical Data?

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Dear Sir,

We were interested to read the article by Kanahara et al. [1] in the January issue of Nephron, relating to the distribution of extracellular matrix proteins and integrins in IgA nephropathy and agree that this is an area worthy of further investigation. Undoubtedly, the interactions between glomerular cells and their matrix are of fundamental importance to the pathogenesis of IgA disease and many other glomerulopathies [2]. Similarly, adhesion molecules play a pivotal role in these interactions [3, 4]. However, we feel that there are several methodological and interpretive issues in the paper which require clarification.

The antibody referred to as targeting the 'fibronectin receptor' is, in fact, directed against the β_1 -chain of the VLA integrins. As such it will detect the presence of all VLA integrins (VLA 1-6 and $\alpha_v\beta_1$) which act as receptors for a variety of ligands (see table 1) in addition to fibronectin. Although this is noted in the penultimate paragraph the use of 'fibronectin receptor' is misleading, particularly as this term was originally used to refer specifically to the $\alpha_5\beta_1$ integrin [5] -though later work confirms that other VLA integrins share this property [6]. In a similar way the 'vitronectin receptor' referred to is the $\alpha_v\beta_3$ integrin which, again as noted, serves as a receptor for a variety of ligands not solely vitronectin. This may partially explain the lack of correlation between the presence of vitronectin and the expression of this molecule though it may of course merely indicate that the vitronectin present has oc-

Table 1. Summary of molecular weights, ligands and main cell reactivity for the VLA integrins

Fig. 1. Normal human kidney stained with an anti- β_1 integrin monoclonal antibody (4B4 Coulter Clone 1/1,000) using the APAAP technique.

cupied the available binding sites thus blocking adherence of the monoclonal to the receptors. Perhaps more importantly we suggest that the histological interpretation of only the increased 'distribution', or extent, of fibronectin and the vitronectin and fibronectin receptors simply

reflects the increased distribution of mesangial matrix associated with proliferative glomerulonephritis. It seems logical that an expansion in matrix will result in an increase in the distribution of receptors associated with it. A more significant finding would be an increase in the intensity of staining for a given area of mesangium – this would suggest an upregulation of the receptors in this area rather than an increase in the area in which receptors might be detected. The key question which does not appear to be addressed fully is whether there is a true change in the expression of integrins and their ligands within the diseased mesangial matrix rather than just an increase in the amount of normal matrix. Similarly, it follows that the association of increased β_1 integrin expression with the clinical and laboratory parameters presented may simply reflect increased damage to the glomeruli (which itself was partly defined as including ‘increased mesangial matrix’). Our final concern is with the interpretation of the histological data presented in the paper. It is difficult to interpret the black and white plates presented, however in one case (fig. 6 of original article) the staining appears to be confined to the loop wall without significant mesangial staining as the authors suggest. In addition, we were surprised to note the limited staining pattern of the β_1 monoclonal on normal renal tissue (fig. 2a of original article). In our experience this antigen is strongly expressed on all three glomerular cells, the tubules, the extraglomerular vessels and in the interstitium (see fig. 1). Despite this we would agree that the role of adhesion molecules in glomerular disease deserves further study. Greater knowledge of the changes in the way in which glomerular cells interact in IgA disease will increase our understanding of this common condition and hopefully lead to new therapeutic developments in the future.

References

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