CHAPTER V

DISCUSSION AND CONCLUSION

Lupus nephritis (LN) is an autoimmune disease that is characterized by activation of inflammatory cells and immune complexes formation of glomeruli, vessels and tubules. The renal pathology of lupus nephritis is characterized by endothelial cells proliferation, small and medium-vessel lesions and diffuse immune-complex deposits. Located at glomerular podocytes and tubular epithelial cells, VEGF plays role in the formation and maintenance of glomerular capillary endothelial functions including glomerular permeability (8). Shulman *et al* showed the renal VEGF expression was reduced in two cases of SLE with diffuse proliferative glomerulonephritis (18). However, this finding was different from a report in LN patients with moderate renal failure (16). The functions of VEGF are 1) enhancing vascular angiogenesis, 2) increasing glomerular permeability and 3) leucocyte chemotaxis. The loss of VEGF could contribute to decreased blood supply and progressive renal damages (54). This study aimed to determine intra-renal VEGF mRNA and protein of lupus nephritis. We quest whether the severity of pathology could affect the VEGF levels and, if so, VEGF expression may be associated with the disease progression.

In this study, Intra-renal VEGF mRNA levels were decreased in lupus nephritis patients as compared with kidney donors (control). This finding is confirmed by immunohistochemistry that VEGF protein was decreased in podocytes and tubular epithelial cells. The intra-renal VEGF mRNA levels were inversely associated with the important histological parameters, including endocapillary proliferation, crescent formation and renal activity score. In the remnant kidney (RK) mice model, *Kung et al.* (13), showed that decrease VEGF expression was associated with intra-renal macrophage infiltration and loss of microvascular structures of the remnant kidney. The reduced VEGF eventually lead to progressive renal damages. Administration of VEGF in RK mice could reduce renal fibrosis and stabilize renal function (14). Many evidences

have shown the loss of peritubular capillaries in progressive renal disease in human (63, 71) and animal model (13, 72), and the impaired intra-renal circulations have attributed to renal fibrosis (71).

The correlation of decreased VEGF levels and crescent formation could be due to two reasons: 1) loss of glomerular podocytes, and 2). inflammatory cells infiltration. Firstly, previous report found urinary VEGF mRNA levels of active lupus nephritis patient was increased and could identify active class IV LN (5). The other groups reported increasing detachment of podocytes into urine of active lupus nephritis and associated with the severity (69) and the loss of renal function (68). Therefore, the loss of glomerular podocytes may be due to altered VEGF expression or vice versa. Secondly reason, decreased VEGF expression may be affected by the pro-inflammatory and chemoattractant cytokines such as MCP-1, MIP-1β, MIP-1α. These cytokines were found in association with crescentic formation and inflammatory infiltrating cells, such as monocytes/macrophage. (73-76).

The most interesting finding of this study is the association between VEGF levels and the short-term renal outcomes, including end-stage renal disease and doubling serum creatinine. Although, renal histological study is the best method of determining the severity of lupus nephritis, the current renal pathology scores are imprecise and have inter-observer variation. The molecular approach in this study show VEGF levels could be a potential prognostic marker. This result suggests that loss of VEGF expression may contribute to ESRD and doubling serum creatinine in lupus nephritis patients.

In conclusion, intra-renal VEGF mRNA and protein were decreased in active lupus nephritis. The levels were inversely associated with severe form of pathology, including endocapillary proliferation, glomerular crescent formation and high activity index. The decreased VEGF levels were associated with poor renal outcomes. This may lead to the novel molecular classification which may be complement to the current diagnostic method of renal biopsy.

Future prospects.

Further study of the specific cell types that produce VEGF in kidney tissue and urinary would elucidate the pathogenetic role of VEGF in progressive lupus nephritis.