CHAPTER I

INTRODUCTION

Background and Rationale

Systemic Lupus Erythematosus (SLE) is a prototypic autoimmune diseases characterized by the production of autoantibodies that affects to multi system disorder. The causes of diseases are indistinct but believe genetic and environmental factors have crucial role in SLE. Lupus occurs worldwide and affects females more than males (10:1), and some racial group, such as African americans and Hispanics, more commonly and severely than others **(1)**. Multi organs involvement in SLE are occurs, especially vital organs, such as nervous system, heart, lungs, blood system and kidneys.

Lupus nephritis (LN) is an autoimmune disease that involves kidneys, especially glomerulus. The presentations can range from asymptomatic urinary abnormalities to rapidly progressive renal failure leading to end-stage renal disease. LN is one of the most severe complications in SLE, occurring in up to 60% of patients with SLE. LN is one of the most leading causes of morbidity and mortality in systemic lupus erythematosus (SLE) **(2)**. The World health organization (WHO) has classified LN based on its severity into 6 groups (class I-class VI). Class IV LN patient is the most common and severe form. The incidence of class IV LN in Thai patients is higher than Caucasians **(3)**. Renal biopsy remains the gold standard for diagnosis of lupus nephritis **(4)**. Although most LN patients have clinical evidences of renal involvement (proteinuria, cellular cast in urine sediment), upto 20 % of patients have normal urinalysis. The renal biopsy study of this subgroup revealed pathology so-called *"silence lupus nephritis."* Many molecular diagnostic techniques are currently developed into diagnostic and prognostic tools. A number of studies have shown that mRNA levels potentially predict outcome and response to therapy in patients with renal disease. Previous study was quantify the urinary chemokine and growth factors mRNAs, including TGF-β, CXC

chemokine receptor-3 (CXCR-3), interferon-inducible protein-10 (IP-10) and vascular endothelial growth factor (VEGF), in LN patients by real-time PCR technique and the result suggested those level higher in LN patients than healthy control and could identify active class IV LN (5). In contrast, the detection for high level intra-renal mRNA of renal tissue repair molecules, fibronectin and transforming growth factor-β (TGF-β), were associated with less deterioration in renal function (6, 7). All togethers, both urinary mRNAs and intra-renal mRNAs may be useful for predicating renal outcome.

Vascular endothelial growth factor-A (known as VEGF) belongs to a family of multipotent cytokines. In the kidney, VEGF expression is most prominent in glomerular podocytes and in tubular epithelial cells. The roles of VEGF in kidney are still unclear but most evidences suggested that necessary for development of the glomerular filtration barrier and control vascular permeability (8, 9). VEGF is an interested molecule in renal diseases. In animal models indicated the function of VEGF on renal pathophysiology. The injected mice at postnatal with VEGF-blocking antibody (10) or soluble VEGF receptor chimeric protein (11) showed that glomerular capillary development was defected, and the glomerular number was also reduced. More recently, the generation mice to podocyte-specific VEGF deletion, mice that lacked all isoforms of VEGF died at birth with hydrops and renal failure, but podocytes-specific overexpression of the $VEGF_{164}$ isoform led to a severe glomerulopathy (12). The remnant kidney model for progressive renal disease showed decrease VEGF expression but increase TSP-1 expression and macrophage accumulation, which presented that correlate with the loss of microvascular (13). Remnant kidney model had reduced fibrosis and stabilizes renal function after treated with VEGF (14). Those previously evidence suggested the function of VEGF in damage renal. For several human renal diseases showed the correlation of VEGF expression and disease progression. Intra-renal expression of VEGF and its receptors showed up-regulate in experimental animals and humans with type-1 and type-2 diabetes. Inhibition of VEGF resulted in beneficial effects on the diabetes-associated renal changes, underlyng a deleterious role of VEGF in pathophysiology of diabetes nephropathy (15). Moreover, VEGF protein in plasma of SLE patients were higher than in healthy control (16, 17), as well as intra-renal VEGF

protein expression, especially class IV LN. However, decrease intra-renal VEGF mRNA in LN patients could be indicates in another finding. *Shulman et al* (18) described the diminish of VEGF mRNA and protein expression in various glomerular disease, including SLE glomerulonephritis, amyloidosis, diabetes and crescentic glomerulonephritis. In particular, SLE glomerulonephritis which were markedly reduce in number in the hypercellular glomeruli.

The renal pathology study is essential for prognostic and diagnostic of lupus nephritis. Furthermore, it may be useful for guiding patient treatment. VEGF may be associated with prognosis of lupus nephritis. We hypothesized that VEGF mRNA and protein expression may alter in kidney biopsy of lupus nephritis. It is interesting whether intra-renal VEGF expression could be associated with clinical outcomes.

Research Questions

Primary Question: Is there a difference between intra-renal VEGF mRNA and protein expression of lupus nephritis and kidney transplant donors ?

Secondary question: 1. Is there an association between intra-renal VEGF mRNA and protein expression and renal pathology ?

2. Can intra-renal VEGF mRNA levels be used to predict renal outcomes ?

Objectives

1. To determine the difference of intra-renal VEGF mRNA and protein in kidney biopsy of lupus nephritis and kidney transplant donors.
2. To determine an association between intra-renal VEGF mRNA and protein and renal pathology in lupus nephritis.

3. To evaluate the prognostic value of intra-renal VEGF mRNA in prediction of renal outcomes in lupus nephritis.

Hypothesis

Since VEGF plays an important role in progression of renal diseases, we hypothesized that VEGF mRNA and protein expression may alter in kidney biopsy of lupus nephritis. The intra-renal VEGF gene expression may be associated with renal outcomes such as worsening renal function or end-stage renal disease.