CHAPTER I

INTRODUCTION

1. Background and Rationale

Apoptosis is cellular balanced control during the development, expansion and death processes.[1] Apoptosis occurs in embryonic development,[2] for instance; transformation from webs to fingers, replacing of tadpole's tail with leg, etc. In addition, apoptosis can occur in normal conditions, for example; sloughing off death skin cells or intestinal tissues, atrophy of the prostate after castration,[3] death of mature granulocytes and sloughing off endometrium during menstruation,[4]etc.

It was found that all living organisms maintain a cellular balance between cell death and cell growth. Abnormal controlled mechanism results in the pathological conditions. If there is too little of cell apoptosis, this can cause various diseases such as cancer, virus infected condition and immunological diseases. If there is too much cell apoptosis, this also causes various diseases, viz. lymphocyte type $CD4^+$ found in immuno deficiency diseases, nervous degenerative diseases, various blood diseases, e.g., aplastic anemia, polycystic kidney disease and ischemia,[5] etc.

Unilateral ureteral obstruction (UUO) is also a condition that demonstrates an increase in cell apoptosis. It was found in several studies of obstructed rats [6] that apoptosis of tubular epithelial cell occurs with an increasing frequency due to malnutrition resulting from the decline in glomerular filtration rate . This decreased rate results in increasing level of

angiotensin II (Ang II) then stimulating growth factor or many related cytokine factors for cell survival.[7] The apoptosis of tubular epithelial cell has a significant bearing on the pathogenesis of kidney as it causes tubular atrophy and renal tissue loss in both human being and animals.[8] If the obstruction continues, it would lead to hydronephrosis and immediate or chronic renal failure.[9] Tubular cell apoptosis is decreased by treatment with angiotensin converting enzyme inhibitor (ACEI)[10] or angiotensin 1 receptor antagonist (ARA).[11]

Furthermore, the studies of immune cell features with UUO[12] have demonstrated an increased number of leukocytes infiltrated in renal tissue, especially macrophages and T lymphocytes, either cytotoxic T cell or T suppressors.[12] This occurs in cortex as well as in medulla after 4 hours, and reaches the peak at 24 hours post obstruction (10 fold above normal rats). However, the levels of circulating lymphocyte have not been observed. The collective mechanism of macrophages and lymphocytes in renal tissue is influenced by an increased level of Ang II during the course of UUO.[13] This increased level of Ang II can be observed either in renal tissue or in plasma.[14,15,16] In the study of chronic renal failure, an increased level of Ang II and reactive oxygen species (ROS) was also demonstrated.[17] The data showed an increase in circulating lymphocyte apoptosis but it declined after ARA treatment. However, the number of circulating lymphocyte in these patients did not observed. Furthermore, an ACEI treatment in chronic renal failure demonstrated an increased level of antioxidant enzyme.[18] Moreover, the study of children with nephrotic syndrome identified an enhancement in apoptosis of peripheral blood lymphocytes which influences abnormal function of T lymphocyte.[19]

At present, there is no study undergone regard to how the process of circulating lymphocyte apoptosis during UUO (with increased Ang II and ROS) including whether how the angiotensin inhibition (by ACEI or ARA) has any role on lymphocyte apoptosis in UUO conditions. Therefore, the present study aims to investigate these regards.

2. Research Questions

1. Do the number of circulating lymphocyte vary at different duration of UUO ?
2. Do the different duration of UUO have variant effect on circulating lymphocyte apoptosis ? And how angiotensin inhibition plays the role on such lymphocyte apoptosis ?

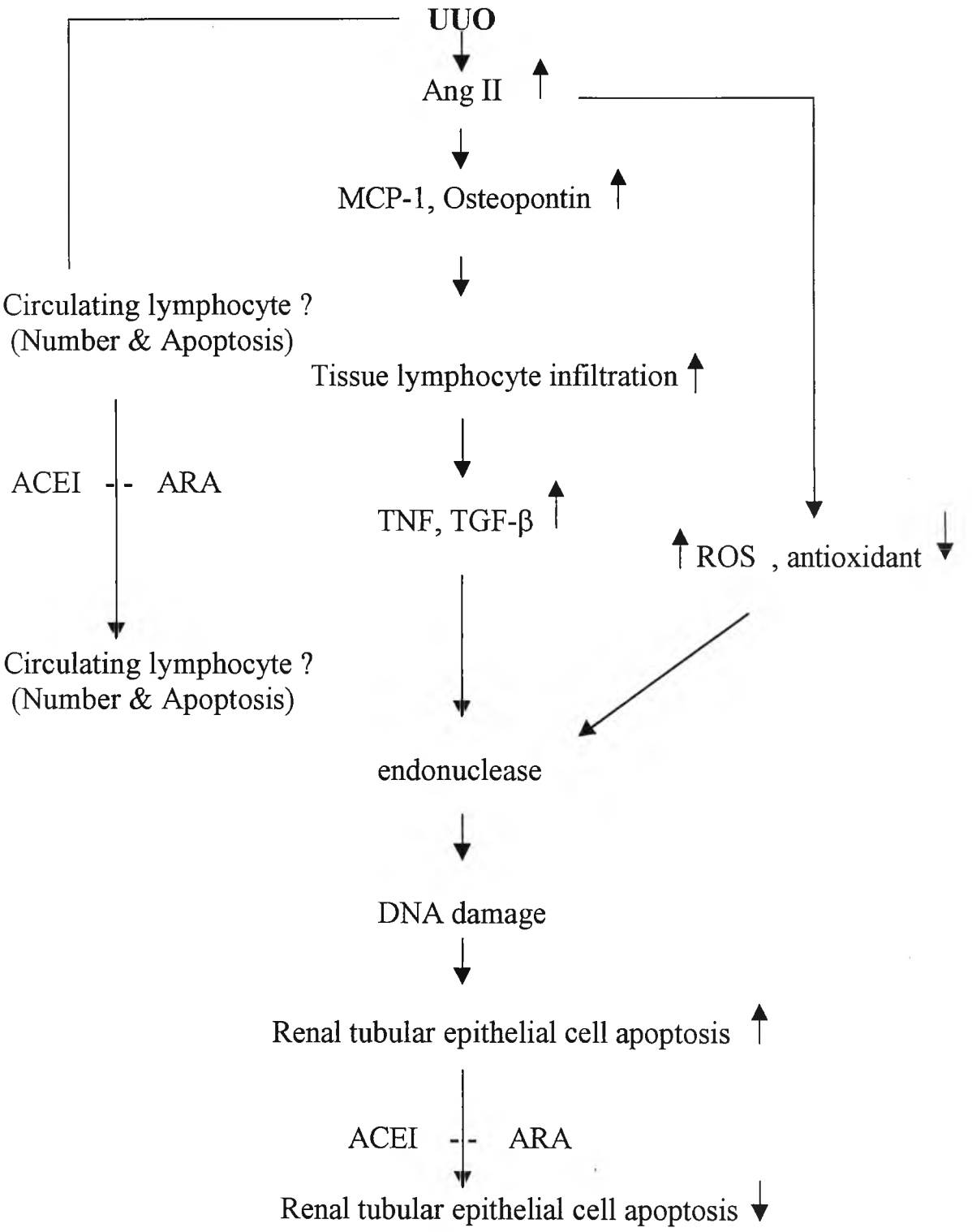
3. Objectives

1. To study the number of circulating lymphocyte in rats with 1- day to 7- day UUO.
2. To study the apoptosis of circulating lymphocyte of rats with 1- day and 7 - day UUO.
3. To study the role of angiotensin inhibition on circulating lymphocyte apoptosis of rats with 1 - day and 7 - day UUO.
4. To compare the effect of ACEI and ARA on circulating lymphocyte apoptosis of rats with 1 - day and 7 - day UUO.

4. Assumption

All rats used for the experiments were approved to make sure that they never had renal disease by means of blood urea nitrogen (BUN) level assessment. The rats with BUN levels below 30 mg % were further studied and collected data.

5. Conceptual Framework



Note : MCP-1 = Monocyte chemoattractant peptide-1

6. Key Words

Unilateral ureteral obstruction (UUO)

Apoptosis

Lymphocyte

Angiotensin

7. Operational Definition

$$\text{Apoptotic Index} = \frac{\text{The number of apoptotic cells x 100}}{\text{The total number of cells}}$$

8. Expected Benefit & Application

- Able to describe the process of circulating lymphocyte apoptosis in UUO condition.
- Be a guideline in describing changes in the number of circulating lymphocytes as well as their apoptosis in UUO condition with a treatment of ACEI or ARA.
- Be the fundamental information for a further research regarding immune system in UUO conditions.