TRAIL MEDIATED APOPTOSIS IN ARTHRITIS

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A thesis submitted to the University of Adelaide in the fulfilment of the requirements for the Doctor of Philosophy (Medicine)

2007

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CHAPTER I : LITERATURE REVIEW

I.1 INTRODUCTION

Arthritis is a term commonly used for diseases that target the joint. Diseases such as, Rheumatoid arthritis (RA), Osteoarthritis (OA), and spondyloarthropathy (SpA) are major inflammatory joint disorders found in the community and are the subject of this thesis.

RA is a common form of arthritis in the community with approximately 1% of all people in Western societies being affected (Emery *et al.*, 2001). The prevalence of rheumatoid arthritis has been reported to vary between 0.3 and 2% of the population in many studies. Some studies reported an estimated prevalence of 0.5% in Spain (Carmona *et al.*, 2002; Dubska *et al.*, 2005) while Symmons et al reported the prevalence of RA was 1.16% in women and 0.44% in men in the United Kingdom (Symmons *et al.*, 2002). In the United States Rasch et al (2003) reported the prevalence of RA to be about 2% of the population (Rasch *et al.*, 2003). In Asian populations, the prevalence varies from below 0.4% in China, Indonesia and Philipines to 0.75% in India (Mijiyawa, 1995). Health care resource expenditure is over 3 times higher in patients with RA compared to people without RA (Sorensen, 2004). There is also an increased mortality rate in RA patients compared with normal subjects due to coronary artery atherosclerosis resulting from the disease (Van Doornum *et al.*, 2002). For example, a study has shown that mortality is nearly two times higher in RA patients in the Spanish population (Martinez *et al.*, 2001).

Rheumatoid arthritis affects females more than males (Pietschmann, 2001) by two to three times. In addition, females tend to develop the first clinical features earlier than males with a median age of about 45 years for women compared to 50 in males (Goemaere *et al.*, 1990). These findings indicate that RA is an autoimmune disease associated with hormonal factors, however, other genetic factors, such as human leucocyte antigens-DR (HLA-DR) genotypes, are also likely to be important (Feldmann *et al.*, 1996).

Synovitis in RA is caused by hyperplasia of the synovial membrane due to a migration of cells from the vasculature as well as proliferation of the residential cells in the synovial membrane. This leads to the formation of pannus which damages cartilage and bone. Reduction in the accumulation of cells in RA synovial membrane is associated with

reduced severity of the disease. The main focus of this investigation is to determine if this increase in cell number is caused by a defect in programmed cell death (apoptosis) (Firestein *et al.*, 1995; Rabinovich, 2000).

Osteoarthritis (OA) is the most common form of arthritis (Peat *et al.*, 2001) and is characterized by focal and slow progressive degeneration of articular cartilage, sclerosis of the subchondral bone, and formation of osteophytes at the joint margins. The pathogenesis involved in OA is probably multifactorial (Felson & Zhang, 1998). OA can be classified as primary (idiopathic) and secondary depending upon the presence or absence of underlying conditions. Primary OA occurs mainly in the middle age or in the elderly, without obvious association with other diseases although there are recognised risk factors, such as obesity, (Felson *et al.*, 2004; Sharma *et al.*, 2000), abnormalities of joints and malnutrition that may predispose individuals to OA (Lorenz & Richter, 2006). Other underlying conditions include genetic (as in some primary OA), biochemical (as in metabolic disease), biomechanical (as in many form of secondary OA) and hormonal factors (Benito *et al.*, 2005; Goldring, 2000; Sandell & Aigner, 2001). Secondary OA may develop at any age in a joint damaged by trauma, disease, or deformity. The histopathological features of OA include depletion of matrix proteoglycans, cartilage fibrillation, cloned or clusters of chondrocytes, and chondrocyte death. In addition, osteophytes formation is a hallmark of OA.

Cartilage and bone degradation in both OA and RA usually leads to chronic pain and disability which is costly to treat. Surgery, such as total knee or hip arthroplasty, may often eventually be required because the joint has limited ability to repair itself. As a result, the medical cost of treating end stage OA and RA patients is high due to the added expense of surgical intervention. Preventing or inhibiting the cartilage damage will not only reduce the disability associated with OA and RA but will also reduce the cost to the community. One factor that contributes to the progressive nature of cartilage degradation in OA and RA is the limited ability of chondrocytes to regenerate. Although OA is not usually associated with inflammation it is possible that a dysregulation of cell death may be involved in the pathogenesis. Stimulation of chondrocyte death observed in OA (Heraud *et al.*, 2000; Kapitonova & Mansor, 2003; Sharif *et al.*, 2004) may be due to apoptosis. It may therefore, be beneficial to inhibit apoptosis of the chondrocyte population and subsequently prevent the cartilage degradation observed in OA or RA.

While the histopathology in RA occurs predominantly in the synovial membrane, histopathological features in OA occur predominantly in the cartilage with minimal changes in the synovial membrane. The synovial membrane in OA may show fibrosis but minimal inflammatory changes are observed compared with RA. However, synovitis can be common in advanced OA (Myers *et al.*, 1990).

Spondyloarthropathy (SpA) describes a group of related rheumatic disorders that have clinically features that are subtly distinct from RA. SpA is a chronic inflammatory disease of the joints, which have varying degrees of involvement of the spine and peripheral joint. SpA disorders are variably associated with the expression of the class I antigen, HLA B27 (Khan, 2002; Pavy *et al.*, 2005), with particularly strong linkage to ankylosing spondylitis (AS) as well as having an association with Reactive arthritis. SpA usually affects the sacroiliac joints with inflammation prevalent in the synovium and the entheses (enthesitis). Entheses are the regions of bone where the ligaments, tendon, joint capsule and fascia attach. Unlike RA in which synovitis is the initial primary pathology seen, synovitis in SpA occurs secondary to the effects on the enthesitis (McGonagle *et al.*, 1998). The synovitis of SpA is also the subject of this thesis in comparison with OA and RA.