CHAPTER 1
INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic autoimmune and inflammatory disease of the joint that approximately affects around 1% of the worldwide population (Muller et al., 2005). Even though the pathogenesis and aetiology of RA remain unrevealed, it is usually considered to be an autoimmune disease (Majithia and Geraci, 2007). The association of genetic and environmental factors, which results in cascade of immune reactions lead to inflammation, cartilage destruction, synovial hyperplasia and bone resorption. (Figure 1.1). This further leads to extreme pain, fever and disability in movement. Joint inflammation (synovitis) in RA primarily affects the joints of hand and foot, but later due to high inflammation, it can affect large peripheral joints. On the long run, kidney, lung, skin and vessels can also be affected as a function of RA severity (Helmick et al., 2008).

![Figure 1.1: Normal and Rheumatoid Arthritis inflamed joint](www.medicine.net)

The bone joint consists of two bones covered by cartilage and aligned by a joint capsule (Figure 1.1). In normal joints synovium is a thin layer which serves as source of nutrient for cartilage. In addition, the cell present in synovium also
produces the joint lubricant called as hyaluronic acid, collagens and fibronectin which serves as structural framework (Haringman et al., 2005). The synovium is divided into intimal or subintimal layer. In synovial lining or intimal layer, the primary cell populations are fibroblasts and macrophages (Choy et al., 2002) whereas; subintimal area includes the synovial blood vessels and has very few cells. In inflamed synovial joint that of RA, all the inflammatory cells like T cells, B cells, macrophages, lymphocytes and mononuclear cells are infiltrated which further differentiate into multinucleated osteoclasts. The intense cellular infiltrate is accompanied by new blood vessel growth (angiogenesis). In RA, the subintimal layer grows into 8-10 cells thick (pannus), which invades and erodes contiguous cartilage and bone (Ceponis et al., 1998).

RA can be controlled by different treatment strategies which include medication through multiple combinations of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Disease Modifying Anti-Rheumatoid Drugs (DMARDs), steroids and painkillers which reduce inflammation. Few antibodies and biologic drugs, which targets to inflammatory signals like IL6, IL8, TNFα, TGFβ reduces the inflammation and are also very effective. But, unfortunately, they can cause serious side effects such as infection because they suppress the immune system in the rest of the body as well. Hence novel target’s which has minimum interference with major function have to be identified.

Further in drug target identification and interaction studies, the biological pathway studies play a pivotal role. Previous literature have stated the role of pathways like signal transduction, TGF-β, NF-kB (Pohlers et al., 2006; Koczán et al., 2008) are already studied in relation to RA and some of the important proteins of these pathways have been identified as drug targets to treat RA. These pathways are not only responsible in progression of this disease but also play role in normal transduction of molecules, gene regulatory networks, signalling pathways. Uncovering the molecular pathways in RA becomes more complex as it is associated with genetic, environmental and more over inflammatory and autoimmune parameters.
Molecular expression studies using microarray technology permits a genome-scale evaluation of gene function. It helps to resolve the long-standing research problem in identifying specific gene expression patterns linking to metabolic characteristics that contribute to disease development and progression. Therefore gene expression studies using microarray data sets can be used to detect transcriptionally altered key signature molecules involved in the pathophysiology of RA. A better understanding of the implications of cellular interconnectedness on disease progression could lead to identification of disease genes and disease pathways, which, in turn, could offer better targets for drug development in diseases (Barabasi et al., 2011). In this direction, Network based approaches are currently used for better understanding of the molecular mechanism of any disease, drug action, targets, pathways and associated side effects (Zanzoni et al., 2009).

In the present study, computational methods using network biology was attempted to get more insight in order to improve the understanding of the complex interactions that occur between molecules in Rheumatoid Arthritis (RA). The objective of the study to identify significant proteins and its associated pathways in Rheumatoid Arthritis (RA) through network biology approach includes three types of network based methods and data platforms for identifying candidate proteins and their interacting patterns in RA. Gene Interaction Map (GIM) of RA genes, RA-Drug’s-target-protein networks (RA-DTP) and microarray data analysis of RA (Macrophages and Synovial Fibroblast) was carried out. The standard centrality parameters (k-Core, Betweenness centrality, Closeness Centrality, Cluster Coefficient and Degree) were used to identify the significant proteins which were further enriched with STRING and Biointerpreter for its biological relevance in relation to RA.