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Editorial
Published: 22 May, 2017

Perspectives and Limitations of Rheumatoid Arthritis Research

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Editorial

Rheumatoid arthritis (RA) is a common, systemic, chronic inflammatory autoimmune disease that affects about 1% of the world population [1]. Expenditures for adults with arthritis and other rheumatic conditions run into billions of dollars annually in the United States [2]. The medical doctors and researchers have been trying to find an efficiency approaching to treat RA. However, there is no cure for RA due to the cause of RA is not yet fully understood. It is believed that an abnormal response of the immune system plays a leading role in the inflammation and joint damage that occurs, however, no one knows for sure why and how the immune system goes awry.

The early RA research focused on blood groups. A significant correlation between the absence of the Rh antigen D and rheumatic disease has been reported [3]. Further studies were focused on the descriptive epidemiology and the results indicated that a genetic effect plays an important role in RA development [4]. A high prevalence of RA has been reported in the Pima Indians (5.3%) [5] and in the Chippewa Indians (6.8%) [6]. However, very low occurrences (0.2-0.3%) were found in the populations of China [7] and Japan [8]. There was no any RA case found in 500 adults in South Africa [9] and in 2000 adults in Nigeria [10]. These findings suggested that some genetic risk factors contribute to RA [11,12]. More studies have demonstrated consistently that having a family history of RA increases the risk of developing RA by about 3-5 times [13]. Twin studies have also provided compelling evidence to support this genetic component [14,15].

Modern molecular biological technologies have extended useful approaches for RA research. Recently, gene expression is used as a tool to investigate pathogenesis in RA and provided useful information for understanding RA [16]. RA susceptibility loci were discovered through candidate gene, linkage, and genome-wide association studies (GWAS). The gene signatures in the synovial tissues of RA and osteoarthritis (OA) have been found using microarray approaches [17].

Citrullination is a process in which the enzymes called peptidyl arginine deiminases (PADs) transform (citrullinate) proteins within the cells when the cells reach the end of their lifespan. Normally, dying cells do not come in contact with the immune system and are not identified as a potential threat to the body [1]. However, in a RA patient, the immune system loses its ability to distinguish between what belongs to the body and what is foreign to the body. These citrullinated proteins are mistaken as antigens by the immune system. In response to these antigens, the immune system produces anti-citrullinated protein antibody (ACPA). The study on genome-wide markers has shown that the heritability of ACPA-positive RA is around 40%-55% [18]. The presence of ACPA is used as an accurate predictor of RA to predict the disease even before the clinically apparent with joint symptoms [1].

The strongest genetic risk factor for RA is the shared epitope (SE) alleles at HLA-DRB1, where each risk allele is associated with an approximately doubled risk of ACPA-positive RA [19]. In RA patients, an increased expression of HLA-DRB1 has been found in various cell types present in synovial tissue but also in peripheral blood B cells [20]. However, molecular basis for the association between at risk DRB1 alleles and RA remains largely unknown.

Using traditional linkage and candidate gene studies to uncover genetic susceptibility has not led to definitive answers regarding the etiology of RA [12]. The most powerful and extensively employed approach in discovering susceptibility variants for RA and the other complex disease traits is GWAS. GWAS has led to the identification and validation of many novel RA risk alleles. However, the detection of rare variation is still a challenge in current genotyping arrays.

White blood cells are key immune system cells that play a central role in the autoimmune response. The relationship between loss self-tolerance and synovial involvement is unclear at this

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Received Date: *12 May 2017*
Accepted Date: *16 May 2017*
Published Date: *22 May 2017*

Citation:
Zhang J. Perspectives and Limitations of Rheumatoid Arthritis Research. Remed Open Access. 2017; 2: 1057.

time, but synovitis occurs when leukocytes infiltrate the synovium [21]. The mechanism of inflammation in RA caused by white blood cells migration has been studied [22]. It has been reported that fibroblast-like synoviocytes (FLS) play a key role in developing RA [23]. Pathophysiology of RA is controlled by both T and B cells with organized involvement of pro-inflammatory cytokines [24]. The study findings have demonstrated that cytokines are responsible for inflammation and joint destruction during arthritis [25]. Understanding the pivotal role of pro-inflammatory cytokine networks in rheumatoid synovium has led to the identification of tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) as relevant therapeutic targets. RA was the first disease for which anti-TNF biologics were used [26].

The antibody-based pharmacodelivery of anti-inflammatory cytokines has been used as an alternative therapeutic strategy for RA treatment [27,28]. Recombinant interleukin 4 (IL-4) has been investigated in preclinical models of rheumatoid arthritis, showing disease-modifying efficacy [29]. The immunocytokine F8-IL10 is currently being investigated in clinical trials in patients with active RA [30].

Physical therapy and medications can help slow the disease's progression. Currently, mild cases of RA can be treated with anti-inflammatory medications (NSAIDs). More severe cases of RA can be managed with anti-rheumatic drugs (DMARDS). These therapeutic advances have radically improved the prognosis of patients with RA, and remission is now an achievable objective. However, only a few patients get longstanding remission with treatment [31].

Meta-analysis provides a new tool to combine data from several studies and increase the power of a study to detect novel associations of modest effect. Many novel RA loci have been discovered more recently through meta-analysis [32]. The efficacy and safety of all five currently available TNF-blockers in the treatment of RA have been studied using meta-analysis [33]. The risk of malignancy among patients with RA has also been investigated by meta-analysis [34].

The recent RA research is focused on identification of the disease earlier in the process before extensive joint and bone damage occurs. The achievements of RA research have brought hope for further improvements in the management of RA [1]. The developments in molecular biology and computational chemistry have provided a new approach to design the agents that specifically target pro-inflammatory cytokines. So far, biological agents, such as TNF inhibitors, have shown therapeutic benefit for RA treatment. However, the costs and side effects could be minimized ideally.

Although the RA studies have made exciting progress, there is still a far way for RA research to go. Future research is needed to deepen our understanding of RA disease. We need to know how the body's defenses heredity infection and environment or lifestyle interact to cause RA. We also need to find targeted therapies that maximize efficacy with fewer side effects and lower cost. Studies on gene therapy and stem cell therapy are new challenges for RA research.

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