

Overview of rheumatoid arthritis: Past lessons and future paths

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Rheumatoid arthritis (RA) is a chronic autoimmune disorder that effects more than 1.3 million people in the United States. RA is an expensive disease that negatively impacts the patient’s quality of life. Inflammation of the synovial joints and destruction of articular cartilage and bones caused by RA can affect a patient’s ability to perform commonplace activities. For RA patients, walking or performing chores can become painful and burdening tasks.

The progression of RA is associated with an array of different immune cells. It is believed that joint inflammation is initiated by dendritic cells (DCs) that could differentiate from joint myeloid progenitors. Antigens presented by DCs to naïve CD4⁺ T cells which subsequently get activated and differentiate into T cell subsets, particularly Th1 and Th17, followed by migrating to the joints. Helper T cells will then secrete inflammatory cytokines and chemokines, recruiting more immune cells such as macrophages, neutrophils and lymphocytes. Through various mechanisms these cells in conjunction with antibodies facilitate degradation of cartilage tissues and cause synovial hyperplasia. Further progression results in activation of osteoclasts and erosion of cartilage and bones as shown in Figure 1. Figure 1 depicts histological tissue sections of joint tissues from a healthy mouse (left) and a mouse with collagen-induced arthritis (right) to emphasize the clinical pathology of the disease.

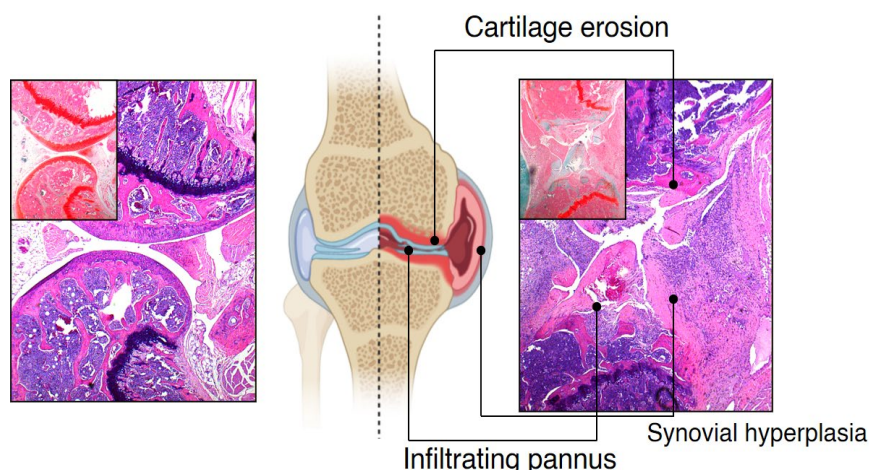


Figure 1: The comparison of healthy and arthritic joint tissues. Tissue sections from normal (left) and collagen-induced arthritic mice (right) were stained with H&E. The Pathological arthritic manifestations were labeled, corresponding to the schematic diagram. Inserted images are the same sections with Safranin O staining to reveal the proteoglycan, a proportional component in articular cartilage. Magnification, x100.

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Anti-citrullinated protein autoantibodies are believed to be responsible for the progression of most cases of RA. The mechanisms associated with the conversion of normal proteins to anti-citrullinated proteins is not fully understood. Agents that cause the manifestation of RA are diverse, from genetic heredity to environmental risk factors that include infection, smoking, pollution, and daily diet. Among the aforementioned risk factors, microbial infections are the most common instigators of aberrant and uncontained immunity which eventually develops into RA.

Known pathological microbes that initiate RA include *P. gingivalis*, *P. mirabilis*, and Epstein–Barr virus (EBV). These pathogens act as superantigens or are capable of molecular mimicry. These pathogenic capabilities are associated with the etiopathogenesis of RA. Researchers have successfully induced the RA-like symptoms in animal models. Researchers discovered that RA inflicted mice were capable of producing autoantibodies against citrullinated proteins or vimentin. For example, antibodies specific for EBV-infected B cells that express EB nuclear antigen (EBNA) were able to cross-react with rheumatoid arthritis nuclear antigen (RANA) [1]. In addition to EBV, alphavirus infections may be capable of initiating an RA response.

Alphaviruses are classified as either New World or Old World. Most alphaviruses are transmitted to birds and/or rodents by a mosquito vector, yet spillover events can occur resulting in transmission to humans. Interestingly, the alphaviruses from Old World, such as Chikungunya Virus (CHIKV), Ross River Virus (RRV), and Semliki Forest Virus (SFV), tend to cause arthritic symptoms. Whereas the New World alphaviruses, such as Venezuelan Equine Encephalitis Virus (VEEV), Eastern and Western Equine Encephalitis Virus (EVEV, WEEV) often induce inflammatory reactions in the central nervous system. Previous studies have suggested the possible causative role of alphavirus infections in the etiopathogenesis of RA as reviewed by Assunção-Miranda et al [2]. The cytokines produced by alphavirus infections is nearly identical to the cytokine profile produced by RA, suggesting a possible link between the two maladies. Furthermore, CHIKV chronically infected patients and RA patients both share the same genetic polymorphism in human leukocyte antigen (HLA) alleles, which are susceptibility risk factors of RA. Autoantibodies have consistently been found in patients infected with alphaviruses that later developed RA. Recently, two separate studies discovered that the arthritis caused by alphaviruses is attributed to the CD4⁺ T cell pathway [3]. FDA approved Anti-rheumatic drugs (DMARDs), such as CTLA-4-Ig and Tofacitinib, are capable of blocking CD4⁺ T cell function. These drugs are typically used to combat RA, but recent studies show they are capable of alleviating acute joint inflammation induced by CHIKV. While the studies focused on acute arthritis, the studies shed light on the pathogenic and therapeutic commonalities between RA and arthritis caused by alphavirus infection. These findings outline potential for future studies that may elucidate the underlying causes of arthritis and explore the application and development of new drugs.

Drugs used to counteract RA are predominately immunomodulatory or immunosuppressive agents, including hydroxychloroquine, sulfasalazine, methotrexate (MTX), leflunomide, D-penicillamine, and azathioprine. The DMARD, MTX, originally designated as an anti-cancer drug, is often used

to treat RA patients. This drug is typically successful against autoimmune diseases and is associated with manageable side effects. RA patients administered MTX are not consistently responsive to the drug though. The adverse effects linked to MTX, such as gastrointestinal disorders, occurs in about 12% of RA patients prescribed the drug. Complications caused by the drug may require patients to seek secondary treatment. These pitfalls emphasize the importance of discovering new therapeutics to remedy RA.

Phytochemicals have recently been identified as promising therapeutic agents. Numerous herbal products have been tested in animal models with autoimmune disorders, revealing promising results against arthritis in animals. However, we still need more preclinical trials and pharmacokinetic research with these phytochemicals before they can be approved for use in treating RA patients. In addition to exploring natural compounds, the successful repurposing of the cancer drug, MTX, as an RA therapeutic has demonstrated the importance of considering off-label uses of current drugs. Recent research performed in our laboratory has shown that some nucleic acid analogues used for cancers could also be used as potent remedies that mitigate arthritis via reduction of tyrosine kinase activity.

The COVID-19 pandemic has substantially halted research that focuses on diseases that are considered unrelated to SARS-CoV-2, including RA. Unfortunately, many people with prior ailments, such as RA patients, are unable to obtain the medical support they require to maintain a manageable lifestyle. People with RA are immunocompromised and therefore face the risk of acquiring severe SARS-CoV-2 infection. This can cause increased mental stress in patients already facing draining symptoms triggered by RA. The implication of hydroxychloroquine as a possible anti-COVID-19 drug, has caused shortages of the drug. Acquisition of a drug commonly used by RA patients has become an increasing challenge. The scientific community must emphasize the importance of continuing research on RA and possible therapeutics during these times. Published research and review articles on RA are also vital resources that can exponentially impact progress in discovering RA cures.

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