MANTECH Publications

Srijana: Journal on Rachana Sharir and Kriya Sharir
Volume 1, Issue 2, July-December, 2022

Arthritis Induced by Collagen

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Abstract

Collagen-induced arthritis (CIA) is a clinical condition in mice used to evaluate rheumatoid arthritis. In order to induce CIA in mice, an emulsion of full Freund's adjuvant and type II collagen is specially injected into them. This study discusses arthritis and the use of collagen to induce arthritis.

***Keywords: -** Rheumatoid arthritis, Collagen-induced arthritis (CIA), Mice, and collagen*

INTRODUCTION

Collagen-induced arthritis (CIA) is an experimental model of autoimmune inflammatory arthritis that resembles clinical rheumatoid arthritis (RA). Both humoral and cellular immunological responses are required for the induction and maintenance of CIA. In most cases, the pathogenic processes of autoimmune arthritis reveal that both MHC and non-MHC genes play important roles in the clinical presentation of the arthritis. The role of cytokine production, such as interleukin (IL)-1, tumour necrosis factor (TNF)-, IL-12, and IL-6, in autoimmune illnesses has been extensively explored and analysed in animal models and human disorders, offering insight into the processes leading to joint destruction.

IL-18 is the member of the IL-1 cytokine family which, like IL-1, is released as the propeptide and cleaved by an IL-1β-converting enzyme (ICE) to yield the bioactive product. It is expressed by a variety of cell types encompassing: the monocytes/macrophages, dendrocytes, Kupffer cells, keratinocytes, the intestinal epithelial cells, the skin cells, synovial fibroblasts, the articular chondrocytes and

osteoblasts (Har-El et al., 1993). The initial function of the IL-18 was thought to be an interferon (IFN)-γ-inducing factor; however, it has also been seen to possess the broad range of the activities in regulating innate and the acquired immune responses (Buck walter et al., 1982). IL-18 acts synergistically with the IL-12 to induce the naive CD4+ T cells to differentiate into Th1 cells and to stimulate IFN-γ production by the Th1 and the natural killer (NK) cells (Hook et al., 1983). IL-18 promotes inflammation by enhancing the TNF-α, IL-1β, IL-2, IL-6 and the granulocyte-macrophage colony stimulating factor (GM-CSF) gene expression, in addition to the chemokines IL-8 and the macrophage inflammatory protein (MIP)-α. Moreover, the IL-18 up-regulates the expression of the adhesion molecules such as the intercellular adhesion molecule (ICAM)-1 and copiouses the prostaglandin E2,the inducible nitric oxide synthetase (iNOS) and leukotriene B4 production by the mononuclear and the mesenchymal cells. Lastly, IL-18 has been shown to promote the inflammation by the recruitment and activation of the neutrophils (Sashinami et al., 2006).

With regard to the joint injury, researchers have shown IL-18 mRNA and protein to be much more abundant in the joints of the rheumatoid patients than the patients with osteoarthritis. It is believed that IL-18 may play a key role in inducing and sustaining the articular Th1-type cell activity and promote the TNF-α production (Mitsui et al., 2010). The capacity of the IL-18 to activate the synovial fluid (SF) neutrophils to release the cytokines, chemokines and leukotriene B4 is also significantly copioused in the RA patients. Preliminary studies of experimental CIA in mice show that treatment with the IL-12 plus IL-18, or with the IL-18 alone, enhance the incidence and severity of the joint injury. In contrast, IL-18 knock-out mice are specifically resistant to CIA, as are mice treated with the neutralizing the anti-IL-18 antibodies. A naturally occurring IL-18 protein antagonist is also able to attenuate the disease in the CIA (Stoll et al., 1998).

In the present study researchers investigate the role of the IL-18 in CIA in the BB rat, because this model has certain pros over the murine model, one being that the rats require only the use of the incomplete Freund's adjuvant (IFA) to induce the arthritis. Thus, by eliminating Mycobacterium tuberculosis (MT), which is specifically needed to assure the high incidence of the CIA in mice, its potential confounding effects on the cytokine

production, are eliminated. Additional advantages include the short latent period before the onset of the arthritis and the greater amount of synovium to study (Okamura et al., 1995). Rats are also susceptible to the adjuvant arthritis, the streptococcal cell wall-induced arthritis and the type XI collagen-induced arthritis, thus providing the alternative models for the comparative studies and investigations (Udagawa et al., 1997).

RESEARCH ON COLLAGEN INDUCED ARTHRITIS

Animal models of the autoimmune arthritis have proven to be much valuable research tools for the study of the pathogenic mechanisms of this disease as well as for the testing new therapies. Several mouse models of the arthritis have been specifically established (Nakamura et al., 1989), including those that require immunization with the antigen— the proteogly can-induced arthritis (PGIA), the streptococcal cell-wall arthritis, CIA and the antigen-induced arthritis; those induced by chemical agents—oil-induced arthritis; and the spontaneous models—tumor necrosis factor-a transgenic mouse and K/BxN T-cell receptor transgenic mouse (Tsutsui et al.,1998).

While each of these models has pros and cons, CIA has been the most widely studied model of the rheumatoid arthritis (RA). It shares several pathological features with RA, and CII is amajor protein in the cartilage, the target tissue of RA (Hunter et al., 1997). Additionally, of the antigen-defined models that are based on the cartilage proteins, it has the shortest duration between immunization and the disease manifestation. The CIA model has been used extensively to identify the potential pathogenic mechanisms of autoimmunity, encompassing the role of individual cell types in the disease onset and progression, as well as to design and test new therapeutics (Micallef et al., 1996). The development of these biologically based therapies has revolutionized the treatment of the RA.CIA is elicited in genetically susceptible strains of mice by immunization with the CII emulsified in complete Freund's adjuvant (CFA)(Netea et al.,2000). The ensuing pathogenesis shares multiple pathologicalfeatures with RA, including synovial hyperplasia, the mononuclear cell infiltration, cartilage degradation, and, like RA, susceptibility is rakished to the expression of specific MHC class II genes. The most notable differences between this model and the RA are that rheumatoid factor is not present in

CIA, there is little or no sex bias in the CIA and that the experimental disease is generally monophasic, although some relapsing mouse models of the CIA have been described (Puren et al., 1998).MHC is plays important role to synthesize CIA in mice (Sreeremya, 2019).

While the presence of the T-cell and B-cell immunity to CII has been reported in RA, it is not clear if this is the causative factor or are sult of the pathogenesis associated with this disease. The original‘ ‘gold standard’’ of the CIA model was the DBA/1 (H-2q) mousestrain; however, in the recent years, several HLA-DR mouse models have been established in which transgenic expression of the HLA-DR1 or the DR4 class II genes associated with susceptibility to RAconfers susceptibility to the CIA in the recipient mouse strain. These data indicate that the DR molecules associated with the susceptibility to RA are at least involved in the immune response to CII (Vidal-Vanaclocha et al.,2000).The immune pathogenesis of the CIA involves both a T-cell and B-cell-specific response to CII. The immune dominant the T-cell determinants of CII that mediate the CIA have been identified for most of the class II molecules that are associated with the susceptibility to this experimental disease, and a few have been studied indetail for their interaction with the class II molecule and the T-cellreceptor (Kohka et al.,1998). Similarly, B-cell determinants targeted by the antibody response to the CII have also been identified, and there is some evidence that antibodies from the RA patients target the same areas of the CII molecule as those from CIA. Identification of the pathogenic B-cell determinants has proven to be more difficultowing to the requirement that the pathogenic antibodies must be mainly able to bind to the triple helical native CII. Unlike other autoimmune models such as EAE, where the T cells are the primarypathogenic mechanism, the pathogenesis of CIA is mediated, in the large part, by the CII-specific antibody that binds to the cartilage and iscapable of fixing complement. Collectively, this information has enabledresearchers to study a wide range of pathogenic mechanisms in this model, as well as to mainly design and test novel therapeutics (Cannetti et al., 2003)

RA

Rheumatoid arthritis (RA) is an autoimmune disease that is mainly characterized by chronic inflammation of the synovial joints, subsequently with progressive, erosive destruction of articular tissues. It affects 1.2% of

population and is associated with significant morbidity and mortality. In the synovial tissues of the RA, numerous cytokines are expressed and are functionally active. They are directly implicated in the immune processes that are mainly thought to play crucial roles in the pathology of RA. In many of rodent models, the cytokine modulation alters the outcome of the arthritis (Leung et al., 2001).

Proteoglycans (PGs) are widely distributed in connecting tissues such as skin, bone, and cartilage by forming a complex with collagen, fibronectin, the laminin, hyaluronic acid, and other glycoproteins. Basic structure of the PGs is a complex glycohydrate, which is composed of the core protein covalently attached with one or more glycosaminoglycan(s). Our previous studies have shown that the PG extracted from salmon cartilage has the immunomodulatory effect. It suppresses the inflammatory response of macrophages induced by stimulation with the heat-killed bacteria (Gracie et al., 1999). In addition, daily oral administration of the PG attenuates the severity of mouse experimental colitis and the experimental autoimmune encephalomyelitis (EAE). Attenuation of typically systemic inflammation in colitis and EAE models by daily oral administration of PG depends on suppression of the T-helper 17 (Th17) lineage differentiation and an induction of Foxp3+ regulatory T (Treg) cells. The previous studies also indicated that ingested PG may contribute to homeostasis of the host immunity mediated through the balance in composition of the gut microbial immunity (Leung et al., 2000).

CONCLUSION

In recent years, the CIA model has been particularly useful in the testing and development of novel biologically based therapies, such as those that target tumour necrosis factor-a, a cytokine produced by macrophages and T cells that is a key inflammatory mediator in the pathophysiology of RA.

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