Rheumatoid Arthritis: A Complex Gene Environmental Interaction

*Smriti Shukla, U.K. Chauhan, Arvind Kumar Tripathi, Mrigendra Kumar Dwivedi and Jitendra Kumar Tripathi

Centre for Biotechnology Studies
A.P.S. University, Rewa (M.P.) India
E-mail: chauhanu@rediffmail.com, arvindt2584@gmail.com, bhaiuswivedi@rediffmail.com, jitendra.bt@gmail.com
*Corresponding Author E-mail: Smritishtukla1785@gmail.com

Abstract
Rheumatoid arthritis is most prevalent systemic autoimmune disorder. In condition of RA immune system target joint via attacking synovial membrane and inflammation in joints occur resulting in chronic pain, difficulty in movement and joint destruction. Mortality in RA is increased because the patients are susceptible for other disease like cardiovascular and respiratory disease. Many genetic factors and environmental factors have been found to be associated with Rheumatoid Arthritis but neither genetic nor environmental factors alone are able to cause RA alone. A complex gene environmental interaction is possibly responsible for the RA and its Pathophysiology. The therapeutics used for the treatment are not very significant and effective.

Keywords: Rheumatoid arthritis, Genetic factors, nongenetic factors.

Introduction
Rheumatoid arthritis is autoimmune disorder characterized by chronic inflammation in joints. The term Rheumatoid arthritis is first coined by Garrod (1939). The prime target of this disease is joints present throughout the body. In general the immune system of human body is consist of many type of cells and proteins to combat against foreign antigens and infection, when something goes wrong with our immune system, our immune system loss the ability to distinguish our body cells from foreign particles and antigen, at this point the condition of autoimmunity arise and our immune system start to destroy our body cells and chronic inflammation should be the result.
According to the Arthritis Foundation, RA affects approximately 2.1 million people in the United States, and about 70% of patients who have the disease are women. Rheumatoid arthritis usually develops between the ages of 30 and 50, but it can occur at any age. Rheumatoid arthritis also affects men and children (called juvenile rheumatoid arthritis and also juvenile idiopathic arthritis). Both the severity and incidence of RA seems to be decreasing. RA sufferers, as many studies have shown, tend to face a high risk for early death, increasing with the severity of their symptoms. The most prevalent cause of death among RA patients is cardiovascular disease. (Solomon D H et al. 2003, Wolfe F et al. 2003.)

The criteria for the diagnosis of RA has been developed by the American College of Rheumatology (ACR) and till now it is standard guidelines applied for diagnosing this RA. (Arnett FC 1988) According to these criteria, RA is diagnosed if a given patient satisfies at least four of seven clinical criteria, and the initial four must have been present in the patient for at least 6 weeks; this latter specification is intended to exclude the several types of virally induced arthritis that can resemble RA. Studies evaluating the success and sensitivity of these criteria in normal clinical situations show them to be reliable and responsive, but the goal is to avoid confusing RA with other conditions. Such confusion is a significant diagnostic possibility due to the often severe systemic effects seen in RA and importantly, its significant overlap in clinical signs and symptoms with other rheumatic diseases. A full metabolic panel and complete blood count with differential and inflammatory biomarkers (erythrocyte sedimentation rate [ESR]/C-reactive protein) are often done, and they often are elevated in patients with RA but ESR could not be a permanent marker for diagnosis of Rheumatoid arthritis because in many other disease and infection ESR could be increased. Two antibodies, rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) also appear elevated and accompany the diagnostic protocol. These all diagnosis could be good assist for diagnosis but they can be present in several other disease or even healthy individuals so only presence or absence of these factors could not be enough to make it sure that patient is suffering from RA. The primary therapeutic strategy is to detect the relevant synovial and other pathogenic processes early in their development, and to treat quickly and aggressively to prevent long term joint damage.

Pathophysiology of Rheumatoid arthritis
RA is a serious and often disabling condition that can cause chronic pain, permanent joint damage, and loss of joint function. In rheumatoid arthritis, the immune system targets synovial membrane and attacks it. The synovial membrane secretes synovial fluid into the joint. Synovial fluid is the joint fluid that lubricates and nourishes the joint. Other tissues can also be targeted by the immune system in rheumatoid arthritis, but the synovium, or synovial membrane, is generally the primary target. When the synovial membrane is attacked, it becomes inflamed (synovitis) and can thicken and erode. As the synovial membrane is destroyed, the synovial fluid is also destroyed because it is not being secreted. The surrounding structures can also become involved leading to the joint deformities that can be seen in rheumatoid arthritis. Inflammatory
mechanisms in the synovial tissues of RA patients differ between early and late stages of the disease.

The disease involves abnormal B cell - T cell interaction, with presentation of antigens by B cells to T cells via HLA-DR eliciting T cell help and consequent production of RF and ACPA. Inflammation is then driven either by B cell or T cell products stimulating release of TNF and other cytokines. Rheumatoid arthritis is considered as an Th1-associated disease Miossec P 1997, But the factors which are needed to initiate the process of abnormal Th-1 cell response has not been fully understood.

The process of inflammation is mediated by cytokines. TNF and IL-1 are the main proinflammatory factors associated with chronic joint inflammation and the concomitant erosive changes in cartilage and bone. Earlier finding suggests that TNFα was an inflammatory mediator, whereas IL-1 was a crucial cytokine in both arthritis and cartilage destruction. TNFα alone was hardly destructive, but it could enhance in a synergistic way the destructive behaviour of IL-1. VandeLoo A A J 1990, Henderson B 1989.

Rheumatoid arthritis could be fully blocked with antibodies against the IL-1 receptor. Probert L 1995. This strongly indicates that 1) IL-1 is the secondary mediator responsible for the arthritic changes, and 2) TNFα alone is neither arthritogenic nor destructive towards joints. Erik Lubberts et al. 2000

IL-17 is a recently discovered cytokine that is secreted by a restricted set of cells, whereas its receptor is ubiquitously expressed on many cell types. Fossiez F 1996, Yao Z 1995 IL-17 production has been demonstrated in RA synovial tissue. Chabaud M 1999.

RANKL binds to its receptor, RANK (receptor activator of nuclear factor κB) inducing NFκB activation via TRAF 6. Schwandner R 2000 The decoy receptor OPG binds with the soluble and cell-bound forms of RANKL and thus prevents their

In RA, the balance between pro-inflammatory and anti-inflammatory cytokines determines the degree and extent of inflammation which can lead to major clinical effects. Anti-inflammatory cytokines and cytokine antagonists counteract the effects of pro-inflammatory cytokines. Hence the relative concentrations of a cytokine to its inhibitor or antagonist will determine its final effect.

The cause of RA is not known, but many possible etiologies have been identified. Important etiologic clues have been suggested by the identification of unique features of populations with a predilection for RA. As an example, the observation of geographic clustering of the disorder in ancient skeletons implies an important role for environmental factors, which are still poorly defined [1]. In addition to environmental factors, hormonal, genetic, infectious, and other variables also contribute to RA in some manner

**Causes of Rheumatoid Arthritis**

A number of genetic and environmental factors have been implicated in the etiology of rheumatoid arthritis (RA). Rheumatoid arthritis is multifactorial disorder. it is not caused by single genetic and environmental factors. But studies suggest that both genetic factor and environmental (non genetic factor) are responsible for arthritis generation. The process of beginning of arthritis is not very clear but a complex gene-environment interaction may be a determinative factor of generation of arthritis.

**Non genetic factors**- many environmental factors have been seen to influence the susceptibility of Rheumatoid arthritis. Hormonal imbalance, intake of contraceptives, diet, tobacco smoking and weight are possible factors which improves the arthritis.

**Smoking and addictions**- The only well-established environmental risk factor is tobacco smoking, which has been shown in a number of studies to be associated with increased RA risk but these findings are significantly associated with patients with Rheumatid factor. (Vessey MP et al. 1987, Silman AJ et al.1996, Karlson EW et al. 1999, Stolt P et al. 2003). Smoking is so far the most established environmental risk factor for developing RA, especially RA characterized by presence of antibodies to citrullinated proteins (anti-cyclic citrullinated peptide, anti-CCP) Pedersen M et al. 2007. however some finding suggest smoking history also has a strong influence on the risk of developing RA associated with the DRB1 ‘shared-epitope’[. Padyukov L et al. 2004, Linn-Rasker SP et al. 2006]. Some studies has shown effect of coffee intake in rheumatoid arthritis but results are very inconsistent. One study demonstrated a significant association between coffee consumption and the risk of rheumatoid factor (RF)–positive RA (Helio¨vaara M et al. 2000). Two other studies showed an increased risk of RA associated with consumption of decaffeinated coffee, but no such association with caffeinated coffee intake (Formica MK et al. 2001, Mikuls TR et al. 2002)
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Some findings are also their to establish the interrelationship between alchohal intake and inversion of rheumatoid arthritis. Study in a Scandinavian cohort also showed a dose-dependent reduction in RA risk, but only in anti-CCP-positive disease. (Pedersen M et al. 2006). Study in caucasian population has demonstrated that consumption of alcohol is associated with a significant and dose-dependent reduction in susceptibility to RA. (Maxwell JR et al. 2010)

Diet- Diets high in red meat and low in vitamin C and other components of brightly coloured fruit and vegetables appear to carry an enhanced risk of RA. Although the relationship with diet is still inconsistent. Fish or fish oil intake and vegetarian diet is not found to be associated with rheumatoid arthritis in denmark (Merete Pedersen et al. 2006) but results are inconsistent because some studies are in favor of association between diet and nutrition with inflammation. The studies of dietary intake of vitamin D and incident RA have come to contradictory conclusions. Merlino et al. (2004) found a strong protective effect of high vitamin D intake in diminishing incident RA, whereas a study by Costenbader et al. (2008) revealed no association between intake and incident RA. However neither study assessed vitamin D from solar exposure. It has been demonstrated that lower intakes of fruit and vegetables, and vitamin C were associated with an increased risk of developing inflammatory polyarthritis (IP). (D J Pattison et al. 2004)

Hormonal Factors- the prevalence of disease in female is higher then male and pregnancy may the disease may flare after a pregnancy these observation indicates that hormonal and reproductive factors have been suggested as potentially involved in the etiology.. Some findings suggest that pregnancy and Oral Contraceptive Pills use have a "protective effect" on the development of RA, although the mechanism remains unclear. (Spector TD et al. 1990). The peak incidence of RA in women coincides with the peri-menopausal age, suggesting a connection with hormonal alterations [Goemaere S et al. 1990]. RA usually goes into remission during pregnancy. It is also very unusual for the disease to begin during pregnancy. However, in the few weeks after delivery, women with RA often experience a relapse and there is a much higher frequency of development of RA. This may be because prolactin, the hormone which is responsible for milk production, enhances inflammation..

Breastfeeding may also aggravate the disease. (Brennan P et al. 1994). The effects of sex hormones on rheumatic diseases are controversial. Some data suggest that estrogens and Hormonal Replacement Therapy may be beneficial in RA [Hall GM 1994, Brennan P 1997, Ostensen M 1999,], whereas other findings did not show amelioration of disease activity by HRT(van den Brink HR et al. 1993). levels of the immune system molecules interleukin 12 (IL-12) and tumor necrosis factor-alpha (TNF-α) may change along with the changing hormone levels seen in pregnant women. This change may contribute to the swelling and tissue destruction seen in rheumatoid arthritis. These hormones, or possibly deficiencies or changes in certain hormones, may promote the development of rheumatoid arthritis in a genetically susceptible person who has been exposed to a triggering agent from the environment.
Possible infectious triggers

It has long been suspected that certain infections could be triggers for this disease. The "mistaken identity" theory suggests that an infection triggers an immune response, A widespread theory is that one or more infectious agents might act as initiator in the pathogenesis of RA by having antigens similar to host antigens, a mechanism referred to as molecular mimicry [Albert LJ et al. 1999 ]

Epidemiological studies have confirmed a potential association between RA and herpesvirus infections, although alternative explanations are possible that patients with RA may be more prone to infection/reactivation. (R Álvarez-Lafuente et al. 2004.)

Epstein-Barr virus (EBV) and Human Herpes Virus 6 (HHV-6). Individuals with RA are more likely to exhibit an abnormal immune response to the Epstein-Barr virus. The allele HLA-DRB1*0404 is associated with low frequencies of T cells specific for the EBV glycoprotein 110 and predisposes one to develop RA.

Normal subjects with antibody to RA nuclear antigen had titers of antibody to Epstein-Barr nuclear antigen equivalent to those of patients with RA and significantly higher than normal subjects lacking antibody to RA nuclear antigen. One interpretation of these results is that patients with seropositive RA derive from a larger population with enhanced immune responsiveness to B lymphocyte nuclear antigens determined by the Epstein-Barr virus. Catalano MA et al. 1979. some finding also indicate that RA patients have either more active EBV infections than controls or an altered regulation of their immune response to this infectious agent. (P B Ferrell et al. 1981.) Anti-EBV antibody responses should be considered as one of the chronic autoantibody responses that are most relevant to the development of RA. (Balandraud N et al. 2004.)

Some infectious organisms suspected of triggering rheumatoid arthritis include Mycoplasma, Erysipelothrix, parvovirus B19 and rubella, but these associations have never been supported in epidemiological studies. Nor has convincing evidence been presented for other types of triggers such as food allergies.

Genetic (inherited) factors: Estimates of the relative genetic and environmental contributions to RA, based on covariance analysis of twin data, suggest that the genetic contribution to disease development approaches 50–60%. (MacGregor AJ et al. 1994) Scientists have discovered that certain genes known to play a role in the immune system are associated with a tendency to develop rheumatoid arthritis. Some people with rheumatoid arthritis do not have these particular genes; still others have these genes but never develop the disease. These somewhat contradictory data suggest that a person's genetic makeup plays an important role in determining if he or she will develop rheumatoid arthritis, but it is not the only factor. What is clear, however, is that more than one gene is involved in determining whether a person develops rheumatoid arthritis and how severe the disease will become. Rheumatoid arthritis (RA) is a heterogeneous autoimmune disorder of unknown cause with variable clinical expression. About 70% of patients are women. Genetic factors play an important role and likely account for about 60% of disease susceptibility and expression. Turesson C et al. 2006
RA has a strong genetic component (Seldin, M 1999, MacGregor, A 2000) and several MHC and non-MHC susceptibility loci have been identified in family-based linkage studies (Osorio, Y 2004, Jawaheer, D. 2001, Jawaheer, D.2003, Cornelis, F. 1998, Shiozawa, S 1998, MacKay, K. 2002). Patients of different ethnic groups share the HLA region as a major genetic risk locus. The largest genetic risk factor predisposing to RA, a common set of alleles at HLA–DRB1, has been associated with RA in populations of both Caucasian and Asian ancestry (Jun KR et al. 2007, Silman AJ et al. 2002). Human leucocyte antigens (HLA) have been estimated to account for approximately 40% of the genetic component of susceptibility to RA [John S 1997].

A study in French population suggest an association between Shared Epitope allele and tobacco smoking for anti-CCP positivity and a tendency toward an interaction between the HLA-DRB1*0401 allele and smoking for anti-CCP positivity in this sample of RA. L Michou (2007)

PTPN22 gene maps to chromosome 1p13.3–p13.1 and encodes a lymphoid-specific phosphatase (Lyp). It is one most common Non-HLA susceptibility allele for autoimmunity is the 1858C->T single-nucleotide polymorphism (SNP) of protein tyrosine phosphatase non-receptor 22 (PTPN22) (Siminovitch KA. (2004), Gregersen PK. (2005)). Lyp is an intracellular PTP and physically bound through proline-rich motif to the SH3 domain of the Csk kinase, which is an important suppressor of kinases that mediate T-cell activation. (Cohen S et al. 1999). The ability of Csk and Lyp to inhibit T-cell-receptor signaling requires their physical association [Cloutier JF 1999]. The PTPN22 1858C->T SNP changes the amino acid at position 620 from an arginine (R) to a tryptophan (W) and disrupts the interaction between Lyp and Csk, avoiding the formation of the complex and, therefore, the suppression of T-cell activation. In vitro experiments have shown that the T-allele of PTPN22 binds less efficiently to Csk than the C-allele does, suggesting that T-cells expressing the T-allele may be hyperresponsive, and consequently, individuals carrying this allele may be prone to not only for rheumatoid arthritis but also for vast range of autoimmune disorders (Bottini Net al. 2004, Begovich AB 2004). Although PTPN22 has been consistently shown to be associated with RA in Caucasians, the 620W risk allele in this gene is not found and thus is not disease-associated in Asian populations. A study on Turkish population also shows lack of association of genetic polymorphism of PTPN22 with Rheumatoid arthritis. (N. Sahin et al. 2009).

Recently, it was reported that IL-18 protein expression is regulated by the IL-18 promoter gene.

There are many cytokines or inflammatory mediators, but the most important in rheumatoid arthritis are tumor necrosis factor (TNF) and interleukin-1. These cytokines are thought to trigger the process of joint damage in rheumatoid arthritis. Some treatments for rheumatoid arthritis block these cytokines, reducing inflammation and joint damage.

Therapeutics options for rheumatoid arthritis (RA) have increased tremendously in the past decade with the introduction of biological agents in 1999. Several different cellular and cytokine targets have been identified, with specific inhibitors now approved to treat RA, including the tumor necrosis factor (TNF) antagonists (adalimumab, etanercept, infliximab), an interleukin 1 (IL1) antagonist (anakinra), an
inhibitor of T cell co-stimulation (abatacept), and a selective depleter of B cells (rituximab). (Bingham CO 3rd. 2008)

Conclusion with future aspects
Rheumatoid arthritis is multifactorial disorder associated with both genetic as well as environmental factors. Many environmental factors has been seen to be strongly associated with rheumatoid arthritis. Most common genetic factors associated with Rheumatoid arthritis is HLA- DRB region. Some cytokines and PTPN22 region is also found to be associated with RA. The therapeutic approach is not very much significance but for the development of new therapy we first think about the complex interaction of genetic polymorphism and environmental factors.

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