ORIGINAL RESEARCH PAPER

Rheumatology

RELATIVE IMPORTANCE OF GENETIC, ENVIRONMENTAL AND IMMUNOLOGICAL FACTORS IN THE PATHOGENESIS OF RHEUMATOID ARTHRITIS

KEY WORDS: Rheumatoid arthritis RA, immunity, genetics, environmental

Hasnayan Sabir Assistant professor, Department of Medicine, AVBRH, DMIMS, JNMC, Savangi, Wardha, Maharashtra.

ABSTRACT

RA is one of the most common autoimmune disorders whose exact ethology is not known. It attacks joint synovium and many other tissues of the body like small vessels, lung parenchyma, muscles, soft tissues, blood cells etc. Pannus is a pathological hallmark of RA. Several SE-positive (SE+) DRB1 alleles have since been reported to be associated with RA. MHC genes with a confirmed role in development of RA include HLA-DRB1 genes, which are thought to be involved in antigen presentation to T lymphocytes. Cigarette smoking has been found to be a specific environmental risk factor for ACPA-positive RA. Conversely, a recent meta-analysis showed that alcohol intake was inversely correlated with the development of ACPA positive RA.

INTRODUCTION:

Rheumatoid arthritis (RA) is an autoimmune disease which attacks joint synovium and many other tissues of the body like small vessels, lung parenchyma, muscles, soft tissues, blood cells etc. Synovitis is mediated by immune complexes (produced by RA factor and unknown antigen) which invite lymphocytes and complement mediated inflammation. The inflammatory cells produce growth factors and proteolytic enzymes such as TNF causing proliferation of synovial cell, thickening and expansion of synovium. These synovial cells produce proteolytic enzymes and synovium (called Pannus) which will erode joint structures resulting in joint deformities seen in rheumatoid. Pannus is a pathological hallmark of RA. Joint involvement in seropositive RA leads to deforming symmetrical polyarthritis of small joints of hands and feet. RA factor and anti CCP (cyclic citrullinated polypeptides) are serological markers for rheumatoid arthritis. The first known cases dated back as far as 4500BC. Although the first recognized description of the disease was in 1800 by the French physician Dr Augustin Jacob Landre-Beauvais [1]. However, the name RA was introduced in 1859 by British rheumatologist Dr Alfred Baring Garrod [2]. The name is based on the term "rheumatic fever" an illness which includes joint pain and is derived by the Greek word 'rheumatos' meaning flowing and the suffix-oid meaning resembling, this giving it the translation as joint inflammation that resembles rheumatic fever [3]. About 1% of the world's population is affected which is a not insignificant minority. RA affects women three times more than men. As it affects so many people it is important to understand more about the pathogenesis of the disease. Immunological, genetic and environmental factors have been thought to each play a major role in the pathogenesis of rheumatoid arthritis.

IMMUNOLOGICAL FACTORS

Inherited susceptibility to RA is associated with the DRB1 genes encoding the human leukocyte antigen (HLA)-DR4 and HLA-DR1 molecules. Transgenic mice expressing these major histocompatibility complex (MHC) class II molecules have been developed to generate humanized models for RA. The class II major histocompatibility complex allele HLA-DR4 (DRB1*0401) and related alleles are known to be major genetic risk factors for RA. Early studies showed that as many as 70% of patients with RA express HLA-DR4 compared to 28% of control individuals. This association strong in individuals who develop RA associated with antibodies to CCP. An association with HLA-DR4 has been noted in many populations except in some populations including, Israeli, Jews, Asian Indians and Yakima Indians of North America. In those groups they have HLA-DR1(DRB*010). More than 20 years ago, Stastny [4]reported that HLA-DR4 is associated with RA. Nine years later, Gregersen et al [4] proposed the shared epitope (SE) hypothesis based on the observation that the RA-associated DRB1 alleles encode a common sequence of amino acids corresponding to residues 67-74. Several SE-positive (SE+) DRB1 alleles have since been reported to be associated with RA and include the DR4 subtypes DRB1*0401, *0404, *0405 and *0408 as well as the DRB1*0101, *1402, and *1001 alleles. Nepom [5] has summarized the relative risk estimates for Caucasians for three of the most frequent SE+ DRB1 alleles in the Caucasian population. The relative risk is 6 for the DRB1*0401 allele, 5 for the DRB1*0404 allele and 1 for the DRB1*0101 allele. Thus, while the relative risk for individuals carrying the DRB1*0401 allele or the *0404 allele is approximately five times higher compared with that for individuals not carrying these alleles, the DRB1*0101 allele does not confer risk on its own. It has been debated whether the RA-associated DRB1 alleles are disease risk genes or prognostic markers for a more progressive disease course, and whether individuals carrying two SE+ DRB1 alleles either have a higher risk of developing disease or develop more severe disease compared with individuals with only one SE+ DRB1 allele [5,6]

GENETIC FACTORS FOR RHEUMATOID ARTHRITIS:

Data from twin studies found that genetics accounted for over 60% of the overall risk for people who develop RA. The risk of developing RA in the general population is about 1%. Therefore, about 1 in 100 people in the general population will develop RA. The risk of developing RA if one's brother or sister (not a twin) has the disease is about 5%. The risk increases further when we consider twins that share the identical genetic material (also called monozygotic twins). If your identical twin has RA, your risk for developing the disease is about 15%. Linkage studies have focused on an area on human chromosome 6 and one area on the short arm of this chromosome called MHC. MHC genes account for one-third of the genetic contribution to RA risk. MHC genes with a confirmed role in development of RA include HLA-DRB1 genes, which are thought to be involved in antigen presentation to T lymphocytes. The growing list of non-MHC genes with a possible role in development of RA include the genes PTPN22 and STAT4, which are thought to be involved in T lymphocyte function, the genes TRAF1-C5 and TNFAIP3, which are thought to be involved in tumor necrosis factor (TNF) production and function, the genes CD40 and PAD14, which are thought to be involved in auto-antibody production, the gene CTLA4, which is thought to be involved in T lymphocyte activation, and the IRF5 gene, which controls macrophage-promoted inflammation.

ROLE OF EPIGENETICS IN GENETIC LINK WITH RHEUMATOID ARTHRITIS:

Chronic inflammation, which is responsible for joint inflammation and then eventual joint destruction, can be divided into two major types. $ACPA^+$ and $ACPA^-$ Rheumatoid arthritis which means presence or absence of HLA Class II alleles. Several genome-wide association studies been done and found that the genetic variants only play a 20% or less role in ACPA positive or negative arthritis [7]. Here comes the role of epigenetics. After studying DNA methylation, it is quite evident that important changes in genes that are unrelated to changes in DNA sequence may provide a link between development of inflammation and joint damage [8]. Promotor genes like CXCL12 and LINE1 are normally repressed by the DNA methylation. There is also new evidence that histone deacetylases (HDAC) can trigger effect of environmental factors like smoking and diet to alter the gene expression for RA. Also, important to mention about the target epigenetic proteins like bromodomain are being studied and new drugs are being developed [9]. These proteins called BET family (bromodomain and extra terminal) cause chromatin transcriptional activation.

ENVIRONMENTAL FACTORS

Cigarette smoking has been found to be a specific environmental risk factor for ACPA-positive RA with the risk increasing in proportion to the number of pack years [10]. Results from bronchoalveolar lavage suggest heightened citrullination, local inflammation & favour specific immune responses against citrullinated autoantigens. Additional autoantibodies may exist in seronegative RA with anti-carbamylated protein (CarP) antibodies being one of the more recently discussed in the literature. Excess of carbamylation has been described in three states of cyanate abundance: inflammation, uraemia and cigarette smoking [11]. Multiple studies have found odds ratios of association between smoking and RA of >2 and estimate that exposure to smoking accounts for ~20–30% of environmental risk for RA [12]. Occupational exposure to mineral oils was found to be a risk factor for ACPA positive RA in men in a Swedish cohort. A study performed in the Malaysian population with professional exposure to silica showed an increased risk of developing ACPA-positive RA, most notably in cigarette smokers. [13] Dietary factors have been seen to be independent risk factors for RA. Lower intake of vitamin D and antioxidants, and higher intake of sugar, sodium, red meats, protein and iron have been associated with increased risk for RA [14-20]. Conversely, a recent meta-analysis showed that alcohol intake was inversely correlated with the development of ACPA positive RA [21] Infections have long been major candidates for auto-immunity induction in RA. Periodontal disease has been reported in different studies as a risk factor. P.gingivalis expresses bacterial forms of peptidyl arginine deiminase which has been shown to citrullinate peptides in-vitro. Notably, antibodies against P.gingivalis were detected in ACPA and RF positive persons [22]. Alterations in gut microbiomes have been described in patients with RA [23]. An abundance of Prevotella copri with loss of Bacteroides has been demonstrated in the stool of RA patients [24]. Correlation between gut and oral dysbiosis and with laboratory measures of RF and ACPA was found in a recent metagenomics study of RA patients [25]. Beneficial effects of probiotics have yet to be indisputably demonstrated in the treatment of RA.Women who are younger at menarche have a relatively low risk for RA, suggesting that sex hormones influence both RA development and severity. During pregnancy, most with RA experience significant reductions in disease activity, but almost all relapse within 3 months of delivery [26]. Oral contraceptives have been found to lower disease severity, but data from initial studies showing protective effects could not be confirmed after adjustment for age [27,28]. Prediction models that incorporate various genetic and environmental factors (e.g. smoking) are being explored [29,30]

CONCLUSION:

RA is one of the most common autoimmune disorders whose exact ethology is not known. From the discussion above it states that the initiation of RA is caused by the interaction of the environment (as one example smoking doubles risk of certain types of RA) on genetically susceptible individuals. RA is a multisystem disease and is associated with a high morbidity and mortality rate. Having a basic understanding of disease activity will help us to develop targeted approaches to pharmacological intervention to decrease this. An example of this is that we know there are several immune mediators that are involved in the pathology of RA and lots of research has been done to create biological treatment modalities to target the defects.

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