Molecular Genetics of Rheumatoid Arthritis and Future Prospectus in Pakistan

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Abstract

The spectrum of rheumatic disease is wide and includes conditions with diverse pathology, although most have in common a heritable risk with a complex genetic basis. Over the past decade intense efforts has been done to understand the contribution of genotype to the expression of disease in terms of both basic pathogenesis and clinical characteristics. The dramatic improvement in technology and methodology has accelerated the pace of gene discovery in complex disorders in an exponential fashion. This review focuses on rheumatoid arthritis and describes some of the recently described genes that underlie this condition and the extent to which they overlap.

Rheumatoid arthritis

Rheumatoid Arthritis (RA) is a multifactorial disease due to a combination of genetic and environmental factors (Dieude and Cornelis, 2005). Its genetic component has been suggested by familial aggregation, twin studies, and segregation analysis (Cornelis et al. 1998). It has been characterized by incomplete penetrance, genetic heterogeneity and almost certainly multiple disease genes (Cornelia and Jorg, 2000). Epidemiological studies have found considerable variations in the incidence and prevalence of RA across time periods and geographic regions. Many factors, both genetic and environmental, such as climate, ultraviolet (UV) exposure and diet could contribute to rate of RA prevalence. Evidence from twin (Aho et al. 1986; Deighton and Walker, 1991) and family studies (MacGregor et al. 2000) suggests that both genetic and environmental factors contribute to susceptibility to rheumatoid arthritis, and disease heritability has been estimated to be 60% (Dib et al. 1996).

In this review we describe insights gained into the pathogenesis of Rheumatoid Arthritis (RA) by the techniques of modern genetics, in particular evidence from genome-wide association (GWA) studies, which provide support for the existence of a common genetic risk basis to several diseases.

The major histocompatibility complex (MHC)

The major histocompatibility complex (MHC) region on chromosome 6 contributes to the risk of almost all autoimmune diseases and its role in immunity in mice was recognized over 60 years ago. In humans, the MHC locus is also known as the HLA (human leukocyte antigen) region, reflecting the initial identification of MHC gene products on the surface of white blood cells. The classical MHC extends over around 4 megabases and comprises three clusters: class I, II, and III. Class I and II regions include genes that encode the α- and β-chains of the MHC I and II complexes, and flank the class III region, which contains an assortment of immunologically relevant genes. Despite extensive study, the mechanisms that link the MHC to disease are largely unknown, although it is supposed that variation in the MHC peptide binding cleft facilitates presentation of self-antigen to autoreactive lymphocytes.

These difficulties in understanding the MHC are not without reason; it contains some of the most polymorphic loci described in the genome and has a highly complicated genetic architecture with some regions exhibiting extended linkage disequilibrium (Horton et al. 2004).

In RA, the MHC accounts for around a third of the genetic liability (Fernando et al. 2008). Alleles at HLA-DRB1 contribute much of this risk. Additional loci contributing to the risk of RA identified by high-density genotyping include HLA-DP in patients with anticyclic citrullinated peptide antibodies (Ding et al. 2009). Again, further work is required to definitively implicate this gene rather than variants in linkage disequilibrium.

Tumor necrosis factor (TNF)

TNF-associated signalling pathway genes play a prominent role in the risk for both Systemic Lupus Erythematosus (SLE) and RA. Associations of variants in TNFAIP3, and the TRAF1-C5 locus have been identified (Ding et al. 2009; Plenge et al. 2007). TNFα-induced protein-3 (TNFAIP3) is a ubiquitin editing enzyme that acts as a negative regulator of NFκB. This can disassemble Lys63-linked polyubiquitin chains from targets such as TRAF6 and RIP1. A second region of TNFAIP3 catalyses Lys48-linked ubiquitination that targets the molecule for degradation by the proteasome (Komander and Barford, 2008). TNFAIP3 modifies key mediators in the downstream signalling of TLRs that use MyD88, TNF receptors, the IL-1 receptor family, and nucleotide-oligomerization domain protein 2 (NOD2) (Sun, 2008). Tnfaip3 knockout mice develop severe multi-organ

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inflammatory disease, and the phenotype is lethal (Lee et al. 2000). The SNP rs10499194 in TNFAIP3 carries an Odd Ratio (OR) of 1.33 for RA, and rs5029939 an OR of 2.29 for SLE (Lee et al. 2000), the latter also conferring an increased risk of haematologic or renal complications (Bates, 2009).

On chromosome 9 the region containing TRAF1 (TNF receptor associated factor 1) and C5 (complement component 5) genes is associated with significant risk for RA .TRAF1 is principally expressed in lymphocytes and inhibits NFκB signalling by TNF. This pathway is blocked in TRAF1 overexpression (Carpentier and Beyaert, 1999) whilst, conversely, Traf1-/- mice are sensitized to TNF and have exaggerated TNF-induced skin necrosis (Tsitsikov et al, 2001). The complement system has long been known to be involved in the pathogenesis of RA. In the collagen-induced arthritis model of RA, C5 deficiency prevents disease de novo and ameliorates existing symptoms and signs (Tsitsikov et al, 2001; Wang et al. 2000). Interestingly, GG homozygotes at the TRAF1-C5 SNP rs3761847 with RA have a significantly increased risk of death (hazard ratio 3.96, 95% confidence interval 1.24 to 12.6, P = 0.02) from malignancy or sepsis, potentially allowing identification of patients for appropriate screening (Panoulas et al. 2009).

Protein tyrosine phosphates, Non-receptor type 22 (PTPN22)

Outside the HLA region, the first reproducible genetic association for RA came with the implication of PTPN22 from a candidate gene approach (Begovich et al. 2004) based on linkage analysis identification of a susceptibility locus at 1p13 (Jawaheer et al. 2003). It has remained the strongest and most consistent association mapped by GWA studies in RA. A role in SLE has also been identified (Harley et al. 2008). The OR for the risk allele is around 1.75 in RA, and 1.5 in SLE. However, it should be noted that this allele (encoding the R620W mutation) is monomorphic or not disease associated in Korean or Japanese patients (Lee et al. 2009; Ikari et al. 2006). PTPN22 encodes lymphoid tyrosine phosphatase (LYP), a protein tyrosine phosphatase that inhibits T cell receptor signalling, decreasing IL-2 production. The disease associated SNP is responsible for a change from arginine to tryptophan at position 620, which inhibits binding to the SH3 domain of carboxy-terminal Src kinase. This in turn appears to enhance dephosphorylation of tyrosine residues in the Src family kinases Lck, FynT, and ZAP-70 (Cloutier and Veillette, 1999; Gjorloff-Wingren et al. 1999). The overall effect of the mutation is a reduction in T cell receptor signalling. The pathogenic effect of this is unclear, but may relate to impaired negative selection in the thymus, or lead to a reduction in regulatory T cells (Vang et al. 2008). Conversely, the R623Q variant of PTPN22, which is a loss-of-function mutation affecting the phosphatase activity of LYP, is protective against SLE (Orru et al. 2009).

Polarization towards TH1 and TH17 phenotypes: STAT4 and IL23

STAT4 encodes signal transducer and activation of transcription factor-4, responsible for signalling by IL-12, IL-23, and type 1 IFNs (Watford et al. 2004). STAT4 polarizes T cells towards TH1 and TH17 phenotypes, which has the potential to promote autoimmunity (Mathur et al. 2007). In RA the OR for the risk allele of SNP rs7574865 is 1.32 in one case-control study (Remmers et al. 2007), with a less strong disease association at rs11893432 in a meta-analysis of GWA studies (OR 1.14) (Raychaudhuri et al. 2008). There is convincing evidence that STAT4 is a risk locus for SLE in multiple racial groups (Hom et al. 2008; Namjou et al.2009), and it may be theorized that interference in type I IFN signalling may be the underlying pathogenic mechanism in this case.

Peptidyl arginine deiminase-4 (PADI4)

Peptidyl arginine deiminase-4 (PADI4) is a member of the enzyme family responsible for the post-translational citrullination of arginine residues in RA synovium, subsequently recognized by anti-cyclic citrullinated protein antibodies. In Japanese [87] and Korean patients (Kang et al. 2004), case-control association studies have identified functional haplotypes of PADI4 conferring risk of RA. However, in Caucasian populations this association is inconsistent (Gandjbakhch et al. 2009; Martinez et al. 2005)

Disease burden in Pakistan

The general prevalence of RA is estimated to be 0.5-1.0% worldwide (Caporali et al. 2009) and 0.1-0.2 % in Pakistani population (Baig, 2003). RA have been reported with different prevalence in different ethnic groups such as in European and American populations RA is more prevalent as compared to Asians (Abdel-Nasser et al. 1997; Lawrence et al. 1998; Gabriel et al. 1999; Alamanos and Drosos, 2005). The high prevalence of RA in Native American populations is up to 6.8 % while it's low in Asian countries (~0.3 %) (Silman and Hochberg, 2001; Akar et al. 2004).

In Pakistan, no work has been done on RA so far at molecular level. Although very little have been contributed to prevalence and epidemiology of rheumatic diseases. Studies performed by A. Farooqi and T. Gibson (1995; 1998) found the low prevalence of major rheumatic diseases in northern Pakistan and high prevalence of rheumatoid arthritis in affluent and poor urban communities of Pakistan.

Nadia et al (2008) indicated that the high frequency of anxiety and depression among patients with common rheumatic disorders and determine the possible relationship of different demographic and clinical variables with anxiety and depression.

Several studies indicate that depression occurs in 13-20% of patients suffering from Rheumatoid Arthritis (RA). By conservative estimates, major depression is two to three times more common in patients with RA than in the general population (Regier et al.1988). Depression increases the burden of RA to the patient and society,

increases worry about the disease and leads to more physical symptoms (DiMatteo et al. 2000; Dickens et al. 2001).

In South Pakistan, the prevalence of rheumatoid arthritis is said to be 0.9/1000 and 1.98/1000 in poor and affluent districts respectively, whereas in North Pakistan, the prevalence of major rheumatic disorders is quoted as 148/1000 (Hameed et al. 1995; Farooqi et al. 1998). Few studies have been carried out in Pakistan to look at the psychiatric morbidity in patients suffering from chronic rheumatic diseases. Information about HLA distributions and their associations with RA among people of South Asian derivation suggest marked ethnic heterogeneity (Malaviya et al 1983).

There are no data from Pakistan and whether or not such genetic influences contribute to the low prevalence of RA determined by us cannot be stated. There are two main reasons for incompleteness of the existing data on RA incidence and prevalence.

First, figures from Pakistan are scanty and need to be improved to allow understanding of intra- and inter-regional variability of RA. Second, several data suggest that both epidemiological and clinical features of RA vary over time indicating the involvement of different genes. Therefore, molecular studies are needed in the same area to identify changing patterns of the disease.

Future prospectus

Molecular characterization of genes involved in rheumatoid arthritis from in Pakistani population is required, which will describe the pathogenesis of RA at molecular level and to explore the possible relationship of the different demographic and clinical variables associated with it.

Apart from genetic factors, various viruses have been implicated in the cause and pathogenesis of rheumatoid arthritis (RA). Hepatitis C virus (HCV) infection, which has been recognized as a cause of some autoimmune diseases and which has been described as sometimes presenting with rheumatic manifestations indistinguishable from RA, might be a candidate (Maillefert et al. 2002; Hsu et al. 2003) Therefore, data needs to be generated in this regard to study the association of hepatitis C virus with RA in our population.

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