Genetics of Lupus—Untying the Gordian Knot!

Rohini Handa

Systemic Lupus Erythematosus (SLE) is a genetically complex autoimmune disease with poorly understood pathogenesis. The heritability of SLE is approximately 66%. Genome-wide association studies have led to mapping of 28 disease susceptibility loci which account for less than 10% of the genetic heritability. In lupus patients defective clearance of apoptotic cells may play an important role in disease pathogenesis. During apoptosis, cells form membrane bound blebs containing intracellular proteins, which act as a source of autoantigens. With defective clearance of apoptotic blebs, cells undergo secondary necrosis and release of nuclear auto-antigens. Apo-1/Fas, also known as CD95, is a 36-kDa transmembrane glycoprotein of the tumor necrosis factor/nerve growth factor receptor family involved in apoptosis of auto reactive lymphocytes. The Fas/Apo-1 gene has been mapped to chromosome 10q24.1. Two positions in the Fas promoter region have been scrutinised in various populations due to their binding capability with transcription factors. These include position -670 which binds with the transcription factor STAT1 and position -1377 which binds with the transcription factor SP1. The association of a functional single nucleotide polymorphism (SNP) at position -670 in the promoter region of the apoptosis gene with disease susceptibility has been studied in many rheumatic diseases like Sjögren's syndrome, rheumatoid arthritis and lupus.

In this issue of JAPI, Pradhan and colleagues report Apo-1/Fas -670A/G promoter polymorphism among SLE patients from western India. A/G genotype was seen in 54% patients, A/A in 31% and G/G in 15% patients as against a frequency of 60%, 10% and 30% in the normal population. The A/A genotype demonstrated significant association with lupus as compared to the normal population. The authors grouped their patients into those with renal lupus and those without. Amongst lupus nephritis patients the distribution of -670 A/G phenotype was A/G 45.7%, A/A 34.31% and G/G 20% as compared with 60%, 28.6% and 11.4% respectively in non nephritis patients. There was no statistically significant association that could be discerned. Lupus patients with A/A genotype demonstrated severe clinical involvement. The lupus patients in this cohort exhibited four fold increase in the mean soluble FAS (sFAS) levels with lupus nephritis patients showing higher sFAS as compared to non nephritis patients.

The published literature on this subject is inconsistent. Molin et al. compared the FAS -670 A/G genotypes of 107 German patients with SLE with 96 healthy controls and demonstrated a trend for association between SLE and the homozygous A genotype. On evaluation of the Japanese, Kanemitsu et al. found the -670A allele to be of higher frequency in SLE patients than in controls. However, this association has not been seen in Iran, Korea and Australia. The contradictory results from various studies are not entirely unexpected. This may be due to racial and ethnic differences. Other reasons could be publication bias or underpowered studies with inadequate sample size. A similar thing has been noted in case of 308-A/G promoter polymorphism where a recent meta-analysis has emphasised the role of ethnicity. In case of this polymorphism, the A/A genotype was associated with SLE in European-derived population. No association was detected in Asian-derived population. Similar results were found between the risk allele A and SLE where a significant association was found in European population, but not in Asian or African populations.

Apart from disease susceptibility, different groups have tried to study the association of different clinical features with the FAS gene polymorphisms, again with varying results. Lee et al found the homozygous A allele at -670 to be associated with development of anti-RNP antibodies while Huang et al demonstrated the association of this with photosensitivity and oral ulcers. It is difficult to draw firm conclusions since the frequency of different clinical features may vary in different ethnic groups.

Elevated levels of sFAS have been demonstrated in more than 50% of patients with lupus and these inhibit FAS mediated apoptosis of lymphocytes. Researchers from Shiraz and Mashhad in Iran have separately demonstrated significantly higher sFAS and Fas ligand levels in SLE compared with controls. Sahebari and colleagues also showed a significant correlation coefficient between the sFAS and disease activity based on SLEDAI2K variables. Additionally, they demonstrated difference between serum levels of sFAS in the active and inactive phases of disease according to SLEDAI. However, other workers have demonstrated that serum levels of sFAS correlate more with organ damage as measured by SLICC/ACR but not with SLEDAI. Clearly, more work is needed to clarify whether sFAS represents disease activity or damage and before it can be incorporated as a surrogate of damage or activity in lupus.

The heterogeneity of lupus is reflected by its genetic complexity and mirrored in its clinical diversity. Polymorphism in Fas gene is but one component of the genetic susceptibility to lupus and sFAS is but one marker of disease activity. The results from one population group cannot be extrapolated to another population group. This is what makes this field challenging, fascinating and, at times, frustrating. More genetic studies are needed to help demystify the enigmatic syndrome that we call lupus today.

References

5. Pradhan VD. A study of APO1/FAS promoter polymorphism


