Correspondence on 'Increased risk of systemic lupus erythematosus in patients with autoimmune haemolytic anaemia: a nationwide population-based cohort study'

We read with great interest a letter by Mo *et al*[1] pointing out that patients with autoimmune haemolytic anaemia (AIHA) had a significantly higher risk of systemic lupus erythematosus (SLE) than non-AIHA individuals. Considering that AIHA is clearly over-represented in patients with SLE, often occurring before the diagnosis of SLE, the authors nicely investigated the association between AIHA and SLE incidence in a nationwide, population-based, matched cohort study and demonstrated a high association (HR=54.7) between AIHA and SLE risk.[1] SLE is a chronic, highly heterogeneous autoimmune disease, characterised by differences in autoantibody profile, serum cytokines and a multisystem involvement.[2] AIHA is a highly heterogeneous pathological condition caused by the increased destruction of red cells in the presence of anti-red cell autoantibodies, due to immune system malfunction, thus resulting in severe tissue oxygenation disturbance.[3] Of note, AIHA may present in association with a spectrum of infections (viral, bacterial and atypical) and is often associated with thrombocytopenia, lupus nephritis and central nervous system activity.[4] Moreover, previous studies have suggested that both diseases may share some genetic and environmental factors, while oxidative stress has also been reported to be a risk factor for AIHA and SLE.[5]

Recently, we presented data suggesting that various shared genetic polymorphisms are associated with an increased susceptibility for both idiopathic thrombocytopenic purpura (ITP) and SLE.[6] In the same framework, the current study by Mo *et al*[1] poses the intriguing question concerning the putative role of a shared genetic background as regards the concurrence of AIHA and SLE. Although the genetics of SLE is very well investigated, the genetic factors involved in the development of AIHA and its underlying molecular mechanisms are still elusive. However, a limited number of studies have pointed to certain genes as potential risk factors for developing these diseases, thus suggesting a shared genetic predisposition in some cases. It has been reported that the human leucocyte antigen (*HLA*)-*B8* and *HLA-DQ6* regions are associated with both diseases,[7 8] while single nucleotide polymorphisms of the *CTLA-4*,[9] *NFATC1*,[10] *LT-a*,[11] *FcgRIIa*,[12] *FOXP3*[13] and *CARD11*[14] genes have been also reported to be associated with the development of these diseases. With regard to AIHA, nine downregulated miRNAs have been detected so far[15] and, interestingly, six of these (miR-20a, miR-146b-5p, miR-223, miR-324-3p, miR-484 and miR-660) are also implicated in both diseases.

In conclusion, lessons learnt so far from the genetic studies focusing on AIHA and SLE suggest that these diseases appear a remarkable biological complexity. Various gene loci involved in both diseases have been identified thus far. The further identification of either shared or disease-specific genetic loci associated with both the development of AIHA and SLE as well as their specific clinical features may help better delineate the mechanisms for both diseases and properly disclose even subclinical associated conditions, in an attempt to choose the most appropriate therapy.[7]

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