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Commentary

Yoga, rheumatoid arthritis & human leukocyte antigen-G

Human leukocyte antigen (HLA) is a complex of genes on chromosome 6 at position 6p21.3. These genes code for surface proteins involved in the regulation of the immune system[1]. Classical HLA genes play an important role in differentiating between 'self' and 'non-self' regulatory immunity in humans. However, non-classical HLA genes such as HLA-G serve a different function than classical HLA. Just like HLA proteins, the HLA-G molecule is also a heterodimer containing a heavy and light chain. Normally, HLA-G shows limited expression in certain tissues and cells of the body. HLA-G has at least seven isoforms produced through alternate splicing. These isoforms are named HLA-G1, G2 through G7. HLA-G1 to G4 are membrane bound through a heavy chain, while HLA-G5 to HLA G7 are soluble. HLA-G has been shown to influence fetomaternal immunogenic tolerance, immune response to transplant and body response in life-threatening tumours[1,2].

HLA-G locus is highly polymorphic, but variability is lower than classical HLA class 1 genes. Although more than 50 coding alleles or haplotypes are known, these are mainly synonymous mutations or in-frame variations[1]. As compared to the coding region, HLA-G 3' UTR has many high-frequency variable sites. Among these, nine variations are considered true polymorphisms because these account for more than 95 per cent of all haplotypes. A 14 bp insertion/deletion (rs 371194629) is an ancestral allele as it is also present in Africans[3]. The 14 bp insertion/deletion has been implicated in the HLA-G transcriptional levels and mRNA stability. The absence of 14 bp segment has been shown to lower mRNA production and its presence stabilizes mRNA, thus resulting in higher expression. The 14 bp presence in transcript also causes lower stability of the mRNA[4]. Another variant +3142G (rs 1063320) regulates the affinity of microRNA binding to the HLA-G transcript. The presence of G allele at +3142 results in stronger binding of microRNAs such as mir-148a, mir-148b and mir-152, thus decreasing HLA-G expression[5].

Rheumatoid arthritis is a common form of inflammatory autoimmune disease. It is a chronic condition and involves slow degradation of bone, cartilage and synovial destruction. The aetiology of the disease is not well understood. General treatments involve non-steroidal and anti-inflammatory drugs, disease-modulating anti-rheumatic drugs and corticosteroids. Many studies have also shown the role of HLA-G in several autoimmune diseases such as myopathies, atopic dermatitis and cutaneous psoriasis[6]. Since HLA-G could divert helper response to Th-2 type, it was hypothesized that HLA-G may be a protective molecule in the inflammatory response in RA as well. It is already known that the genetic variants of HLA-G gene can regulate its expression; so it is possible that the genotypes are associated with inter-individual variability in the context of susceptibility and severity of RA.

Yoga comprises of physical, mental and spiritual practices and disciplines that originated in ancient India, and now popular world over. It is believed to be mind–body stress-relieving exercise. Studies have shown that yoga exercises could ease chronic pain, bring out more flexibility of joints and result in better sleep[7]. Another study found that 21 day yoga exercise regimen resulted in the elevation of soluble HLA-G, which is an established immune modular[8]. The yoga-performing patients had fewer requirements of anti-inflammatory drugs also.

The study by Gautam *et al*[9] published in this issue of IJMR was carried out as a randomized control trial to evaluate the influence of HLA-G common functional polymorphisms on disease severity in RA patients undergoing yoga therapy. The authors enrolled 140 RA patients selected after complete clinical evaluation by a rheumatologist. The patients

were randomized and divided into two groups – yoga and non-yoga. Participants of both the groups were on conventional routine drug therapy for at least six months before enrolment. Yoga group patients undertook an eight-week programme along with routine medications. Yoga sessions included a set of *asanas, pranayama* and *dhyana* for approximately two hours daily, five times a week for eight weeks, under the supervision of a trained specialized yoga instructor. Both yoga and non-yoga groups were advised to maintain their normal activities and continue with prescribed medications. Peripheral blood samples were taken from both groups at the start and end of the yoga trial. Serum levels of soluble HLA-G were determined by ELISA, and disease activity was evaluated by standard DAS28-ESR. After the trial, it was noticed that soluble HLA-G levels significantly improved in yoga group as compared to non-yoga controls. In addition, the authors genotyped all participants for HLA-G 14 bp ins/del and +3142G>C polymorphisms using standard PCR.

From the analysis of results of the present study,[9] the studied genotypes of HLA-G did suggestively influence the levels of HLA-G as low producing sHLA-G susceptibility genotypes +3142GG and 14 bp ins/ins showed a significant increase of sHLA-G levels, but in both yoga and non-yoga groups. In addition, no significant association was found between change in the sHLA-G levels and disease activity post-intervention based on genotypes in either of the groups. The authors concluded that RA improvement and response with yoga are independent of *HLA-G* +3142G>C and 14 bp ins/del genotype.

Therefore, it can be inferred that HLA-G is only one of the many variables in the disease severity of rheumatoid arthritis. However, in future studies, it may also be imperative to include various genetic variants in the panel to evaluate their influence and interactions using appropriate statistical tools. The present study has been carried out in a limited number of participants from a single centre. In addition, disease duration, diet and lifestyles of patients may also be considerably different. Therefore, there is a need to carry out the study in a larger number of cases in different populations. Any genetic epidemiology study also mandates independent replication in different cohorts before clinical implementation.

The practice of yoga involves low-cost, risk-free exercises which have been shown to be highly beneficial in many inflammatory and other lifestyle diseases. However, much is still unknown about the mechanistic pathways and inter-individual variability in response to yoga exercises. Therefore, the template of the present study opens new vistas to build a strong scientific basis of yoga practice.

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