Leptin-related polymorphisms and SLE

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Leptin is a hormone/cytokine that is mainly produced by adipocytes and has a range of actions that span from the control of metabolic balance to the modulation of adaptive and innate immune responses. Many investigations have indicated that the pro-inflammatory activities of leptin can contribute significantly to the promotion and maintenance of autoimmune responses. It is not known whether the abnormal elevation of leptin in patients with systemic lupus erythematosus (SLE) - an autoimmune disease characterized by multi-organ involvement and the presence of autoantibodies - can reflect the chronic inflammatory status of the disease or can contribute to the pathogenesis of the disease. To partly address this question, a recent investigation analyzed several leptin-related gene polymorphisms in SLE in large numbers of individuals from different ancestral groups. The study identified weak associations with certain SNPs that did not remain significant after correction for multiple testing. This review discusses the implications of those findings for the pathogenesis of SLE and for the possibility of leptin-based modalities of therapeutic intervention in the disease.

Introduction

As in most autoimmune disease, the pathogenesis of systemic lupus erythematosus (SLE) includes environmental factors that trigger abnormal immune responses in genetically predisposed individuals. Most of the times, individuals that carry an increased susceptibility to develop SLE express selected genetic polymorphisms that contribute to the modulation of pathways that have critical roles in the mechanisms that lead to the development, maintenance and progression of the disease. As such, genetic polymorphisms can influence the expression and/or activity of certain genes that are relevant to the SLE disease process, thereby affecting predisposition and, ultimately, disease outcomes and response to therapy. Although many genes have been tested by genetic association studies for possible contribution to an increased risk of SLE [1-2], gene association studies investigating leptin-related polymorphisms in the disease have been sparse and inconclusive, until recently [3].

Why leptin and SLE

In SLE, an exquisite gender bias exists, being women affected more than men (independently of race and/or ethnicity). This aspect has been linked to gender-related differences that include differential gene expression and hormonal disparity [4]. For example, certain sex hormones in SLE can create favorable conditions that facilitate autoreactive cell sensitization to stimulation/activation, ultimately promoting autoimmune responses [5].

Leptin is a sexually dimorphic hormone whose circulating
levels in normal individuals are five to ten times higher in females than in males [6]. This aspect, together with the observation that leptin concentration is abnormally elevated in autoimmune mice and in patients affected by autoimmune disease [6], led to wonder whether certain gene polymorphisms in SLE patients could contribute to the pathogenesis of the disease [3, 7]. Additionally, past studies indicated an abnormal increase in serum/plasma leptin levels in SLE patients (independent of disease activity) [8-12].

A study in a small numbers of subjects with homogeneous ethnicity tested the possibility that specific polymorphisms in the leptin receptor gene could associate with an increased predisposition to develop SLE [7], building on the observation that among the several SNPs identified in the leptin receptor gene, the Q223R polymorphism (where an A to G transition in exon 6 encoding for the extracellular domain of the leptin receptor) could alter signal transduction or leptin binding (the leptin receptor exists in at least six alternatively spliced, with only a long form capable to signal intracellularly) [6]. The study found that carriers of variant genotype (A/G + G/G) (odds ratio [OR] = 2.52) or G allele (OR = 1.49) had an elevated risk for SLE, being the LEPRQ223R polymorphism specifically associated with an increased risk of SLE [7]. However, the study lacked power to reach generalized conclusions (i.e., whether analogous associations might occur in different ethnic groups or in large cohorts) since it involved only 100 Kashmiri SLE patients and an equal number of healthy controls.

**Leptin-related polymorphisms and SLE**

More recently, a large study genotyped a collection of DNA samples from 8,269 cases and 7,437 controls belonging to four different ancestral groups to test the possibility that leptin pathway-related gene polymorphism could contribute to risk of SLE [3]. The study was rendered possible by the fact that conspicuous numbers of samples were contributed by the Large Lupus Association Study 2 (LLAS2), whose participating institutions are located worldwide (United States, Asia and Europe). To delineate the possibility of associations between leptin-related gene polymorphisms and increased susceptibility to develop SLE, the genetic variants tested in the study included not only those for the leptin gene and its receptor but also for genes that indirectly influence and/or are influenced by leptin. The polymorphisms that were investigated included those of the leptin gene (LEP) [14] because of the obvious possible role in regulating expression and/or function and/or catabolism of leptin. Leptin receptor (LEPR) polymorphisms (all isoforms) [15] were studied for a possible influence on leptin catabolism and/or sustained leptin activity. The other gene polymorphisms that were included were those of peroxisome proliferator-activated receptor (PPAR)-γ (PPARG) [16-18] (because leptin can downregulate PPAR-γ expression to increase release of pro-inflammatory IL-1β, IL-6 and TNF-α [19-20]) and growth hormone secretagogue receptor (GHSR) because its opposing actions on leptin result in the inhibition of pro-inflammatory cytokines [21-22]. From the above genes, haplotype-tagging single nucleotide polymorphisms (SNPs) were selected for genotyping using a customized SNP genotyping array. To avoid genotyping of all SNPs for the genes of interest yet maintain the ability to capture the majority of diversity within each region, haplotype tag SNPs were selected for genotyping according to the Hapmap Project [23], together with SNPs with potential functional consequences. After data cleaning and quality control measures, the selection led to the genotyping of 7 SNPs for LEP, 10 SNPs for LEPR, 3 SNPs for GHSR and 12 SNPs for PPARG for subsequent use in genetic association test. Possible association with SLE was tested in 15,706 case-control subjects from four different ancestral groups: European American (EA: 3,966 cases vs. 3,543 controls), African American (AA: 1,527 cases vs. 1,812 controls), East Asian (AS: 1,272 cases vs. 1,270 controls) and Hispanic (HS: 1,504 cases vs. 812 controls). It was found that in LEP the A allele of rs12706832 associated with decreased risk of SLE in AA (OR = 0.84), whereas the A allele of rs3828942 associated with increased risk of SLE in AA (OR = 1.16). In LEPR, the C allele of rs6690625 and A allele of rs1892535 associated with decreased risk of SLE in HS (OR = 0.79 and 0.82, respectively). In GHSR, the G allele of rs2948694 associated with decreased risk of SLE in AA (OR = 0.84), whereas the C allele of rs3828942 associated with increased risk of SLE in HS (OR = 1.16). In LEPR, the C allele of rs6690625 and A allele of rs1892535 associated with decreased risk of SLE in HS (OR = 0.79 and 0.82, respectively). In GHSR, the G allele of rs2948694 associated with decreased risk of SLE in HS (OR = 0.81). In PPARG, the A allele of rs12633551 and rs3856806 associated with decreased risk of SLE in EA (OR = 0.80 and 0.88, respectively). Although these data detected significant association signals at several loci, none showed statistically consistent association when analyzed in multiple ancestral groups. Meta-analysis combining all four ancestral groups showed multiple SNPs in PPARG exhibiting association with SLE, yet after correction for multiple tests, only the association of rs6690625 in LEPR with SLE in HS remained significant. As such, the data did not support associations between the chosen leptin-related polymorphisms and an increased risk of SLE.

Despite those findings, it must be acknowledged to use caution in drawing definitive conclusions about a possible lack of associations between leptin-related polymorphisms and SLE. For example, the study identified certain associations with selected ethnicities, implying a possibility that certain genes might provide an increased risk for SLE if present in specific backgrounds. Also, the study focused only on selected SNPs, and the analysis of additional SNPs might uncover unknown possibilities.

**Will these findings influence leptin-based intervention in**
SLE?

While not identifying associations between leptin polymorphisms and SLE in multiple ethnicities, those results are not in conflict with the possibility that leptin activities could play an important role in the pathogenesis of SLE. In this sense, genetic association studies between BlyS-gene related polymorphisms and SLE also had suggested a lack of association with the disease [24-25]. BlyS is an important pro-inflammatory cytokine that, like leptin, is abnormally elevated in SLE patients [26]. Importantly, BlyS promotes SLE both in mice and in humans [26], and BlyS antagonism can protect from SLE [27] even if there is no associated polymorphism of BlyS or BlyS receptor BCMA with SLE [24-25]. Of interest, BlyS antagonism reduces SLE disease manifestations in humans efficiently enough to gain the approval by the FDA as a new therapeutic agent in SLE after a gap of more than 50 years [28]. One possible explanation could be that the increase of BlyS levels in SLE patients might represent a consequence of multiple interactions between related genes and/or genes and environment, and similar considerations could be applied to the findings between leptin polymorphisms and SLE, where genes other than PPRG and GSHR might possibly influence leptin modulation. Another consideration is that some associations were observed in subgroups of SLE patients. Therefore, follow up analyses should be done, employing multivariate analyses on subsets of patients (divided according to organ involvement, disease manifestations and positivity for certain autoantibodies). In case associations are found, functional assessments should evaluate whether stratification could identify individuals at increased risk for SLE.

Conflicting interests

The author has declared no conflict of interests.

References


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