The polymorphism rs13259960 in *SLEAR* predisposes to systemic lupus erythematosus

With the support by the National Natural Science Foundation of China and the Chinese Academy of Sciences, the research team led by Prof. Chen RunSheng (陈润生) at the Key Laboratory of RNA Biology, Institute of Biophysics, Chinese Academy of Sciences, uncovered a mechanism by which the risk variant at rs13259960 modulates *SLEAR* expression and predisposes to systemic lupus erythematosus, which was published in *Arthritis Rheumatol* (2020, Jan 12, DOI: 10.1002/art.41200).

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease and affects almost all parts of the human body. SLE shows a strong familial aggregation. Although the exact etiology of this disease is not well characterized, it is believed to be triggered by a complex combination of genetic, environmental and hormonal factors. Over the past decade, genome-wide association studies have identified a large number of genetic variants associated with human diseases and traits, however, presently little is known about the genetic significance of long noncoding RNA (lncRNA) in SLE. Chen's group has long been devoted to the investigation of noncoding RNAs. They carried out the first study on SLE susceptibility variants in lncRNA genes in Han Chinese, and identified a new susceptibility locus (rs13259960, $P_{combined} = 1.03\times10^{-11}$, OR=1.35) in a lncRNA gene which they named *SLEAR* (Systemic Lupus Erythematosus Associated RNA).

More excitingly, they found that the rs13259960 polymorphic site is located in an intronic enhancer which could recruit STAT1 to the promoter of SLEAR and facilitate *SLEAR* transcription. The rs13259960A>G SNP was shown to impair the STAT1 recruitment, resulting in a decreased SLEAR level compared with the A allele. SLEAR was expressed at significantly lower levels in SLE patients as compared to controls, and its reduced activity implies an increased risk of SLE. They further investigated the functional role of SLEAR and its underlying regulatory mechanism in SLE development. Studies of the SLEAR target genes suggest regulation of apoptosis is a main function of this lncRNA. In addition, they found that SLEAR expression negatively correlated with degree of apoptosis in SLE patients. Moreover, they found SLEAR interacted with ILF2, hnRNP F and TAF15 to form a complex for transcriptional activation of the downstream anti-apoptotic genes. These findings suggest a mechanism by which the risk variant at rs13259960 modulates SLEAR expression and predisposes to SLE and may give insights into the SLE etiology. This work paved the way for studying how changes in a base in a non-coding sequence could affect biological function.

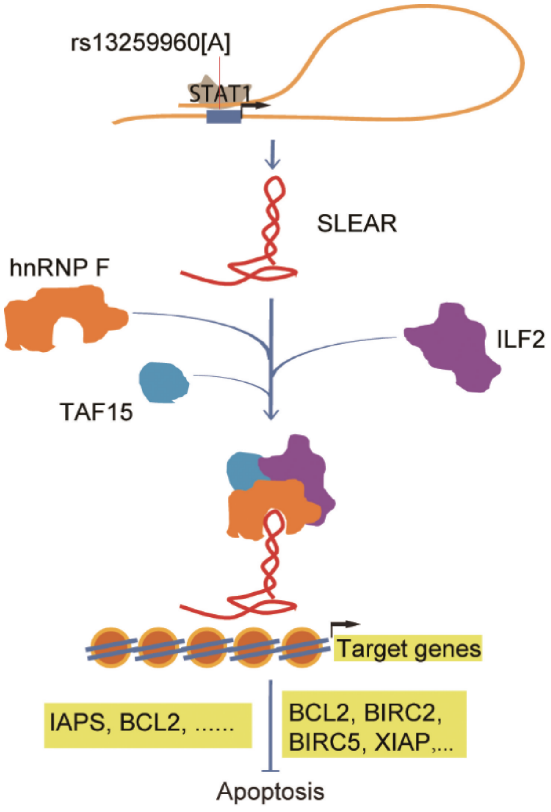

Figure Proposed functional role of SLEAR in modulating SLE risk.