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Genetics and Epigenetic in Systemic Lupus Erythematosus

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1. Introduction

Systemic lupus erythematosus (SLE) (OMIM #152700) is the prototype of a multiorgan autoimmune disease and still considered as a disease with an ambiguous etiology. The disease predominantly affects women during the reproductive years at a ratio of eight women per one man (Lopez, 2003). Its pathogenesis is multifactorial lying on genetic and environmental factors in which it occurs in genetically-predisposed individuals who have experienced certain environmental triggers resulting in an irreversible loss of immunologic self-tolerance. The nature of these environmental triggers is largely unknown. It is most likely that it requires a number of environmental triggers occurring together or sequentially over a limited period of time. The concept has therefore emerged of 'threshold liability' in which disease develops when a threshold of genetic and environmental susceptibility effects is reached (Jönsen,2007). Epigenetics, the control of gene packaging and expression independent of alterations in the DNA sequence, is providing new directions linking genetics and environmental factors. It has become clear that besides genetics, epigenetics plays a major role in complex diseases with complex immunological pathogenesis like lupus. Convincing evidence indicates that epigenetic mechanisms, and in particular impaired T cell DNA methylation, provide an additional factor. Interpreting the precise contribution of epigenetic factors to autoimmunity, and in particular to SLE, has become an active research area.

Herein, we will discuss our current understanding of SLE as an autoimmune disease and as a complex genetic disorder. Through the review of the current list of best validated SLE disease susceptibility candidate genes, in particular considering how the known and potential function of these genes may allow us to articulate the genetic of SLE pathogenesis. In addition we will review the effect of epigenetics on SLE pathology.

1.1 SLE, the disease

This complex autoimmune disease results on defects of multiple immunologic components of both the innate immune system and the adaptive immune system including altered immune tolerance mechanism, hyperactivation of T and B cells, decreased ability to clear immune complexes and apoptotic cells, and failure of multiple regulatory networks (Firestein, 2008). Moreover it is likely that immunological dysfunction precedes the onset of clinical disease by many years, making it a particularly challenging disease to study (Arbuckle, 2003).

SLE is a heterogeneous disease that has a diverse range of clinical symptoms, resulting from a widespread immune-mediated damage and it is presented differently from patient to patient (Arnett, 1988). The most common clinical manifestations of this disease include an are erythematous rash, oral ulcers, polyarthralgia, polyserositis, nonerosive arthritis, renal, hematologic, neurologic, pulmonary and cardiac abnormalities. Eleven criteria were identified for SLE clinical presentation, at least four of the 11 coded criteria need to be present for a clinical diagnosis of SLE (Arnett, 1988; Hochberg, 1997; Tan, 1982). Ethnic and genetic heterogeneity contributes to the complexity in SLE clinical presentation. Differently from Multiple sclerosis and although the disease is progressive in nature, no severity criteria have been developed to subgroup SLE patients (with the exception of kidney disease) (Tsao, 1998). A more detailed classification of SLE this heterogeneous disease would significantly help in its genetic analysis. Analyses conditioned on specific disease traits suggest that genetic effects arising from particular linkage regions may contribute to specific clinical or immunological features of SLE (i.e. the presence of haemolytic anaemia or the production of dsDNA antibodies) (Ramos, 2006; Hunnangkul, 2008). A similar picture has arisen from the study of mouse models. However, now it is widely accepted that SLE occurs in phases during a period of time that can be also of years. Therefore, the following steps in the development process of SLE have been suggested: i) genetic predisposition, ii) gender as an additional predisposing factor, iii) environmental stimuli which start immune responses, iv) appearance of autoantibodies, v) regulation of the autoantibodies, T and B cell fails with the development of the clinical disease, vi) chronic inflammation and oxidative damage as causes of tissue damage influencing morbidity (Gualtierotti, 2010).

1.2 Genetic contribution in the pathology of lupus

A genetic contribution to human lupus is well established. The strong genetic contribution to the development of SLE is supported by the high heritability of the disease (>66%), a higher concordance rate for SLE in monozygotic twins than in dizygotic twins or siblings (24–56% versus 2–5%, respectively) which was observed over 30 years ago, and the high sibling recurrence risk ratio of patients with SLE (between eightfold and 29-fold higher than in the general population) and up to 10% of SLE patients have a relative with lupus (Deapen, 1992). Clustering of SLE is fairly rare occurring only in 1/1000-2000 cases. Except in the rare cases of complement deficiency, the inheritance pattern of SLE does not follow simple Mendelian rules as we would expect for a single major gene effect, instead a polygenic model of susceptibility provides the best explanation for the familial clustering. Suggesting that genetic risk in most lupus patients arises from the combination of a number of relatively common variations in several different genes, each of these variations have a modest effect size, contribute to disease genesis. Despite this knowledge, however, it is a challenge to fully understand the genetic pathogenesis of the disease. This is essentially because SLE features a polygenic genetic model, which according to today's evidence may involve as many as 100 genes, and every gene only has a moderate effect size. Genetic studies can enhance our understanding of disease pathogenesis better. During the past few years, progress in biomedical science, bioinformatics, and experimental technology has given us new tools rapidly advanced our understanding of the genetic basis of systemic lupus erythematosus (SLE) and allowed a deeper investigation of SLE genetics and genomics. High throughput genotyping/sequencing platforms, high-throughput expression-level study technologies, etc., have brought forth many new insights. In particular, the genome-wide association study (GWAS) approach, with its ability to screen

hundreds of thousands of SNPs across the genome without previous knowledge of candidate regions or genes, has not only supported some findings from previous candidate gene studies, but also discovered convincing evidence for novel genetic loci that may be implicated in SLE (Hardy, 2009; Hirschhorn, 2009). Although the number of genes involved in susceptibility to SLE is increasing in number with the advances in research and technology, however, the complete list of genes that fully account for disease susceptibility is not completed yet. Table1 represents the top SLE candidate genes categorized by chromosomal location.

Most of the genes proven to be associated with susceptibility to SLE are involved in three types of biological process: 1) immune complex processing, 2) toll-like receptor function and type I interferon production, and 3) immune signal transduction in lymphocytes. Several genes without an obvious immunologic function in SLE have been discovered from recent GWA studies such as: KIAA1542, PXK, XKR6, ATG5, etc. (Harley, 2008). These novel gene (loci) discoveries, which are assumed the most powerful and interesting results from GWA studies, can lead us to new pathways or mechanisms that we previously didn't know. The genetic heterogeneity between ethnic populations has been suggested to be important in SLE risk (Yang, 2009), showing the need for further GWAS in the various populations. Genetic loci for SLE in an ethnic group are not always replicated in the other ethnic groups, especially between Whites and Asians (Kim, 2009). However, some loci have been shown consistent associations across ethnicities such as; HLA-DRB1, FCGRs (FCGR2A and FCGR3A), STAT4, and IRF5, BLK, TNFAIP3, BANK1, and MECP2, providing common mechanisms in the development of SLE across ethnic groups. For example: In a large collection of different ethnic groups including European American, Korean, African American, and Hispanic American, relatively high-density genotyping across STAT1 and STAT4 genes has confirmed the association of multiple STAT4 SNPs and common risk haplotypes with SLE in multiple racial groups (Namjou, 2009).

The ethnical diversity in gene association with SLE can be explained due to various reasons: *First*, different genetic backgrounds in the various populations from different ancestries result in the different genetic risk factors for the same disease (Namjou, 2009; Kochi 2009; Tian , 2008). *Second*, SLE as most of the complex traits in human are developed by combined genetic factors and environmental factors for a long period of time. *Third*, the other explanation of inconsistency in genetic association among populations is that disease-associated SNP is unlikely to be the causal variant and rather is more likely to be in strong LD with the biologically relevant variant (Hardy, 2009; Graham, 2009). To date, since it is not feasible to test all variants of human genome even in a GWA study, the aforementioned reasons as reasonable explanation of non-reproducible genetic studies between populations.

1.3 SLE and Copy Number Variation (CNV) and Mendelian forms of SLE

1.3.1 Copy Number Variation (CNV)

CNV is exhibited in up to 12% of the human genome (Ku, 2010). Therefore, it is increasingly believed that large-scale deletion or duplication of DNA segments is a major source of human genetic variation (Ku, 2010). CNVs appear to play an important role in several common diseases (International Schizophrenia Consortium, 2008; Sebat, 2007). The relative contribution of CNVs, to the genetic component of SLE is unclear. Comprehensive studies of CNVs in SLE are expected in the coming years. Although evidences of the involvement of CNVs in SLE susceptibility are accumulating, for

example; CNV was found in various genes involved in the pathology of SLE such as: the Fc receptor region (Fanciulli, 2007), Complement Factor 4 in the HLA class III region (Yang,2007), the histamine H4 receptor (HRH4) (Yu, 2010), however, a definitive role for the CNV has not been convincingly disentangled from nearby, linked risk variants (Fanciulli, 2007; Yang,2007).

1.3.2 Mendelian manner of SLE

A number of rare variants that cause SLE in a Mendelian manner have been identified throughout the years, including disruption of several complement pathway components (Harley, 1998). The Mendelian forms of SLE shed light onto pathways critical in pathogenesis, but account for only a small portion of the overall disease incidence (Harley, 1998).

2. Genes involved in the susceptibility to SLE

Herein we will describe the involvement of the key genes involved in the susceptibility to SLE. The genes will be introduced according to their location on the chromosomes.

2.1 Chromosome 1

There is considerable evidence supporting that multiple genes on this chromosome contribute to the development and expression of SLE (Tsao, 2000).

2.1.1 Fcγ receptors: FCGR2A, FCGR3A, FCGR2B and FCGR3B, (1q23-24)

The Fragment crystallizable receptors (FcRs) Fcγ receptor family (FCGRs: FCGR2A (CD32a); FCGR2B (CD32b); FCGR3A (CD16a) and FCGR3B (CD16b)) are a heterogeneous group of hematopoeitic cell surface glycoproteins that bind to the Fc region of immunoglobulins and facilitate the efficiency of antibody-antigen interactions with effector cells of the immune system. These receptors regulate a variety of cellular and humoral immune responses including phagocytosis, immune complex clearance, degranulation, antibody-dependent cellular cytotoxicity, transcriptional regulation of cytokine and chemokine expression, and B cell activation. The cellular distribution and Ig isotype (IgA, IgD, IgE, IgG and IgM) specificity influence the regulatory roles of Fc receptors. In broad terms, FcγRs can be classified into high or low affinity receptors based on their affinity for IgG or into activating (FcγRI, FcγRIIA/C, FcγRIII) or inhibitory (FcγRIIB) receptors based on their signaling activity and associated functions as they stimulate or inhibit immune functions such as phagocytosis, cytotoxicity, degranulation, antigen presentation and cytokine production via immune tyrosine activating or inhibitory motifs (ITAM or ITIM). In humans, three major classes of IgG-receptor have been described; FcγRI (CD64), FccRII (CD 32), and FcγRIII (CD16). These classes can be further sub-divided into discrete isoforms such as FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIIA and FcγRIIIB that exhibit significant differences in their affinity for individual IgG sub-classes and tissue distribution. One of the difficulties of studying the Fcγ-receptor region on chromosome (1q23-24) is the high level of sequence similarity between each of the Fcγ-receptor genes suggests that the whole Fcγ-receptor gene cluster arose from the duplication of a single ancestral gene. Another complicating factor at this locus is the presence of copy number variation (CNV).

In human patients as well as in experimental animal models, FcγRs have been implicated in immune dysfunction and the development of autoimmunity. The best correlation between impaired FcγRs function and autoimmune pathogenesis is seen in systemic lupus. Various functional variants in FCγR2A, FCγR2B, and FCγR3A have been identified as risk factors for SLE (Nimmerjahn, 2008). These variants might lead to the defective clearance of immune complexes from the circulation therefore will contribute to the deposition in tissues such as the kidney and blood vessels (Lehrnbecher, 1999a; Tsokos, 2001).

FcγRIIA receptor contains ITAM on cell membranes of neutrophils, monocytes, macrophages, dendritic cells and platelets. It is the major receptor for the IgG2 subclass, which is a poor activator of classical complement pathway. It is the only FcR for clearing IgG2-bound immune complexes. The association of FCGR2A alleles with SLE has been studied intensively in several populations (Brown, 2007). Mutations in FCGRs have been shown to alter the function of monocytic cells and B-lymphocytes. For example; the nonsynonymous SNP which result in the substitution of Arginine at amino acid position 131 (R131) of FCGR2A (R131; rs1801274) to Histidine within the ligand binding domain of FcγRIIa diminishes binding to IgG2 results in impaired IgG2-mediated phagocytosis (Parren, 1992a,b; Warmerdam, 1991a,b; Clark, 1991; Salmon, 1996). FcγRIIA R131, might contribute to the risk of proliferative lupus nephritis by activating phagocytes, releasing proinflammatory cytokines and reduced clearance of immune complexes (ICs) (Bredius, 1993; Karassa, 2002). Karassa *et al*. conducted a meta-analysis regarding this polymorphism which included 17 studies, involving a total of 3114 SLE patients and 2580 non-SLE controls of European, African, and Asian descent, demonstrating that the R131 allele was associated with SLE (Karassa, 2002). In other studies conducted in Asians, it has been shown that the FCGRIIA-R131 allele was correlated with certain disease phenotypes. Kobayashi *et al.* studied Japanese SLE patients with or without periodontitis, and found that the R allele was significantly correlated (Kobayashi, 2007). Siriboonrit *et al*. also found in a Japanese cohort that the R allele was significantly increased in patients with lupus nephritis (Siriboonrit, 2003). In various ethnic groups (Europeans, African Americans and Koreans), R131 (rs1801274) showed inconsistent association with susceptibility to SLE, lupus nephritis, or both (Duits, 1995; Yap, 1999; Chen, 2004; Salmon, 1996; Song, 1998). Ethnic differences, disease heterogeneity, genotyping error due to extensive sequence homology among FCGR genes and random fluctuations in small samples might explain these inconsistent associations.

FcγR3IIA receptor contains ITAM on cell surfaces of natural killer (NK) cells, monocytes, and macrophages. FcγR3A alleles with differential affinity for IgG1 and IgG3 have also been shown to be associated with SLE patients from ethnically diverse groups (Yap, 1999). The nonsynonymous SNP, where valine (V158) of FcγRIIIA changes to phenylalanine (F158) (rs396991) was shown to reduce the IgG1-, IgG3-, and IgG4-binding capacity of the receptor compared to V/V homozygotes. This polymorphism, normally termed FcγRIIIA-176 F/V or FcγRIIIA-158 F/V when excluding the leader sequence, was first reported to be of significant correlation with SLE in the Asian population (Japanese) by Kyogoku et al (Tsuchiya, 2005). Studies in human cohorts have shown that SLE is significantly associated with both alleles, R131 and F158, that encode lower affinity isoforms of FcγRIIA and FcγRIIIA respectively (Lehrnbecher, 1999b). F158 homozygotes bind IgG1- and IgG3-containing ICs less efficiently than V 158 homozygotes, and confers less efficient clearance of ICs than other alleles was associated with SLE susceptibility(Koene, 1998). However, the association between FcγR3A-V/F158 polymorphism and susceptibility to SLE and/or lupus

nephritis has been variable in several studies (Tsao, 2004). A meta-analysis of more than 1,000 subjects in each of the three categories (SLE without or without renal involvement, and non-SLE controls) has concluded that the F158 allele confers a 1.2-fold risk for developing lupus nephritis in patients of European, African, and Asian descent but not for SLE susceptibility without renal involvement (Karassa, 2003).

The FcγRIIA-R131 and FcγRIIIA-F158 are often inherited together on the same chromosome as a single-risk haplotype for SLE (Magnusson, 2004). The presence of multiple risk alleles might interact to enhance the risk for SLE (Sullivan, 2003). The relative importance of FcγR2A-H/R131 and FcγR3A-V/F158 to disease progression might depend on the IgG subclass of pathogenic auto antibodies in an individual patient.

A novel polymorphism in FCGR3A, the rs403016 located in the Exon 3 which causes a non-synonymous substitution, the FCGR3A-72R/S, has been found to be associated with SLE in a Chinese SLE cohort, where the R allele contributes to disease susceptibility (Ye, 2006; Pan, 2008).

In a meta-analysis carried out by Lehrnbecher et. al., the development of SLE was significantly associated with the alleles encoding the low affinity isoforms of both FcγRIIA (FcγRIIA–R/R131) and FcγRIIIA (FcγRIIIA–F/F158) (Lehrnbecher, 1999b). More recently, a similar meta-analysis study carried out by Karassa and colleagues found that an FcγRIIA–R/H131 polymorphism represents a significant risk factor for the development of SLE but had no clear effect on susceptibility for lupus nephritis in a large patient cohort (Karassa, 2002).

Lower level evidence exists for a non-synonymous mutation in FcγRIIIA proposed to alter IgG binding affinity, a promoter SNP in FCGR2B that alters transcription factor binding and receptor expression and, in Asian populations, a non-synonymous SNP in exon 6 of FCGR2B suggested to influence B-cell activation (Brown, 2007).

FcγRIIB: FCGR2B receptor is expressed on B cells, dendritic cells, monocytes/macrophages, and mast cells. It contains an ITIM that regulates B-cell survival and proliferation by down-modulating B-cell receptor signaling, and by decreasing antibody-mediated phagocytosis in macrophages (Daeron, 1997).

A nonsynonymous SNP in the transmembrane domain of FcγRIIB (Ile187Thr) that alters the inhibitory function of FcγRIIB on B cells is associated with SLE in Asian populations,(Kyogoku, 2002; Siriboonrit, 2003; Chu, 2004) but not in other populations partly owing to their low allele frequencies (Li, 2003; Kyogoku, 2004; Magnusson, 2004). The FcγR2B encoded by the Thr187 allele results in impaired inhibition of B-cell activation and promotes autoimmunity (Floto, 2005). A functional promoter haplotype (–386G/–120T) of FcγRIIB that confers increased transcription of FcγRIIB has been associated with 1.6-fold risk for SLE in Caucasian Americans (Su, 2004). This haplotype is not in LD with FcγRIIA and FcγRIIIA polymorphisms and is likely to have an independent association with SLE (Kyogoku, 2002).

FcγRIIIB: FCGR3B is expressed solely on neutrophils. It lacks an ITAM domain, so the transmission of intracellular signals is likely to involve cooperation with other transmembrane proteins. Of particular interest are data suggesting that this is achieved through an interaction with complement receptor 3/integrin α_M (Krauss, 1994; Poo, 1995; Stockl, 1995). It is considered low affinity receptor for the Fc region of immunoglobulins gamma. It binds to complexed or aggregated IgG and also monomeric IgG. Contrary to FCγR3A, is not capable to mediate antibody-dependent cytotoxicity and phagocytosis. It may serve as a trap for immune complexes in the peripheral circulation which does not activate neutrophils.

Six SNPS exist in FCGR3B, underlying three different allotypic variants of FCGR3B (NA1, NA2 and SH). The association reported by Hatta *et a.l.*(Hatta, 1999) between the NA2 allotype and SLE in a Japanese population has not been replicated, suggesting that the association between SLE and this genomic region might be influenced by other genetic variations. Both duplication and deficiency of FCGR3B were reported in normal individuals (Clark, 1990; Koene, 1998). The inheritance pattern of FCGR3B in some families affected by SLE has suggested that the copy number variation might be the underlying condition.

The number of copies of FCGR3B in a cell can vary from none to four, with a gene-dose effect that reduced FcγRIIIB copy number being a risk factor for glomerulonephritis in SLE patients. In addition, FCGR3B copy number varies significantly with non-Mendelian inheritance, suggesting that the association of FCGR3B copy number with lupus nephritis is an independent risk factor (Aitman, 2006). Since human FCGR3B is expressed mainly in neutrophils, and it is postulated that SLE patients with low FCGR3B copy number have reduced neutrophil expression, which leads to reduced glomerular clearance of immune complexes, and brings forth susceptibility to SLE and other autoimmune disorders. This observation supports that copy number polymorphism at orthologous regions of diverse genomes is associated with immunologically related disease. It also suggests that genome plasticity, manifested by gene duplication/deletion and copy number polymorphism, is a common cause of genetically complex phenotypes. Fc receptor-like genes (FCRLs): FCLs clustered at 1q21–22 encode proteins that are structurally homologous classical FCGRs. To enhance our understanding of the functional roles of *Fcγ* receptors in SLE, an integrated approach to simultaneously assess CNVs, allotypic variants, SNPs and the functional diversity of these receptors in large-scale case–control studies including multiple ethnic populations is needed to dissect the relative contribution of various variants in this complex FCGR locus to SLE.

2.2 Protein tyrosine phosphatase non-receptor 22 (PTPN22) (1p13)

PTPN22 is a negative regulator for T-cell signal transduction in cellular immunity. It is considered to be the strongest common genetic risk factor for human autoimmunity besides the major histocompatibility complex (MHC) and as an important candidate gene in SLE. A number of candidate gene studies found (SNP rs2476601) R620W polymorphism in the proximal protein-rich SH3-binding domain (+1858T/C), to be associated with the increased risk of SLE (Orozco, 2005). This has been confirmed in a meta-analysis (Lea, 2011) and SLE GWA analysis. This polymorphism was found to be associated with several autoimmune diseases in Caucasians, including T1D, autoimmune thyroid disease, RA and SLE, but not with multiple sclerosis (MS). SNP rs2476601 is not polymorphic in Koreans and Japanese and almost absent in African populations (Gregersen, 2006) while it is more common in northern Europeans (8–15%) compared with southern Europeans (2–10%) (Gregersen, 2009). Suggesting the presence of genetic heterogeneity across various ethnicities.

The lymphoid tyrosine phosphatase protein (LYP), which is encoded by *PTPN22*, is known to regulate immunological synapse formation. LYP is involved in the down-regulation of T-cell activation through its interaction with a negative regulator of TCR signaling C-terminal Src tyrosine kinase (Csk); this interaction is prevented by the arginine to tryptophan amino acid substitution consequent upon the associated mutation rs2476601 R620W (C1858T) (Begovich, 2004; Bottini, 2004).

One would expect this R620W substitution to result in increased T-cell signaling and activation; however, experimental evidence suggests the opposite with TCR signaling

actually reduced in cells carrying the tryptophan variant protein (Vang, 2005). A number of explanations have been proposed including an effect of the mutation on the tyrosine phosphatase activity of LYP, or an effect on the binding of other ligands or the conformation of LYP in response to these ligands (Vang, 2008). At a cellular level the mechanism by which reduced T-cell activation may actually increase the potential for autoimmunity remains a matter for speculation, although the suppression of regulatory T-cells is a possibility (Vang, 2008). A connection between PtPn22 and the type I IFN pathway has been suggested on the basis of elevated serum IFN-α activity and decreased tumor necrosis factor (TNF) levels in patients with SLE carrying the rs2476601 risk allele (Kariuki, 2008). By contrast, another *PTPN22* polymorphism, the loss-of-function mutation Arg263Gln in the catalytic domain (R263Q), leads to reduced phosphatase activity of PtPn22, and, therefore, increases the threshold for TCR signaling has been associated with protection against SLE in European-derived populations (Orru, 2009).

2.3 Interleukin 10 (IL 10) 1q32.1

IL-10 is an important immunoregulatory cytokine in man with both immunosuppressive and immunostimulatory properties (Mosmann, 1994). It is characterized with anti-inflammatory and stimulatory activities, and plays a critical role in the regulation of cellular and humoral immune responses. IL-10 is also involved in the pathology of human autoimmune disease (Llorente, 1994; Cash, 1995; Perez, 1995), particularly in the dysregulation of B-cell function in systemic lupus erythematosus leading to autoantibody production (Itoh, 1995; Llorente, 1995). In addition, its ability to induce T-cell anergy (Luscher, 1994) and inhibit major histocompatibility complex class-I expression (Matsuda, 1994) may be important in its apparent contribution to tumor-related immunosuppression (Kim, 1995; Suzuki, 1995; Fortis, 1996).

It has been known that IL10 production is under strong genetic influence (Westendorp, 1997). Two CA-repeat microsatellites, IL10R (-4 kb) (GeneBank accession number AF295024) and IL10G (-1.1 kb) (GeneBank accession number X78437), and single nucleotide polymorphisms (SNPs) were reported in IL10 promoter that has potential association with IL10 production. These SNPs are located at positions -A3575T, -A2849G, -A2763C, -A1082G, -C819T, and -A592C from the transcription start site. It has been known that -A1082G, -C819T, and -A592C combined to form three haplotypes; GCC, ACC, and ATA linked with different IL10 expression level (Crawley, 1999).

IL-10 has been associated in the pathogenesis of SLE; Increased *IL10* production by peripheral blood B cells and monocytes from patients with SLE is known to correlate with disease activity (Hagiwara, 1996), increased IL-10 productions promotes B-cell hyperactivity and autoantibody production (Llorente, 1995). The association between IL10 promoter haplotypes (defined by three SNPs in the *IL10* promoter region -627C→A, -854C→T and -1117G→A. These single base-pair substitutions produce three different haplotypes, GCC, ACC and ATA,) (Turner, 1997; Eskdale, 1997a) and SLE has been have been reported in European, Hispanic American and Asian populations (Eskdale, 1997b; Mehrian, 1998; Chong, 2004). A large-scale replication study in populations from the USA and Sweden has confirmed *IL10* as a SLE susceptibility locus (Gateva, 2009). However, they were found to have significant association with lupus nephritis.

Levels of IL-10 secretion have been correlated to specific IL10 promoter polymorphisms; a study has shown that the SNP haplotypes in the distal promoter of IL-10 correlate with different IL-10 production phenotype in normal individuals, and high IL-10 haplotype is

associated with SLE in African-Americans, which may be a part of their genetic susceptibility to SLE. A meta-analysis of 15 IL-10 studies has shown that the G11 allele is associated with SLE in whole studied populations, and among the promoter SNPs, −A1082G polymorphism, which is found in Asian population only, was also associated with SLE (Nath, 2005). Based on these analyses, IL-10 polymorphisms confer SLE risk in an ethnicity-specific manner (Gateva, 2009; Eskdale, 1997; Mehrian, 1998; Chong, 2004).

2.4 Complement receptor 1 (CR1, CD35), (1q32)

Genome scans have shown linkage (lod score >1.0) at chromosome 1q32, which contains complement components, like complement receptor 1 (**CR1**), complement receptor 2 (CR2), and C4b-binding protein (C4BP) genes and IL10 family members; IL10, IL19, IL20, and IL24, which play a significant role in the pathogenesis of SLE (Johanneson, 2002; Tsao, 1999). The C3b/C4b complement receptor (Gene ID: 1378) (CR1, CD35) is a polymorphic transmembrane single chain glycoprotein expressed on red cell surface binds to C3b and C4b and clears circulating C3- and C4-bearing immune complexes containing (Dykman, 1984).

Functional and structural polymorphisms of CR1 have been reported. The functional polymorphism determines the quantitative expression of CR1 on erythrocytes, i.e. HH, HL, and LL (H = allele correlated with high expression, L = low) (Wilson, 1986). The structural polymorphism exists in its molecular size (Dykman, 1983). The extracellular portion of the CR1 molecule consists of three to five groups of seven short consensus repeats termed long homologous repeats (LHR). The most frequent type of CR1 (F or A) is comprised of four extracellular LHRs and expresses one binding site for C4b and two binding sites for C3b (Wong, 1983). The S (or B) variant of CR1 is characterized by additional C3b binding site on a fifth LHR (Wong, 1989). A meta-analysis for the CR1 functional polymorphisms in SLE shows no significant association of CR1 L allele, L/L genotype, and L/L+L/H genotypes with SLE. However, the same meta-analysis of CR1 structural polymorphisms suggested an association of CR1 S (structural variant of CR1) to be associated with SLE in Caucasians (Nath, 2005).

2.5 Tumor necrosis factor (ligand) SuperFamily, member 4(TNFSF4), 1q25

TNFSF4 (also known as OX40L; 1q25) encodes a cytokine that is expressed on CD40-stimulated B cells, activated antigen-presenting cells (APCs) and vascular endothelial cells. Also its unique receptor, TNFRSF4 (also known as OX40; 1p36), is primarily expressed on activated CD4+ T cells. Their interaction induces the production of CD28-independent co-stimulatory signals to activate CD4+ T cells (Baum, 1994). OX40L-mediated signaling inhibits the generation and function of IL-10-producing CD4+ type 1 regulatory T cells, but induces B-cell activation and differentiation, as well as IL-17 production in vitro (Ito, 2006a; Li, 2008).

These two tumor necrosis factor (TNF) superfamily members (OX40L and OX40) located within proximal intervals showing genetic linkage with SLE (Cunninghame, 2008; Chang, 2009; delGado-Vega, 2009).TNFSF4 has been identified as a susceptibility gene for SLE in multiple studies. Protective and risk haplotypes at TNFSF4 were identified in a study of two cohorts from Minnesota and UK, a haplotype in the upstream region of TNFSF4, marked by SNPs rs844644 and rs2205960, has been shown to correlate with increased cell surface TNFSF4 expression and TNFSF4 transcript and to be associated with SLE (Graham, 2008).

Associations between some *TNFSF4*-tagging SNPs and an increased risk for SLE have been confirmed in GWAS in Chinese populations and in a European replication study; these results were also replicated in four independent SLE datasets from Germany, Italy, Spain and argentine. It has not been fully established how TNFRSF4/ TNFSF4 interactions influence T-cell subset profiles. Most evidence suggests a bias towards a Th2 pattern of cytokine release, although there is also evidence for a down-regulation of regulatory T-cell subsets (Ito, 2006b; Lane, 2000). There is also good evidence that signaling through TNFSF4 can induce B-cell activation and differentiation (Stuber, 1995&1996). TNFRSF4/ TNFSF4 signaling is therefore bi-directional, and the precise immunological consequences of this complex pathway are yet to be clarified. Further studies are needed to localize causal variants and to understand how these polymorphisms affect the pathogenesis of SLE.

2.6 C-reactive protein (CRP), 1q23.2

CRP is a sensitive marker of inflammation. The genes for CRP (CRP) map to 1q23.2 within an interval linked with SLE in multiple populations. It is hypothesized that polymorphism of CRP gene contributes to susceptibility to systemic lupus erythematosus (SLE).

Basal levels of CRP were influenced independently by two polymorphisms at the CRP locus, CRP 2 and CRP 4. Furthermore, the latter polymorphism was linked/associated with SLE and antinuclear autoantibody production. Thus, the polymorphism associated with reduced basal CRP was also associated with the development of SLE.

CRP is normally involved in phagocytosis of apoptotic debris and immune complexes in innate immune response. Defective clearance of products of apoptosis may be the source of autoantigens in SLE, and such phenomenon may also be enhanced by FcγR2A polymorphisms, with FcγR2 receptor being the main receptor for CRP (Bharadwaj, 1999).

During the active phase of SLE, despite the presence of marked tissue inflammation, CRP levels are abnormally low due to reduced synthesis (Russell, 2004). Family-based studies of association and linkage have identified the minor allele of rs1205 in the 3'UTR SNP of CRP to be associated with SLE and antinuclear antibody production (Russell, 2004), and the number of CA repeats correlated with disease risk in a Spanish cohort (Russell, 2004). Also, a single dose of CRP has recently shown to reverse lupus nephritis and nephrotoxic nephritis in mice, suggesting the acute-phase response of CRP may hinder tissue inflammation and damage (Rodriguez, 2005). These results are promising, and future investigation of this gene will not only allow better understanding of the genetic influence of CRP but also its pathophysiology and possible therapeutic options.

Two of several polymorphisms in the CRP gene, designated CRP2 (G/C) and CRP4 (G/A) have been demonstrated to have an impact on baseline serum concentration of CRP, with the C- and A-alleles being associated with lower concentrations (Russell, 2004). Furthermore, the CRP4 A-allele was shown to confer increased susceptibility to SLE in 586 families (P=0.006) (Russell, 2004). The A allele at *CRP* 4 had a relatively high frequency in European and Asian-Indian populations (~0.3) and was present in Afro-Caribbean families too, but at a lower frequency (0.14).

2.7 Poly(ADP-ribose) polymerase (PARP), (1q41–42)

PARP is an enzyme (PARP-1 EC 2.4.2.30) is induced by DNA strand breaks caused by several agents and utilizes NAD to form polyADPR, bound to acceptor proteins. It is responsible for DNA repair, proliferation, stress response, apoptosis, and genomic stability (Oliver, 1999). The involvement of PARP-1 in autoimmune diseases has been suggested

especially in systemic lupus erythematosus (SLE) due to the decreased levels of activity and mRNA in SLE patients (Haug 1994). Autoantibodies to PARP are frequently found in patients affected with autoimmune diseases, some of which may prevent caspase-3-mediated PARP cleavage during apoptosis, resulting in the accumulation of autoimmune cells (Decker, 2000). On chromosome 1q41–q42 a 15-cM region has been linked with susceptibility to SLE (Tsao, 1997), this linkage has been confirmed in several independent studies. In a family-based TDT analysis, PARP alleles had skewed transmission to affected offspring, but this finding is not consistent in other multi-ethnic studies (Tsao, 1999).

A polymorphic CA tandem repeat within the PARP promoter region suggested to affect transcription activity has been associated with SLE in some but not other similar studies (Oei, 2001). A study investigated the association of PARP promoter CA tandem repeats polymorphisms with SLE susceptibility in Taiwan. Nine alleles ranging from 12 to 20 repeats were disclosed. No statistically significant association with SLE susceptibility was found in this population however; PARP microsatellite polymorphisms demonstrate associations with clinical subphenotypes such as discoid rash and arthritis, anti-cardiolipin IgG and anti-ds-DNA antibody production. These indicate that PARP CA repeats may play a key role in lupus pathogenesis involving DNA repair of cell damage and consequent autoantibody production. Tsao *et al* demonstrated a skewed transmission of PARP alleles in a family study with the PARP CA8 allele as susceptible and the PARP CA14 allele as a protector of lupus transmission (Tsao, 1999).

In a Korean study, PARP polymorphisms could not prove any statistically significant association with the risk of SLE was observed, however, they found that two single-nucleotide polymorphisms (SNPs -1963A/G and +28077G/A) were significantly associated with an increased risk of nephritis, and one non-synonymous variant [+40329T/C (V762A)] was also significantly associated with an increased risk of arthritis, while the -1963A/G polymorphism showed a protective effect on arthritis in Korean SLE patients (Hur, 2006).

2.8 Toll-like receptor 5 (TLR5), 1q41–q42

At least 10 different *TLR* have been cloned from the human genome to date. Toll-like receptors (TLR) are type I transmembrane proteins contain an extracellular leucine-rich region involved in pathogen recognition and a conserved intracellular Toll/IL-1 receptor domain that activates a signaling pathway. Stimulation of the TLR pathway ends in NF-κB activation and transcription of immune response genes, such as cytokines and chemokines. TLRs play an important role in the activation and regulation of both adaptive and innate immunity. They are considered as excellent candidate genes for genetic susceptibility studies for autoimmune diseases. TLR5 is a critical regulator of inflammatory pathways and maps to chromosome 1q41. Activation of TLR5 triggers production of proinflammatory cytokines, such as IL-6, which, in turn, can stimulate B cells to proliferate, differentiate, and secrete antibodies. Dysregulation of this process may lead to excessive production of cytokines as well as autoantibodies (Dean, 2000).

It was hypothesized that the stop codon variant C1174T (rs5744168) (Arginine to a stop codon at position 392 (R392X) in TLR5, is associated with susceptibility to SLE. This hypothesis was tested by using a TDT in a Caucasian SLE cohort and found that the TLR5 stop codon polymorphism, but not other TLR5 alleles, is associated with protection from developing SLE as subjects with 1174T produced less proinflammatory cytokines (IL-6, TNF-α, and IL-1β) (Hawn, 2003; Hawn, 2005). In addition the same group found that this association was most pronounced in individuals who are seronegative for anti-dsDNA

autoantibodies (Tsao, 1999; Hawn, 2005). TLR5^{R392X} may provide protection from SLE by decreasing production of proinflammatory cytokines during infection with flagellated bacteria, which may influence formation of the adaptive immune response. These results suggest a role for the innate immune response in the development of SLE that involves flagellated bacterial infections.

3. Chromosome 2

Locus 2q32- q37 encodes the Programmed cell death 1 gene (PDCD1), Cytotoxic T-lymphocyte associated protein 4 (CTLA4) and STAT4 transcription factor. All were proven to be associated to susceptibility to SLE.

3.1 Programmed cell death 1 gene (PDCD1/ CD279) (2q37)

PDCD1 codes for an immunoreceptor, PD-1, member of the CD28/CTLA4/ICOS co-stimulatory receptor family that bears an inhibitory immunoreceptor tyrosine-based motif (ITIM). It is expressed on activated T- and B-cell surfaces to regulate their peripheral tolerance (Agata 1996; Finger, 1997). PDCD1 is upregulated in T cells following activation, and inhibits TCR signaling and T/B cell survival. It is considered a strong candidate for SLE association.

The human *PDCD1* has an intron enhancer which contains binding sites for other transcription factors that are involved in lymphocyte development and T cell differentiation. PDCD single nucleotide polymorphism (SNP) (PD1.3A, the minor A allele of 7146 G/A) in this intron enhancer alters a binding site for the runt-related transcription factor (RUNX1). The PDCD1 enhancer has a very high GC content (from 50 to 75%). The A allele of the PDCD1 enhancer SNP changes a potential methylation site from CpG to CpA that is surrounded by many other potential methylation sites. Methylation is a known mechanism of regulation of gene activity (Avni, 2000). Whether methylation is involved in the regulation of PDCD1 is under investigation. Changes in methylation can condition the developmental stage of PDCD1 expression.

SNP 7146 G/A was shown to be association with SLE susceptibility and its contribution to SLE development was confirmed in Europeans and Mexicans by inducing lymphocytic hyperactivity in these patients (Prokunina, 2002). PDCD-1 polymorphisms may be a shared genetic factor for multiple autoimmune diseases in humans, and the cellular function leading to disease onset awaits further investigation. PDCD1 7209 CT or 7209 TT genotype exhibited 3.28-fold increased risk of SLE in the Polish and Taiwanese populations (Mostowska, 2008).

The most logical explanation of the mechanism of disease susceptibility for PDCD1 was suggested by Alarcón-Riquelme M *et al* (Alarcón-Riquelme, 2003); The stated: "So what effects could the aberrant function or expression of PDCD1 have in early lymphocyte differentiation that may lead to autoimmune disease, in particular SLE? It mainly depends on at what stage of differentiation does the RUNX1–PDCD1 interaction take place whether it occurs before clonal receptor rearrangements or after. As PDCD1 seems to act during positive selection in the thymus, at least in the mouse, this leads us to suggest that the human mutation may be promoting positive selection of early autoreactive progenitors, leading to an increased "susceptibility" to expand autoreactive T or B cells after antigenic stimuli, however the amount of information to date on PDCD1 in lymphocyte development and its regulation is still an open question".

3.2 Cytotoxic T-lymphocyteassociated protein 4 (CTLA4), (2q33)

CTLA4 is a structural homologue of CD28. It is a negative costimulatory molecule that inhibits T cell activation, and may help to limit T cell responses under conditions of inflammation and prevents autoimmune diseases by promoting anergy. It competes with the binding of CD28 on antigen presenting cells (APCs), and transduces inhibitory signals by activation of serine/threonine phosphatases. Genetic variability in CTLA4 has been implicated in the development of several autoimmune diseases including SLE (Matsushita, 1999). SLE patients have increased levels of soluble CTLA-4. A single nuclear polymorphism (SNP) CT60A/G within the 3'UTR of CTLA4 decreased the production of a spliced variant with inhibitory activity, which indicates the importance of CTLA-4 in providing protection against autoimmunity (Ueda, 2003).

SLE in Caucasians, CTLA-4 polymorphisms of its promoter and exon-1 regions was found to be associated to SLE. Later, in a Chinese cohort, the CTLA-4 promoter (-1722 T/C) polymorphism showed positive evidence (Liu, 2001 & Xu, 2004). However, several genetic studies investigating CTLA-4 polymorphisms and SLE have been negative. Among the positive studies, different mutations were identified within the CTLA4 promoter (−1722T/C, −1661A/G, −319C/T) and exon 1 (+49G/A) in various ethnic groups (Lee, 2005). More work is needed to delineate the genetic relationship between CTLA-4 and SLE.

3.3 Signal transducer and activator of transcription 4 protein (STAT4), (2q32)

STAT4 play key roles in the interferon and Th1 signaling pathway through mediating responses to IL-12 in lymphocytes, and regulates T helper cell differentiation. STAT4 also is known to mediate signals induced by immunologically relevant cytokines including, like IRF5, the Type 1 IFNs (Darnell, 1994 & Watford, 2004). In response to these cytokines, STAT4 activation plays an important role in directing a Th1 T-cell response, and mediates the production of Th1-type cytokines such as IFN-α (Morinobu, 2002; Nguyen, 2002; Nishikomori, 2002). In addition, STAT4 signaling also mediates type 1 IFN signaling in antigen-presenting cells, and may be necessary for the production of IFN-α by these cells (Frucht, 2003 & Fukao, 2001).

STAT4 variation and SLE risk was initially reported in 2007 from a case–control association study (Remmers, 2007). This was subsequently confirmed in both GWA studies. Three SNPs in STAT4, rs7574865, rs11889341, and rs10168266, were then shown to be in significant association with SLE in a Japanese population, with the rs7574865 T allele, in the third intron of STAT4, showing the strongest significance. Interestingly, this rs7574865 risk variant is associated with a more severe SLE phenotype that is characterized by disease onset at a young age (<30 years), a high frequency of nephritis, the presence of antibodies towards double stranded DNA, (Taylor, 2008; Kawasaki, 2008; Sigurdsson, 2008) and an increased sensitivity to IFN-α signaling in peripheral blood mononuclear cells (Kariuki, 2009). In a meta-analysis including Europeans and Asian patients of SLE and RA, the rs7574865 T allele was found to be consistently associated with both diseases (Ji, 2010). Possible functional relevance of risk STAT4 variant has recently strongly suggested by in vivo experiment in SLE patients, in which risk variant of STAT4 (T allele; rs7574865) was simultaneously associated with both lower serum IFN-a activity and greater IFN-α induced gene expression in PBMC in SLE patients.

A risk haplotype (spanning 73 kb from the third intron to the seventeenth exon of STAT4) common to European, Americans, Koreans and Hispanic Americans was also identified

(Namjou, 2009). Functionally, either type I IFN or interleukin (IL)-12 induces phosphorylation of STAT4, which has a signal transduction role in these pathways. Individuals carrying one or more risk alleles of both IRF5 and STAT4 have an increased risk for SLE, suggesting a genetic interaction between these two genes (Sigurdsson, 2008).
The important roles of STAT4 in both innate immunity and Th1 immune response, recent enormous body of evidence of consistent association of STAT4 with SLE in multiple racial groups indicates that a risk variant or a certain risk haplotype of STAT4 has a crucial role in SLE pathogenesis that has yet to be completely determined and could provide new therapeutic targets for SLE and the other autoimmune diseases in future.

4. Chromosome 3

4.1 Phox homology (PX) domain Kinase (PXK), (3p14.3)

PXK is of unknown function. PXK domain containing serine/threonine kinase and act as modulator of Na, K-ATPase enzymatic and ion pump activities (Mao, 2005). It was identified as a novel candidate gene for systemic lupus erythematosus (SLE) from genome-wide association studies (GWAS) in Caucasians (Suarez-Gestal, 2009). The association of PXK rs6445975 with SLE observed in Caucasians was not replication study in Hong Kong Chinese and Koreans (Kim, 2011; Yu, 2011; Yang, 2009). It is possible that PXK has different genetic contribution on SLE between Caucasians and Asians and that the gene is associated with disease subphenotypes rather than with overall susceptibility.

5. Chromosome 4

5.1 BANK, BLK and LYN

All three of these genes play a critical role in controlling the activation of B cells following signaling through the B-Cell Receptor (BCR). Following ligand binding and BCR aggregation, an early intracellular event is the recruitment and activation of Src-family protein tyrosine kinases, including BLK and LYN, which mediate further intracellular signaling. The exact role of these kinases in determining cellular events has yet to be determined with certainty.

5.2 B-cell scaffold protein with ankyrin repeats (BANK1), (4q24)

BANK1 is a B-cell scaffold protein that is tyrosine phosphorylated through the B-cell receptor (BCR) upon B-cell activation, which in turn associates with the tyrosine kinase *Lyn* (Src family of tyrosine kinase) and the calcium channel *IP3R* which results in calcium ion release from the stores of the endoplasmic reticulum (Yokoyama, 2002 & Kozyrev, 2008). *BANK1* is thought to alter B cell activation to increase SLE risk. Polymorphisms in *BANK1* may cause B-cell hyper-responsiveness.
GWAS in European-derived populations have identified associations of *BANK1* and *LYN* with susceptibility to SLE (Kozyrev, 2008 & Guo, 2009). For BANK1 three functional variants with either a non-synonymous SNP (rs10516487; Arg61His), a branch point-site SNP (rs17266594; located in an intron) or a SNP in the ankyrin domain (rs3733197; Ala383Thr) might contribute to the sustained activation of B-cell receptors and the subsequent B-cell hyperactivity that is commonly observed in SLE (Kozyrev, 2008). However, the best functional evidence was found for rs17266594, which altered a branch point upstream of exon 2, resulting in the generation of a novel short isoform, but little

quantitative difference in *BANK1* expression overall. With the exception of the rs10516487 SNP of *BANK1*, which showed a weak association with SLE in an Asian GWAS, the remaining SNPS of *BANK1* have not been confirmed in either Chinese or Asian GWAS, partly owing to the low frequencies of the SNPS in these populations (Chang, 2009).

6. Chromosome 5

6.1 TNIP1 (Tumor necrosis factor α-induced protein 3 (TNFAIP3) interacting protein 1), also known as ABIN (A20-binding inhibitor of NF-κB)-1, (5q32-q33.1)

TNIP1 expression is induced by NF-κB, and in turn, overexpression of TNIP1 inhibits NF-κB activation by TNF (Verstrepen, 2009). TNIP1 was shown to inhibit TNF-induced apoptosis independently of A20 (Oshima, 2009). Two recent GWAS revealed association of TNIP1 intronic SNPs rs7708392 and rs10036748, which are in strong linkage disequilibrium (LD) with SLE in the Caucasian (European-American and Swedish) and Chinese Han populations, respectively (Han, 2009 & Gateva, 2009). Association of TNIP1 with SLE was also confirmed in a Japanese population.

To date, at least 11 splice variants of *TNIP1*have been identified (Verstrepen, 2009). Presence of alternative exon 1A and 1B, as well as splice variants lacking exon 2, has been described. Because rs7708392 is located between exon 1B and exon 2, it is possible that this SNP may influence the usage of the splicing isoform. It is also possible that other causative SNPs in tight LD with rs7708392 may exist. Such a possibility would be addressed by resequencing the entire *TNIP1* gene. *TNIP1* is a shared SLE susceptibility gene in the Caucasian and Asian populations, but the genetic contribution appeared to be greater in the Asians because of the higher risk allele frequency in the population.

7. Chromosome 6

7.1 Major Histocompatibility Complex (MHC), (6p21.31)

A body of evidence has been collected to establish the pivotal role of major histocompatibility complex (MHC) in immune tolerance. The classical MHC locus (6p21.3) 3.6Mb contains at least 250 expressed genes. This locus is divided into the Class I and II regions that encode the antigen-presenting HLA proteins and Class III MHC that contains 58 genes, located between Class I and II regions, only some its genes are of potential immunological interest (e.g. TNF-α and TNF-β, C4A, C4B and C2) and others which have poorly defined function. There is particularly strong linkage disequilibrium between genetic markers in this region which is strongly association with SLE in all GWA studies. It is therefore difficult to establish whether any associated variant is functional or simply observed due to linkage disequilibrium with functional polymorphisms elsewhere. It was as early as 1971 that Grumet *et al.* reported possible relationship between the HLA genes and SLE (Grumet, 1971). MHC alleles on 6p11–21 have shown the most significant association. Although the genetic structure of the MHC makes it a particularly challenging region to study, significant progress has been made over the last year.

The Class II HLA genes are of particular importance, which encode antigen-presenting molecules that play a pivotal role in T-cell immunity. Most evidence has highlighted the DR loci, which are one of the Class II HLA gene complexes. The HLA-DRB1 gene is of particular importance in SLE. For the HLA-DRB1 gene, the serotype of DR2 holds the strongest evidence of disease association. Three class-II-containing-SLE-risk haplotypes (DRB1*1501

(DR2)/DQB1*0602, DRB1*0301) (DR3)/DQB1*0201, and DRB1*0801 (DR8)/DQB1*0402) are consistently associated with SLE in Caucasian populations by family-based TDT (van der Linden, 2001).

Within the MHC class III region, there are genes that encode TNF-α and -β, lymphotoxin-β, complement components C2 and C4, and heat shock protein 70 (Hsp70). In particular, TNFs, C2, and C4 have been implicated in SLE susceptibility. TNF-α is a multifunctional proinflammatory cytokine involved in regulating a wide spectrum of biological processes including cell proliferation, differentiation, and apoptosis, while TNF-β mediates a variety of inflammatory, immunostimulatory, and antiviral responses. Polymorphisms in these genes have been implicated in SLE susceptibility (Pan 2011 & Bettinotti, 1993).

Complement component genes within the MHC class III region include C2, C4A, C4B, and factor B. These genes are closely linked and are usually inherited as a group known as complotype. Deficiencies in complement pathway genes C2, C4, C1q and C3 appear to cause SLE in some people (Kallel-Sellami, 2008). Polymorphisms in C2, C4A and C4B are in linkage disequilibrium with HLA-B and HLA-DR alleles (Alper, 2007) and may predispose to SLE. Also the complete deficiencies of the early components are highly associated with human SLE (Yu, 2007). A homozygous deficiency in one of the early complement components, including C1q, C1r, C1s and C4 in the classical activation pathway, alone can be strong enough to cause the disease, a situation similar to a single gene defect in an autosomal recessive disease. Respectively, 93% and 78% of patients with complete C1q and C4 deficiencies eventually develop SLE or a lupus-like disease (Yu, 2007 & Botto, 2002). In addition, the concordance rates for siblings with homozygous deficiency of C1q or C4 to develop SLE are 90% and 80%, respectively, which are even higher than the rate in monozygotic twins (26–60%) with other genetic defects (Tsao, 2008). Complete deficiency of complement C4 is among the strongest genetic risk factors for human systemic lupus erythematosus (SLE). Further work will be required to determine the effect arising from C4A. C4 is the most polymorphic protein of the complement system. It is encoded by two genes, C4A and C4B, which have minor sequence differences. The resulting proteins have different functional characteristics, with C4A better able to bind immune complexes (Schifferli, 1986). The C4 genes are inherited in a discrete 'RCCX module', which contains one C4 gene (either C4A or C4B) along with three neighboring genes (RP, CYP21 and TNX) (Yang, 1999). The Class III MHC carries between one and four copies of this module; hence each diploid genome has between two and eight C4 genes, which may be either C4A or C4B (Yang, 2007). Carrying less than two copies of C4A has been identified as a risk factor for SLE (Yang, 2007).

The common European haplotype AH8.1 carries multiple variants that have been associated with SLE including DRB1*0301 (DR3), the TNF -308A allele and the C4A complement null allele. Many studies were unable to break down this haplotype below a 1Mb interval covering most of the Class II and II regions (Alper, 2007).

7.2 PR domain containing 1, with ZNF domain - APG5 autophagy 5-like (PRDM1-ATG5 region), (6q21)

PRDM1 acts as a repressor of beta-interferon gene expression. The protein binds specifically to the PRDI (positive regulatory domain I element) of the beta-IFN gene promoter. While, the ATG5 candidate gene function is still obscure and needed to be determined however, both known to play important roles in immunity. Genome-wide association studies suggested the PRDM1-ATG5 gene region as a systemic lupus erythematosus (SLE)-

associated locus both in Caucasian and Asian populations, presumably through upregulating gene expression (Zhou, 2011; Harley, 2008; Gateva, 2009; Han, 2009).
Significant positive correlations with ATG5 expression were identified, suggesting ATG5 as a candidate gene in the region (Harley, 2008). Later GWAS from a Chinese population denied the association between polymorphisms in *ATG5* and SLE, but replicated the association between the intergenic region of *PRDM1-ATG5* (rs548234 and rs6568431) and SLE ((Han, 2009). At the same time, from Caucasian replication data, both *PRDM1* (rs6568431) and *ATG5* (rs2245214) were suggested as candidate genes, because rs6568431 was more close to *PRDM1* and rs6568431 has an r^2 of less than 0.1 with rs2245214. Meta-analysis consolidated the association between rs548234 and SLE ($p=1.28\times10^{-16}$).

7.3 Tumor necrotic factor α-induced protein 3 (TNFAIP3), 6q23

The gene product of *TNFAIP3* is a zinc-finger A20 protein, a ubiquitin-modifying enzyme, which is essential for proteasome degradation and termination of proinflammatory responses mediated by nuclear factor kappa B, thereby preventing inflammation. In humans, genetic surveys have suggested a role for *TNFAIP3* in susceptibility to complex genetic autoimmune disorders, including systemic lupus erythematosus (SLE) (Graham, 2008; Musone, 2008; Bates, 2005; Han, 2009).
Genetic association between variants in *TNFAIP3* and SLE suggest that alterations in activity and/or expression of *TNFAIP3* influence SLE pathophysiology (Graham, 2008; Musone, 2008; Bates, 2005; Han, 2009). Independent genetic associations of SLE and *TNFAIP3* in European-ancestry (EA) subjects have been localized to a region 185 kb upstream of *TNFAIP3* that was first identified with rheumatoid arthritis (Plenge, 2007; Thomson, 2007; Plenge, 2007), a region 249 kb downstream of *TNFAIP3* and a 109 kb haplotype spans the *TNFAIP3* coding region (Musone, 2008; Bates, 2005; Han, 2009) that includes a suggested causal coding variant in exon 3 (rs2230926 T>G; F127C) that reduces the ability of A20 to attenuate NF-κB signaling (Musone, 2008).
Evidence for association with SLE was observed also for a variant within *TNFAIP3* (rs5029939, GWAS *P* value = 2.55×10^{-8}) and two flanking SNPs (rs10499197, GWAS *P* value = 2.11×10^{-6}; rs7749323, GWAS *P* value = 9.63×10^{-7}) in strong LD with rs5029939 (r2>0.95). A SNP located ~185 kb upstream of *TNFAIP3* reported to be associated with risk for RA (204,206) (rs6920220) demonstrated modest association in the SLE GWAS dataset (GWAS P value = 0.01)
By fine mapping and genomic resequencing in ethnically diverse populations Adrianto I *et al*, fully characterized the *TNFAIP3* risk haplotype and isolated a novel TT>A polymorphic dinucleotide (deletion T followed by a T to A transversion) associated with SLE in subjects of European ($P = 1.58 \times 10^{-8}$) and Korean ($P = 8.33 \times 10-10$) ancestry (Adrianto, 2011). This variant, located in a region of high conservation and regulatory potential, bound a nuclear protein complex comprised of NF-κB subunits with reduced avidity. Furthermore, compared with the non-risk haplotype, the haplotype carrying this variant resulted in reduced *TNFAIP3* mRNA and A20 protein expression. These results establish this TT>A variant as the most likely functional polymorphism responsible for the association between *TNFAIP3* and SLE (Adrianto, 2011).
One hundred and twenty seven (127) SNPs in the region of *TNFAIP3* on 6q23 and 347 ancestry informative markers (AIMs) in five diverse ethnic populations were analyzed by Adrianto I *et al*, They discovered a peak associations in European and Asian populations

were seen at markers rs6932056 and rs4896303 in 38 kb and 30 kb downstream of *TNFAIP3*, respectively (Adrianto, 2011).

8. Chromosome 7

8.1 Interferon regulatory factor 5 gene (IRF5), 7q32

IRF5 is one of the key genes of the interferon (IFN)-α pathway. IRF5 is a transcription factor that is responsible for the innate immune response during viral infection. IRF5 is important for trans-activation of type 1 IFN and IFN-responsive genes and for the production of pro-inflammatory cytokines interleukins such as; IL-6, IL-12, and tumor necrosis factor-α (TNF)] after toll like receptor (TLR) signaling induced by immune complexes containing self-antigens and nucleic acids (Takaoka, 2005). *IRF5* is one of the most strongly and consistently SLE-associated loci outside the MHC region in various ethnic groups and was detected using both candidate gene and GWAS approaches (Lee, 2009). Interest in type 1 (IFN-α and -β) IFN pathways was stimulated by the discovery that there is a general up-regulation IFN-inducible genes in SLE (Baechler, 2003 & Bennett, 2003). The best current genetic model proposes an SLE risk haplotype carrying multiple functional SNPs. Several SNPs in IRF5 (rs2004640, rs752637, rs729302, rs10954213etc.) were first found to be associated with SLE in Caucasians (Niewold, 2008; Kim, 2009).

In vitro functional evidence exists for at least two of these polymorphisms at SNP (rs2004640) creates a novel splice site in exon1B allowing the expression of a novel IRF5 isoform (Graham, 2006 & Sigurdsson, 2005) while the second polymorphism (rs10954213) located in the 3′ UTR creates a functional polyadenylation site and hence a shorter and more stable gene transcript (Cunninghame, 2007). To our knowledge, the most consistent evidence of association for this gene with SLE, across different populations including, was observed in the rs2004640 T allele. A meta-analysis has been conducted to study the association of the rs2004640 T allele with SLE; it included 12 studies in Europeans and Asians, it has been concluded that this polymorphism is associated with SLE susceptibility across different ethnic groups (Lee, 2009). In addition, the gene has a polymorphic 30 bp indel (insertion/deletion) in exon 6, which contributes to the diversity in the isoform pattern of IRF5, and a 5 bp indel near the 5'UTR upstream of exon 1A (Sigurdsson, 2008 & Dideberg, 2007).

To understand how IRF5 variants may predispose to SLE we need to understand the physiological role of the Type 1 IFN pathways. The majority of cells produce Type 1 IFNs as part of their early response to viral infection. Particularly large amounts are produced by plasmacytoid dendritic cells, perhaps stimulated by the recognition of viral RNA and DNA through TLR7 and TLR9. In SLE, it is possible that this is also triggered in response to inadequately cleared nucleic acid antigens released from apoptotic cells (Ronnblom, 2002). Type 1 IFNs exert a multitude of downstream effects on the immune system. Perhaps critically, they stimulate Th1 pathways and sustain activated T cells, while also lowering the threshold for B-cell activation through the B-cell receptor (BCR) and promoting B-cell survival and differentiation (Ronnblom, 2002; Braun, 2002; Le Bon, 2001; Marrack, 1999). It can therefore be seen that genetic variants that prolong or alter the actions of IRF5 could result in a prolonged proinflammatory response, and potentially break immunological tolerance. Interestingly, IRF5 signaling has also been shown to play a role in the regulation of cell cycle and apoptosis raising the possibility that susceptibility variants of IRF5 exert their effects at multiple levels (Barnes, 2003).

8.2 Ikaros zinc finger 1(IKZF), 7p12.2

IKZF1 encodes a lymphoid restricted zinc finger transcription factor named Ikaros, which is critically important for the normal development of all lymphoid cells. It regulates lymphocyte differentiation and proliferation (Georgopoulos, 1994), as well as self-tolerance through regulation of B-cell receptor signaling (Wojcik, 2007). Data derived from both GWAS and large replication studies identified *IKZF1* as a novel SLE susceptibility locus in Chinese and European-derived populations (Han, 2009). Yap et al. reported that IKZF1 was involved in the regulation of STAT4 in human T cells, which suggested that STAT4 and IKZF1 might cooperate with each other and play roles in the development of SLE (Yap, 2005). Hu W. *et al,* demonstrated that *IKZF1* mRNA expression levels in PBMCs from patients with SLE were significantly lower than those in healthy controls (Hu, 2011).
Association of SLE and disease phenotype with IKZF1 was studied in Chinese Han origin SLE patients were the allele frequency of rs4917014 (IKZF1) was significantly different in two subphenotypes: renal nephritis (p=0.02) and malar rash (p=0.00038) (He, 2010).

9. Chromosome 8

Several studies have revealed association of SLE susceptibility to different genes within a 700 kb region of locus 8p23.1 (Hom, 2008; Graham, 2008; Harley, 2008). This region contains several candidate genes, including BLK, XKR6, FAM167A/C8orf13 and C8orf12, these genes were in significant linkage disequilibrium (LD), making it difficult to determine whether the different reports are detecting the same association signal. Budarf ML *et al.* found significant association to both the BLK (rs2618476) and XKR6 (rs6985109) genes (Budarf, 2011). Although these two SNPS are separated by 620 kb, there is relatively strong correlation between them (r^2=0.39), allowing the possibility that they may represent the same signal. Here in we will review the evidence of association of both genes BLK, XKR6 with susceptibility to SLE (Budarf, 2011).

9.1 B lymphoid tyrosine kinase (BLK), 8p23.1

BLK encodes a nonreceptor tyrosine-kinase of the src family of proto-oncogenes, which mediates intracellular signaling and influences cell proliferation and differentiation. The human BLK gene was mapped to chromosome 8 at p23.1, and is expressed only in B lymphocytes (Drebin, 1995). The protein has a role in B-cell receptor signaling, B-cell development and tolerance of B cells (Reth, 1997). B cell receptor (BCR) signaling requires a tight regulation of several protein tyrosine kinases and phosphatases, and associated co-receptors. Break of the balance between positive and negative signaling molecules likely modifies the BCR signaling thresholds. Such alterations, together with other factors, may contribute to the disruption of selftolerance in SLE.
BLK has apparently become one of the most important and consistent non-MHC gene for SLE and the other autoimmune diseases across multiple ethnic groups and is one of three key genes (BLK, LYN and BANK) involved in BCR signaling found to be strongly associated with SLE proves the importance of this pathway in disease pathogenesis. B-lymphoid tyrosine kinase (BLK) was one of the top hit in more than one GWA analyses, while LYN was associated with high significance in the International Consortium for Systemic Lupus Erythematosus (SLEGEN) study only. BLK has been implicated in the pathogenesis of SLE and has been investigated in numerous ethnically diverse studies.
GWAS in European-derived populations identified a SNP (rs13277113; located in the promoter region of BLK, maps to the intergenic region between *FAM167A*/C8orf13 and

BLK), of which allele A is associated with reduced expression of *BLK* but increased expression of *FAM167A* (previously referred to as C8orf13) in patients with SLE (Ito, 2010). Another *BLK* SNP (rs2248932), located 43 kb downstream of rs13277113, is also associated with SLE where the risk C allele of rs2248932 was associated with the lower levels of BLK mRNA expression (Zhang, 2010).

Both SNPs have subsequently been confirmed as SLE-associated in Asian populations (Zhang, 2010 & Ito, 2009). Genotyping SNP rs2248932 in SLE patients of Chinese Han confirmed that SNP rs2248932 in BLK gene was significantly associated with SLE ($P = 1.41 \times 10^{-8}$). The association of BLK in Chinese SLE patients was consistent with a dominant model. In contrast to the Caucasian, this risk allele was the major allele in the Chinese Han; the risk allele frequency was higher in Chinese Han than in Caucasian. No association was found between this SNP and any subphenotype of SLE. Fan *et al* performed a meta-analysis to test the association of two SNPs rs13277113 and rs2248932. A significant associations of rs13277113 and SLE were observed for dominant model (AA + AG vs. GG, OR: 1.518), and recessive model (AA vs. AG + GG, OR: 1.553); so were rs2248932 and SLE for dominant model (TT + TC vs. CC, OR: 1.34), and recessive model (TT vs. TC + CC, OR: 1.34) (Fan, 2010).

9.2 X Kell blood group precursor-related family, member 6 (XKR6), 8p23.1

XKR6, a member of a novel family of PDZCBM containing proteins sharing homology with the *C. elegans* gene *ced-8*, which has been implicated in regulating the timing of apoptosis (Giallourakis, 2006). *XKR6* contains an intronic microRNA, hsa-miR-598, which is highly expressed in human peripheral blood mononuclear cells, especially activated B-cells (Lawrie, 2008). Dissecting the relative contribution of XKR6 to SLE risk is likely to be a complicated undertaking, especially given that a polymorphic inversion under apparent selection pressure on 8p23 encompasses the *XKR6*, *C8orf12*, *C8orf13*, and *BLK* genes, all of which have been implicated in SLE risk in GWAS studies (Deng, 2008).

9.3 Yamaguchi sarcoma viral (v-yes-1) related oncogene homolog' LYN, 8q12.1

LYN is a Src-tyosine kinase involved in B cell activation by phosphorylating the ITAM domain of the BCR-associated Ig α/β signaling molecules, in turn recruiting and activating the tyrosine kinase SYK, which initiates multiple activating signals. LYN also mediates inhibitory signals by phosphorylating inhibitory receptors such as CD22 and FcγRIIb and may therefore have a critical role as a modulator of B-cell activation thresholds. In the Genome wide association studies (GWAS) of SLE, three B cell signaling molecules *BLK, LYN* and *BANK1* (Hom, 2008; Kozyrev, 2008) were found to be associated with SLE. The best characterized functionally is LYN among the other two kinases *(BANK, BLK)* shown to be associated with SLE. These data suggest that aberrant regulation of B cell signaling may be one mechanism for generating hyper-responsive B cells, which might lead to aberrant B cell development, selection and ultimately influence the production of autoantibodies. Expression of Lyn is significantly decreased in both resting and BCR stimulated peripheral blood B cells from two-thirds of SLE patients compared to controls (Liossis, 2001). Further, statistically significant alterations at the transcriptional level were confirmed by a 2.5-fold decrease in Lyn mRNA in SLE patients compared to healthy individuals. Another group analyzed the level and subcellular distribution of Lyn in SLE

B cells and found that slightly more than half of the SLE patients analyzed had reduced levels of Lyn protein, which was subsequently determined to be due to increased ubiquitination of the protein. Functional differences in LYN ubiquitination have been also associated with SLE risk (Flores-Borja, 2005).

Two SNPs, rs7829816 and rs2667978, showed significant association in some of the cohorts tested, but failed to consistently replicate in all cohorts (Harley, 2008). Lu R. *et al* has performed one of the largest studies to examine the possible genetic association of *LYN* with SLE in multiple large populations of different ancestries (European-derived, African American and Korean). Their study has replicated a previously observed association with rs7829816 (Harley, 2008), however, data from Lu R. *et al* study suggested that this association is not a dominant lupus effect. The strongest and most consistent association found in this study was at rs6983130, which is within the first intron at the 5′ end near the primary transcription initiation site. This SNP showed the strongest association in the European-American female population. A strong gender influence was found with this SNP when analyzing only female subjects. Rs6983130 also showed associations with autoantibodies which is strongly associated with the development of SLE, specifically anti-dsDNA, anti-chromatin, anti-52 kDa Ro and anti-Sm.

10. Chromosome 10

10.1 Mannose-Binding Lectin (MBL), (10q11.2-21)

MBL is very similar to C1q in its structure and function. It is an important element of the innate immune system. MBL comprises a trimer of three identical polypeptides, and several trimmers further combine to form a bouquet-like structure (Holmskov, 1994). MBL recognizes carbohydrate patterns, found on the surface of a large number of pathogenic micro-organisms, including bacteria, viruses, protozoa and fungi and initiates the lectin pathway for opsonization and clearance of pathogens in an antibody-independent manner.

MBL gene comprising four exons and there is only one single functional gene. The normal structural MBL alleles is named A, while the common designation for the 3 variant structural allele B (Gly54Asp), C (Gly57Glu) and D (Arg52Cys) are O. MBL expression is influenced by polymorphic sites in the upstream part of the MBL gene nucleotides substitutions at positions -550, -221 and +4. Absent or low levels of serum MBL is a result of these polymorphisms and might be associated with the development of SLE (Takahashi, 2005 & Pradhan, 2010). Case-control genetic studies of MBL polymorphism were performed in various Ethnic groups. MBL genotyping in SLE confirmed that the MBL functional variants are associated with SLE (Ramasawmy, 2008). Serum MBL levels fluctuate during the course of SLE disease activity and MBL genotypes have been found to be useful in assessing the risk of infection during immunosuppressive treatment the majority of the SLE patients receive.

Two possible explanations for associations between MBL deficiency and occurrence of SLE were proposed (Korb, 1997): (a) MBL can bind to and initiate uptake of apoptotic cells into macrophages (Ogden, 2001 & Okada, 2002), and abnormal clearance of apoptotic cells caused by MBL deficiency may result in overexpression of autoantigens; (b) viral infection is believed to be one of the causes of SLE (Okada, 2002), and MBL deficiency may lead to more frequent infections.

11. Chromosome 11

11.1 Interferon regulatory factor 5 /PHD and RING-finger domains 1(IRF7/ PHRF1) locus, 11p15.5

IRF7 is a transcription factor that can induce transcription of IFN*a* and in turn IFN*a*-induced genes downstream of endosomal TLRs, similar to IRF5 (Barnes, 2004). A SNP near IRF7 was found to be associated with SLE susceptibility in the International Consortium for SLE Genetics (SLEGEN) genome-wide association study (Harley, 2008). The associated SNP (rs4963128) was located 23 kb telomeric to IRF7 in a gene of unknown function named PHD and RING-finger domains 1 (PHRF1; also known as KIAA1542 or CTD-binding SR-like protein rA9). This SNP was in high linkage disequilibrium ($r^2 = 0.94$) with the rs702966 SNP in IRF7 (Harley, 2008). The PHRF1 gene contains PHD-finger and RING-finger domains, and has not been functionally characterized to date. PHD and RING-finger domains both chelate zinc ions, and PHD domains are frequently found in proteins which mediate protein–protein interactions in the cell nucleus (Bienz, 2006).

There is a hypothesizes that the SLE-associated variant discovered in the IRF7/PHRF1 locus in the SLEGEN study (International Consortium for Systemic Lupus Erythematosus Genetics, 2008) could be due to a polymorphism in IRF7 that predisposes to increased IFN*a* production. Then, Salloum R. *et al* have proven this hypothesis by analyzing serum IFN*a* in SLE patients as a quantitative trait to determine associations with haplotype-tagging SNPs in the IRF7/PHRF1 locus (Salloum, 2009). In a joint analysis of European American and Hispanic American subjects, the rs702966 C allele was associated with the presence of anti–double-stranded DNA (anti-dsDNA) antibodies (P=0.0069). The rs702966 CC genotype was only associated with higher serum levels of IFN*a* in European American and Hispanic American patients with anti-dsDNA antibodies (joint analysis $P = 4.1 \times 10^{-5}$) (International Consortium for Systemic Lupus Erythematosus Genetics, 2008). However, the rs702966 C allele was not associated with anti-dsDNA in the African American subjects, and no other significant associations were seen in this group. In African American patients, the rs4963128 T allele downstream of IRF7 was associated with the presence of anti-Sm antibodies ($P = 0.0017$), where subjects with the rs4963128 CT and TT genotypes had higher IFN*a* levels than those with the CC genotype ($P = 0.0012$). The striking differences observed within the African American cohort separated by the presence or absence of anti-Sm antibodies suggest 2 independent patterns of association with IRF7/PHRF1 variants, which cannot be explained by European admixture at the locus. It is possible that the rs4963128 T allele marks a particular element in African-derived chromosomes that associates with anti-Sm antibodies and is not present in the other ancestral backgrounds (Salloum, 2009). Salloum R. *et al* hypothesized that the rs702966 C allele and elements in linkage with it may function similarly across all ancestral backgrounds, although the effect of the anti-Sm–rs4963128 T allele interaction on serum levels of IFN*a* in African Americans is independent of the effect at the rs702966 C allele (Salloum, 2009).

12. Chromosome 16

12.1 *Integrin* α*M* (ITGAM), 16p11.2

ITGAM is a single-pass type I membrane protein predominantly expressed primarily on neutrophils, macrophages and dendritic cells that is involved in various adhesive interactions to stimulated endothelium, and also in the phagocytosis of complement coated particles. Together with integrin chain β2, *ITGAM* forms a functionally active heterodimer,

the integrin αMβ2 molecule to form the cell surface receptor, known as complement receptor 3 (CR3) or Mac-1, can bind a variety of ligands including intercellular adhesion molecule 1 (ICAM-1), the C3bi fragment of activated complement C3, fibrinogen, and factor X. *ITGAM* is perhaps more familiarly known as CD11b or CR3, and it thereby takes part in the uptake of complement-coated particles and the clearance of immune complexes.
The identification of ITGAM as a major susceptibility gene was perhaps the greatest surprise of the GWA analyses because it has been subject to expression studies in the past with little convincing evidence for a role in SLE (Harley, 2008 & Hom, 2008). A non-synonymous SNP in ITGAM, rs1143679, functional mutation results in an Arg77His (R77H), was first associated in European and African descendants SLE patients, where the G allele contributes to disease susceptibility (Nath, 2008 & Han, 2009). This amino acid does not lie within any known ligand binding site, but may alter the confirmation of the I/A domain to which many ligands do bind. This variant could therefore influence leucocyte trafficking mediated via ICAM-1, or equally it could influence the CR3-mediated uptake of apoptotic cells or immune complexes. Functional data is awaited with interest. However, the consistent association of rs1143679 was not replicated in Asian population (Korean and Japanese) because this SNP was monomorphic for 'G' allele (Han, 2009). This result suggests that the genetic association of ITGAM with SLE is unlikely in Asians. However, another group studied Chinese SLE patients living in Hong Kong and found that rs1143679 was associated with SLE, and another related SNP in the gene, rs1143683, was also identified (Yang, 2009). Therefore, it needs to be confirmed in larger number of SLE case–controls in Korean and Japanese populations.

12.2 Deoxyribonuclease DNase I, 16p13.3

DNase I may be the most important nuclease for the removal of DNA from nuclear antigens. Several lines of evidence suggest that defects in DNase I activity play a role in SLE pathogenesis. Studies in SLE patients and in mouse models support the involvement of *DNase I* among the genes involved in the clearance of apoptotic cells. The first evidence was reported by Chitrabamrung *et al.* (Chitrabamrung, 1981) more than two decades ago. These authors found decreased DNaseI activity in patients with SLE. It has been shown that a *DNaseI* knockout mouse develops a lupus-like syndrome (Napirei, 2000) and a nonsense mutation on the DNASEI gene leading to a non-functional protein has been identified in two Japanese girls with SLE. These girls had very low DNaseI activity and high titers of anti-nucleosome and anti-double-stranded DNA (dsDNA) antibodies. Subsequent analysis of several series of SLE patients from different populations showed that this mutation is extremely rare. Bodan˜o A *et al.*, have described two Spanish SLE patients with very low serum DNase I activity harboring three new mutations in the DNASEI coding sequence that account for the reduced enzymatic activity (Bodan˜ o, 2004). The frequency of these new mutations was below 1% both in SLE patients and in the population. Bodan˜o A. *et al.* also found other DNASEI single-nucleotide polymorphisms (SNPs) but there was no evidence suggesting a functional role for them. These studies support the involvement of DNase I in the pathogenesis of SLE.
In a Korean SLE population, 16 SNPs from the DNaseI were studied using a case–control approach. In parallel, common autoantibodies were also examined for the same population. None of the SNPs were in significant association with SLE, however, a non-synonymous SNP in exon 8, namely rs1053874 (which was also known as +2373A/G, and which causes Gln244Arg substitution), was significantly associated with an increased risk of the

production of anti-RNP and anti-dsDNA (Shin, 2004). However, the same SNP (+2373A/G) has shown association between the GG allele and SLE susceptibility in Spanish population, but no association with the majority of antinuclear antibodies (anti-dsDNA, anti-ssDNA and anti-RNP) and no effect on DNase I activity (Bodaño , 2006). This discrepancy could be related to heterogeneity between the populations.

13. Chromosome 17

13.1 Monocyte chemo-attractant protein 1 (MCP1), 17q11.2-12

MCP-1, currently also designated CCL2, encodes a β-chemokine that recruits monocyte, eosinophils, and memory T cells to inflammatory sites, to regulate adhesion molecule expression and T-cell functions in acute and possibly chronic inflammation (Charo, 2004). Evidence in human and animal studies suggests a significant role of MCP-1 in the progression of glomerular and tubulointerstitial injuries and glomerulonephriti in patients with SLE (Stahl, 1993; Rovin, 1996; Saitoh, 1998; Rovin 1998). In particular, MCP-1 has been shown to be pathogenic for kidney injury in murine lupus nephritis (Shimizu, 2004), and reported to be involved in glomerulonephritis in SLE patients, in which elevation of serum MCP-1 correlates with disease activity (Tesar, 1998). An increased urine MCP-1 (uMCP-1) level was detected in SLE patients during active renal disease (Rovin, 2005).

SNP (rs1024611) -2518A/G and G/G in MCP1 promoter region may modulate the levels of MCP-1 expression and increased susceptibility to SLE and lupus nephritis in patients from North America (Tucci, 2004). However, the Involvement of the MCP-1 –2518 A>G promoter polymorphism in SLE development and its contribution to some clinical manifestations of SLE remains controversial (Tucci, 2004; Aguilar, 2001; Hwang, 2002; Kim, 2002; Brown, 2007; Liao, 2004; Ye, 2005). In a Spanish study for example, −2518G polymorphism is noted to be associated with cutaneous vasculitis but not SLE or lupus nephritis as genotyping of −2518A/G polymorphism shows no difference in allelic or genotype frequencies in SLE patient and healthy controls (Aguilar, 2001). Further investigation is needed to delineate if ethnic heterogeneity contributes to this gene polymorphism and SLE susceptibility.

14. Chromosome 19

14.1 Tyrosine kinase 2 (TYK2), 19p13.2

TYK2 is part of the Janus kinase that binds to the interferon (IFN)-α receptor (IFNAR), on the cell surface of IFN-producing cells. Binding of IFN-α to its receptor, leads to the phosphorylation and therefore activation of TYK2 (Richter, 1998). Active TYK2 then phosphorylates IFNAR to allow binding of STAT3 and STAT5 (David, 2002) which leads to expression of IFN-α. Deficiency of *TYK2* leads to defects of multiple cytokine pathways, including type I interferon, IL-6, IL-10, IL-12, and IL-23, and to impaired T-helper type 1 differentiation and accelerated T helper type 2 differentiation (Minegishi, 2006). More research needed to clarify which of these pathways is critically affected by the *TYK2* risk allele.

TYK2 gene has been linked to the formation of anti-dsDNA antibodies of Caucasian SLE patients (Namjou, 2002). TYK2 rs2304256 was associated with increased risk of discoid lupus erythematosus (P=0.012). In a joint linkage and association study of 44 SNPs in 13 genes from type I IFN pathway in the Scandinavian population, TYK2 and interferon regulatory factor 5 (IRF5) genes displayed strong association with SLE susceptibility (Sigurdsson, 2005).

The most remarkable result from this study has probably been the association signal observed with the rs2304256 nonsynonymous SNP of TYK2 (OR = 0.79) because this has been a controversial SLE genetic factor. The rs2304256 SNP introduces a valine to phenylalanine change in the Janus homology domain 4 of *TYK2* whose functional relevance has not yet been tested. This nonsynonymous SNP showed the strongest association among the 11 TYK2 SNPs studied in Scandinavian families (Sigurdsson, 2005), but was not associated in a study of UK families (Cunninghame, 2007). This latter study, however, found association with another TYK2 SNP (rs12720270) that was not associated in the Scandinavian study. Finally, the International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN) GWA study excluded association with the rs12720270 SNP (the rs2304256 SNP was not included in the GWA panels)(International Consortium for Systemic Lupus Erythematosus Genetics, 2008).
TYK2 single nucleotide polymorphisms (SNPs), rs2304256, rs12720270 and rs280519, were genotyped in the Japanese population by Kyogoku C *et. al.* in a case-control association study. Linkage disequilibrium (LD) among TYK2 SNPs was examined and no association was revealed with SLE therefore it was concluded that TYK2 is not a genetic risk factor for SLE in a Japanese population (Kyogoku, 2009).

15. Chromosome X

15.1 Interleukin-1 receptor-associated kinase 1/Methyl-CpG-binding Protein 2 locus (IRAK1/MECP2), Xq28

IRAK1, a serine–threonine protein kinase, regulates multiple pathways in both innate and adaptive immune responses by linking several immune-receptor- complexes to TNF receptor-associated factor 6 in mouse models of lupus, *Irak1* is shown to regulate nuclear factor κB (NFκB) in TCR signaling and Toll/interleukin-1 receptor (TLR) activation, as well as the induction of IFN-α and IFN-γ, (Jacob, 2009) implicating IRAK1 in SLE. In a study of four different ethnic groups, multiple SNPs within *IRAK1* were associated with both adult-onset and childhood-onset SLE (Jacob, 2009). The identified polymorphism C203S in IRAK1 is not in any known functional domain, therefore it was suggested that the association may actually be with its neighbor, methyl-CpG-binding protein 2 (*MECP2*).
MECP2 is an X-linked gene located in a region of LD with *IRAK1*, encoding a protein that represses transcription from methylated promoters, has also been associated with lupus. Polymorphisms in *MECP2* may have relevance to the epigenetic DNA methylation changes found in lupus and discussed below. There is evidence for altered methylation in SLE, (Webb, 2009) as well as differential expression of potentially methylated genes, (Pan, 2009) although, as with *IRAK1,* a contributing causative SNP is not immediately obvious. Indeed, it is possible that both of these strong candidates contribute to the effect.
A large replication study in a European-derived population confirmed the importance of this region (*IRAK1–MECP2*) to SLE. The location of *IRAK1* and *MECP2* on the X chromosome raises the possibility that gender bias of SLE might, in part, be attributed to sex chromosome genes. Further work is required to identify the causal variants (Sestak, 2011).

15.2 Toll-like receptor (TLR7), Xp22.2

TLR7, the protein encoded by this gene is a member of the Toll-like receptor (TLR) family which is single transmembrane cell-surface receptors expressed on many types of cells including macrophages and dendritic cells, plays a fundamental role in pathogen

recognition and activation of innate immunity. TLRs generally exist as homodimers. They are highly conserved from Drosophila to humans and share structural and functional similarities. TLR are activated by molecules associated with biological threat and are highly specific towards evolutionary conserved entities on microbes, such as bacterial cell-surface lipopolysaccharides, flagella and unmethylated CpG islands.

Activation of toll-like receptors initiates downstream signaling cascades, initially via the adapter molecules MyD88, Trap, Trif and Tram, leading to NF-kappa-B activation, cytokine secretion and the inflammatory response, regulate intracellular kinases and gene expression. The signaling cascade coupled to toll-like receptor activation is very similar to that of interleukin-1 receptor (IL-1R) activation. It has been suggested that some toll-like receptors may have endogenous ligands, such as Hsp60 and fibrinogen, and this has promoted speculation that endogenous toll-like receptor activators may have a pathological role in autoimmune disease. TLRs play an important role in the pathogenesis of SLE (Vollmer, 2005 & Christensen, 2006). The role of nucleic acid binding TLR7 has become quite apparent in both SLE animal models and human patients. This receptor promotes autoantibodies and cytokines responsible for chronic inflammation (Christensen, 2007 & Savarese, 2008). A recent fine mapping of the 23-kb TLR7 region using 11 SNPs in 1434 SLE cases of Eastern Asian descent versus 1591 controls showed the association of two TLR7 SNPs with SLE (rs5935436 in the promoter, $p=1.8x10^{-3}$; rs3853839 in the 3′-UTR, $p=6.7x10^{-4}$) (in press).

16. Epigenetics involvement in the pathology of SLE

The controversy, we came cross in the previous section, in the association of immunologically related genes with susceptibility to SLE and the incomplete concordance in monozygotic twins affected with SLE, while they carry the same SLE susceptibility genes, are clear indications that genetics is not the only factor that influences susceptibility to SLE. This means that some non-genetic factors can modify gene expression through epigenetic mechanisms, potentially contributing to SLE. The field of epigenetics is rapidly growing especially in studying autoimmune diseases. Epigenetics is the study of heritable modifications in gene function that alter the phenotype without modifying the genetic sequence, these modifications result in the activation or complete/partial gene silencing (Hirst, 2009). It is becoming clear that epigenetic modifications contribute to a variety of pathogenetic processes in which environmental and genetic factors are involved. Much of the variability in severity, organ involvement, and response to therapy among patients with systemic lupus erythematosus (SLE) is blamed on differences in gene expression. That, in turn, is due to epigenetic mechanisms, one of the "master regulators" of gene expression.

Accumulating epidemiological, clinical, and experimental evidence supports the conclusion of the critical role of epigenetic factors in immune programming. Compelling evidence has been gathered supports a role for epigenetic alterations in the pathogenesis of SLE. For example, inhibiting DNA methylation in normal $CD4^+$ T cells induces autoreactivity, and these autoreactive cells promote autoantibody production. Furthermore, transferring hypomethylated T cells into syngeneic mice causes a lupus-like disease (Richardson, 1990 & Yung 1997). Understanding this mechanism provides the basis for clarifying how the complex interactions of the genome and epigenome shape immune responses and maintain immune tolerance to self-antigens.

In this section we will discus, in brief, some of the epigenetics mechanisms that are involved in the SLE pathogenesis. These mechanisms play an essential role in gene regulation

Gene	locus	function	P-values	ORs
PTPN22	1p13	T-cell signaling	$<1x10^{-5}$ - $5.2x10^{-6}$	1.49-1.53
FCGR2A	1q21-23	Immune complex clearance Fc Receptor	0.0016 - $6.78x10^{-7}$	1.30-1.35
FCGR3B	1q23.3	Immune complex clearance Fc Receptor	$2.7x10^{-8}$	2.21c
FcGR3A	1q23.3	Immune complex clearance Fc Receptor		1.6
CRP	1q23.2	sensitive marker of inflammation	$6.4x10^{-7}$	
TNFSF4	1q25.1	T-cell signaling	over: $1.91x10^{-6}$	over: 1.63 (T/U) and 1.28b
NMNAT2	1q25.3	Catalyzes the formation of NAD(+)from nicotinamide mononucleotide (NMN) and ATP.	$1x10^{-10}$	1.18
IL10*	1q31–q32	1q24	4.0×10 −8	1.2
TLR5	1q41-q42	innate immunity		
STAT4	2q33	TLR–IFN signaling	$2.8x10^{-9}$ - $8.96x10^{-14}$	1.53-1.50
PDCD1 (CD279)	2q37	pro-B-cells differentiation		1.2
CTLA4 (CD152)	2q33.2	transmits an inhibitory signal to T cells		
PXK	3p14.3	Bind and modulates both Na, K-ATPase enzymatic and ion pump activities	$7.10x10^{-9}$	1.25
BANK1	4q24	B-cell signaling	$3.7x10^{-7}$	1.38
TNIP1	5q33	TNF–NFκB signaling		1.3
The MHC	6p21.3	T-cell signaling	$2.71x10^{-21}$- $1.7x10^{-52}$	2.01-2.36
ATG5	6q21		$1.36x10^{-7}$	1.19
PRDM1	6q21	B-cell signaling	1.74×10 −8	1.3
TNFAIP3	6q23	TNF–NFκB signaling	$2.9x10^{-12}$	1.7
IRF5	7q32	TLR–IFN signaling	$1.65x10^{-11}$ - $3.61x10^{-19}$	1.54-1.72
ICA1	7p21.3		$1.90x10^{-7}$	1.32
IKZF1	7p12	B-cell signaling		1.4
BLK	8p23.1	T-cell signaling	$1x10^{-10}$ -$7x10^{-10}$	1.22-1.39
XKR6	8p23.1		$2.51x10^{-11}$	1.23
LYN	8q12.1		$5.4x10^{-9}$	1.30
C8orf12	8p23.1	miscRNA gene	$4.00x10^{-10}$	1.22
BLK–FAM167A–XKR6 locus	8p23.1	B-cell signaling	$1.7x10^{-8}$	1.2-1.6
MBL	10q11.2-21	element of the innate immune system		
KIAA1542 (near IRF7)	11p15.5	Interferon and TLR7/9 Signaling	$3.00x10^{-10}$	1.28
ITGAM	16p11.2	Neutrophil activity	$3x10^{-11}$ - $1.61x10^{-23}$	1.33-1.62

CD226	18q22.3	member of the Ig-superfamily		
TYK2	19p13.2	Janus kinases (JAKs) protein interferon signaling pathway		
UBE2L3	22q11.2	encodes a member of the E2 ubiquitin-conjugating enzyme	$7.53x10^{-8}$	1.22
SCUBE1	22q13.2	adhesive molecule	$1.21x10^{-7}$	1.28
MECP2	Xq28	Chromosomal protein that binds to methylated DNA	$1.2x10^{-8}$	1.39
IRAK1	Xq28	responsible for IL1-induced upregulation of the transcription factor NF-kappa B		
TLR7	Xp22.2	innate immunity		

Table 1. Top SLE candidate genes categorized by chromosomal location.

through covalent modifications of DNA and histones, and determine regional chromatin structure with consequences on gene expression. We will also discuss the involvement of MicroRNAs (miRNAs) as an epigenetic factor involved in the pathology of SLE.

16.1 Histone covalent modification

The basic chromatin subunit is the nucleosome, which consists of DNA wrapped twice around a histone core. Nucleosomes are then organized into higher order structures forming chromatin fibers (Felsenfeld 2003). Chromatin in its native form is tightly compacted and inaccessible to transcription factors and the transcription initiation machinery. However, histone "tails" protrude from the nucleosome, and are covalently modified by *acetylation, methylation, phosphorylation, ubiquitination, and SUMOylation (*SUMO (small ubiquitin-related modifier) (Felsenfeld 2003). These modifications serve as signals, referred to as the "histone code", that initiate a number of processes including the localized remodeling of chromatin from a compact, transcriptionally silent configuration to a more open structure accessible to the transcription initiation machinery.

16.2 DNA methylation and autoimmunity

DNA methylation refers to the methylation of cytosines in CpG pairs (cytosine and guanine residues separated by a phosphate, which links the two nucleosides together in DNA). Most CpG pairs in the mammalian genome are methylated, with some unmethylated pairs found in the regulatory elements of active genes. Most unmethylated CpGs are found in GC-rich sequences, termed CpG islands. CpG islands contain multiple binding sites for transcription factors, and serve as promoters for the associated gene. Methylation of these promoters can lead to gene silencing where transcriptionally active chromatin is characterized by unmethylated DNA. Convincing evidence indicates that DNA can be actively demethylated and therefore affect gene expresssion. For example, several CpG pairs in the *IL-2* promoter demethylate within 20 minutes of T-cell stimulation, prior to initiation of DNA synthesis (Bruniquel, 2003).

DNA methylation is catalyzed by the enzyme DNA methyltransferases (DNMTs) while and histone acetylation is controlled by histone acetylases (HATs) and deacetylases (HDACs). It is hypothesized that the processes of DNA methylation and histone deacetylation work together through the formation of DNMT/HDAC transcriptional repressor complexes that work in silencing gene expression through establishing a repressive chromatin environment

(Cameron, 1999). However, DNMTs and HDACs lack DNA-binding domains, and are therefore dependent on transcription factors (TFs) for their recruitment to DNA. Zhao M *et al.* set out a study to uncover mechanisms underlying the hypomethylation and hyperacetylation of genes involved in lupus autoimmunity by investigating the involvement of specific TFs. They assessed the activities of 225 TFs in $CD4^+$ T cells from SLE patients relative to healthy controls using a newly developed screening method (Qiao, 2008), and found that the activity of regulatory factor X 1 (RFX1) is significantly downregulated in SLE $CD4^+$ T cells (Zhao, 2010). Follow-up analyses confirmed the result of Zhao M *et al.* study and further revealed that both the expression and activity of RFX1 protein are reduced in SLE $CD4^+$ T cells. Zhao M *et al* (Zhao, 2010) also provided evidence indicating that RFX1 recruits the co-repressors HDAC1 and DNMT1 to the promoter region of CD11a and CD70, thus regulating their expression in $CD4^+$ T cells. Taken together, our findings indicate that reduction of RFX1 plays an important role in inducing autoreactivity and autoantibody overstimulation in SLE.

In addition, DNA hypomethylation appears to induce $CD4^+$ T cell autoreactivity and the inhibition of DNA methylation with 5-azacytidine caused CD4+ T-cell autoreactivity. This lupus-like autoimmunity correlated with overexpression of ITGAL (CD11a) and TNFSF7 (CD70) (Lu, 2002 & 2005). CD11a and CD70 overexpression in these $CD4^+$ T cells is associated with hypomethylation of their respective promoters (Lu, 2002 & 2005). CD11a is the alpha chain of the heterodimeric integrin lymphocyte function-associated antigen-1 (LFA-1) (CD11a/CD18) (ITGAL/Integrin beta-2). Overexpressing LFA-1 by transfection caused an identical autoreactivity (Yung, 1996).LFA-1 plays a central role in adhesive interactions between T cells and other immune system cells including macrophages, dendritic cells and B cells. This protein is also essential for the recruitment of leukocytes into sites of inflammation, antigen-specific T cell activation, helping B cell, as well as alloreactive, cytotoxic T cell and natural killer responses (Shimaoka & Springer, 2003). LFA-1 deficient lupus mice have significantly increased survival, decreased anti-DNA autoantibody formation, and reduced glomerulonephritis (Kevil, 2004). CD70 is expressed on activated T cells and increases pokeweed mitogen (PWM)-stimulated immunoglobulin (Ig) G synthesis, indicating B cell costimulatory functions (Kobata, 1995). Demethylated, autoreactive CD4+ T cells overstimulate antibody production by B cells and kill macrophages (Richardson, 2007), relaeasing apoptotic nuclear material that stimulates lupus-like autoantibodies (Denny, 2006). T-cell hypomethylation correlates with disease activity in SLE, suggesting that DNA hypomethylation may be a key player in the pathogenesis of the disease (Corvetta, 1991).

Furthermore, CD4+ lymphocytes undergo global histone H3 and H4 deacetylation and consequent skewed gene expression. Although multiple lines of evidence highlight the contribution of epigenetic alterations to the pathogenesis of lupus in genetically predisposed individuals, many questions remain to be answered. Attaining a deeper understanding of these matters will create opportunities in the promising area of epigenetic treatments.

16.3 MicroRNAs (miRNAs) and autoimmunity

MicroRNAs (miRNAs) are newly discovered, small (about 23-nucleotide), noncoding ribonucleic acids (RNAs) that function in the posttranscriptional regulation of about 30% of mRNAs by binding to their 3′-untranslated region (3′-UTR), thus targeting them for degradation or translational repression. miRNA are known to regulate cellular processes such as apoptosis, cell cycle, differentiation, and immune functions. The powerful gene regulatory role of miRNAs is now well recognized, where the recent discovery of the gene-

regulatory role of miRNAs has led to a paradigm shift in the understanding of expression and function of the mammalian genome. The field of miRNA research gained widespread attention with the recognition of aberrant expression and/or function of miRNAs in a broad range of human diseases including autoimmune diseases (Pauley, 2009).

Recent research evidence has emerged showing the critical role of miRNAs not only for the development of the immune system but also for the function of both innate and adaptive arms of the immune system (Taganov, 2007; Xiao, 2009; Gantier, 2007; O'Connell, 2010; Lodish, 2008; Sonkoly, 2008; Baltimore, 2008). Using state of the art quantitative mass spectrometry two investigators measured the response of thousands of proteins after introducing microRNAs into cultured cells and after knockdown mir-223 in mouse neutrophils. Their results are consistent with each other and demonstrate that changes in the level of a single miRNA may have a significant impact on the levels of hundreds to thousands of proteins (Baek, 2008). These important studies are the first to show the impact of microRNAs on the proteome which indicated that for most interactions microRNAs act as rheostats to make fine-scale adjustments to protein output (Baek, 2008 & Selbach, 2008). Tang et al have shown that miR-146 regulates the level of at least TRAF6, IRAK1, STAT-1, and IFN regulatory factor 5 (IRF-5), all of which are important for the IFN pathway (Tang, 2009). The reported reduction of miR-146 in PBMCs from SLE patients (Tang, 2009) will likely affect the levels of these factors significantly and contribute to overexpression of type I IFN and, thus, disease activity.

It is intriguing that independent studies have demonstrated an increased level of miR-146 in RA patients, but a decreased level in SLE patients, as compared with healthy controls. Given that RA and SLE are both systemic rheumatic diseases, one may be surprised by the finding that miR-146 levels are contradictory in these diseases, and yet, it should not be surprising, since this may simply be reflecting a difference in the overall cytokine profiles between the two diseases, with type I IFN playing a dominant role in SLE, whereas TNFα, interleukin-1 (IL-1), and IL-6 are the principle cytokines in RA. In the coming years, one can expect research reports on miRNA expression in many other autoimmune diseases, as well as more-complete profiling data, with disease activity correlations or a lack thereof.

17. References

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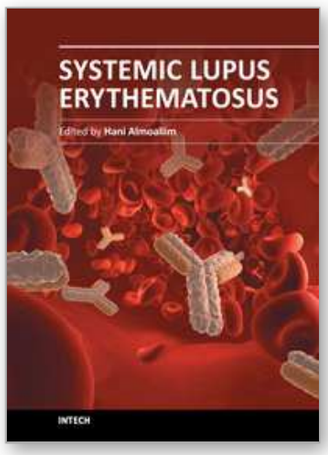

Systemic Lupus Erythematosus

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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

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