The genetics of systemic lupus erythematosus and implications for targeted therapy

Andrea L Sestak, Barbara G Fürnrohr, John B Harley, Joan T Merrill, Bahram Namjou

ABSTRACT

Observations of familial aggregation ($\lambda_s=8–29$) and a 40% identical twin concordance rate prompted recent work towards a comprehensive genetic analysis of systemic lupus erythematosus (SLE). Since 2007, the number of genetic effects known to be associated with human lupus has increased by fivefold, underscoring the complexity of inheritance that probably contributes to this disease. Approximately 35 genes associated with lupus have either been replicated in multiple samples or are near the threshold for genome-wide significance (p $>5 \times 10^{-8}$). Some are rare variants that convincingly contribute to lupus only in specific subgroups. Strong associations have been found with a large haplotype block in the human leucocyte antigen region, with Fcy receptors, and with genes coding for complement components, in which a single gene deletion may cause SLE in rare familial cases and copy number variation is more common in the larger population of SLE patients. Examples of newly discovered genes include ITGBAM, STAT4 and MEG2/IRAK1. Ongoing studies to build models in which combinations of associated genes might contribute to specific disease manifestations should contribute to improved understanding of disease pathology. In addition, pharmacogenomic components of ongoing clinical trials are likely to provide insights into fundamental disease pathology as well as contributing to informed patient selection for targeted treatments and biomarkers to guide dosing and gauge responsiveness. Besides these potentially valuable new insights into the pathophysiology of an enigmatic, potentially deadly, and, as yet, unsolved disease, genetic studies are likely to suggest novel molecular targets for strategic development of safer and more effective therapeutics.

Before 2007, nine established lupus susceptibility genes and genetic regions had been identified. Human leucocyte antigen (HLA) typing work in the 1970s identified genes encoded in the major histocompatibility complex region as being of potential importance in systemic lupus erythematosus (SLE), and this conclusion has been supported by the majority of the linkage and association studies conducted since (see Sestak et al. for review). In addition to the class I, II and III HLA molecules themselves, tumour necrosis factor (TNF) and complement proteins C2 and C4 lie within this highly linked region. Depletion of complement has long been known to be a feature of SLE, and these genes were also heavily studied before the onset of modern genetic technology. The strongest single genetic risk factor for SLE is a complete deficiency of one of the early complement components of the classic pathway such as C1q, C2, C4A and C4B, even though these deficiencies are relatively rare, only 1–2% in most cohorts. Despite this long-standing knowledge of association, however, targeted therapy has not been pursued in this area. For most patients, complement levels are low due to consumptive processes, not germ line defects, and supplementing serum complement with recombinant protein would only feed the fire. Early linkage studies pointed to the importance of three additional genes in the aetiology of SLE; the Fcy receptors, which lie in a linkage region on chromosome 1q23, and PDCD1, which is found in the 2q35–37 linkage region. Missense mutations of FCGR2A (H131R) or FCGR3A (F176V) alter their affinity to individual IgG subclasses and are thought to influence the processing of immune complexes and foster autoimmunity. A disease-associated non-coding single-nucleotide polymorphism (SNP) in PDCD1 alters its expression levels through disruption of DNA binding to runt-related transcription factor 1, and this altered expression is thought to disturb the self-tolerance mechanism, leading to autoimmunity in both lupus and rheumatoid arthritis (RA).

The final two genes well established before the genome-wide association scan era were discovered through candidate gene studies. Protein tyrosine phosphatase non-receptor 22 (PTPN22) contributes to risk in a number of autoimmune diseases, and in 2004 it was described in rapid succession to associate with SLE, RA, type 1 diabetes and autoimmune thyroid disease. Since the associated allele (R620W) leads to gain of function, there is an ongoing search for phosphatase inhibitors that may have anti-inflammatory potential through downregulating this pathway, one of which is gold. Interferon regulatory factor 5 (IRF5) became a target of interest after the discovery that SLE patients tend to upregulate interferon-induced gene transcripts. In European-derived samples three major susceptibility polymorphisms have been identified; rs2046400 creates a new splice site; rs10954213 creates a polyadenylation site, producing a shorter and more stable transcript; and a 30-bp insertion/deletion of exon 6 influences transcription initiation of several target genes. Functional work determining the relative impact of these variants remains to be pursued before IRF5 can be considered a therapeutic target.

RECENT ADVANCES IN LUPUS GENETICS

Since 2007, seven genome-wide association studies (GWAS) have been completed and published for SLE, the first five in European-derived populations and the last two in Asians. Running simultaneously with the GWAS in SLE were eight scans in
RA, also in populations of various racial origins, revealing both unique genes and loci that appear common to these autoimmune diseases. 35–42 Genome scan technology is improving in areas such as the detection of copy number variation, which is an important feature of C4 contribution to risk in SLE 43 and may contribute to additional loci, such as the family of Fcγ receptors. 44–46 Although many risk haplotypes have been identified through genome-wide scans, candidate causal variants are not immediately obvious for the vast majority of them. Deep sequencing is in progress to recover rare causal variants suspected to hold some of the missing genetic causality.

Primarily through the work done in these GWAS, the number of convincingly associated genes for lupus has been raised to more than 30 (see table 1). In addition, genes that have previously or simultaneously been identified to contribute to SLE susceptibility by candidate gene or linkage approaches were corroborated by GWAS. There are a number of SLE-associated genes in the major histocompatibility complex region, and whether these associations reflect the effect of HLA-DR or make independent contributions to disease pathology remains to be determined. 47 Recent attention has been focused on newly identified genes such as BANK1, IRAK1/MECP2, ITGAM, MECPP, STAT4 and TNFAIP3, and we will briefly describe these below.

**BANK1**

B-cell scaffold protein with ankyrin repeats (BANK1) is tyrosine phosphorylated through the B-cell receptor (BCR) upon B-cell activation, which in turn associates with the tyrosine kinase Lyn and the calcium channel IP3R and results in calcium ion release from the stores of the endoplasmic reticulum. 48 Polymorphisms in BANK1 may cause B-cell hyperresponsiveness. 31

**IRAK1/MECP2**

The serine/threonine kinase IRAK1 (interleukin-1 receptor associated kinase) is part of the Toll/interleukin-1 receptor and nuclear factor kappa B signalling pathway by linking several immune receptors to the central adaptor protein TRAF6 (TNF receptor-associated factor 6). The identified X-chromosomal polymorphism C203S in IRAK1 is not in any known functional domain, however, and the association may actually be with its neighbour, methyl-CpG-binding protein 2 (MECP2). 49 50 MECP2 encodes a protein that binds methylated DNA and is involved in the transcriptional regulation of methylation-sensitive genes. There is evidence for altered methylation in SLE, 50 as well as differential expression of potentially methylated genes, 51 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.

**Integrin αM**

Integrin αM (ITGAM) is a single-pass type I membrane protein predominantly expressed in monocytes and granulocytes that is involved in various adhesive interactions of monocytes, macrophages and granulocytes. Together with integrin chain β2, ITGAM forms a functionally active heterodimer, the integrin αMβ2 molecule, a receptor for fibrinogen, factor X and intracellular cell adhesion molecule 1. ITGAM is perhaps more familiarly known as CD11b or complement receptor 3, the receptor for iC3b fragment that is produced during complement activation, and it thereby takes part in the uptake of complement-coated particles and the clearance of immune complexes. It was identified as genetic risk factor for SLE in the exploration of a strong linkage interval 52 and independently confirmed in GWAS. 30 34 The risk allele (rs1148679) in ITGAM encodes an amino acid shift (R77H), which was also correlated with renal, discoid and immunological manifestations in patients with SLE. 53

**STAT4**

The association of a SNP (rs7574865) located in the third intron of signal transducer and activator of transcription 4 (STAT4) was found for SLE and RA in a case–control study, 35 which was subsequently confirmed by GWAS in multiple populations of different ancestries. 12 30 55 STAT4 mediates the expression of genes involved in a variety of immunological pathways such as cellular differentiation, proliferation and apoptosis. 36 Similar to IRAK, STAT4 can influence both innate and adaptive immune responses, as type I interferons, interleukin 12 (IL-12) and IL-23 are potent mediators of STAT4. 57 80

**TNFAIP3**

Multiple polymorphisms for susceptibility to SLE and RA and other autoimmune-mediated diseases were recently found for TNFα-induced protein 3 (TNFAIP3). 50 59 60 The gene product of TNFAIP3 is a zinc-finger A20 protein, with A20 being an ubiquitin-editing enzyme essential for proteasome degradation and termination of proinflammatory responses mediated by nuclear factor kappa B, thereby preventing inflammation.

There are many other genetic regions implicated in SLE through GWAS and candidate gene studies. Some of these associated SNP and haplotypes do not fall within coding regions, and the calcium channel IP3R and results in calcium ion release from the stores of the endoplasmic reticulum.
and their function may remain a mystery for some time. The potential cross-regulation by microRNA sequences and other epigenetic effects is just beginning to be explored. Models of gene–gene interaction are also likely to be important, as well as pathway analysis. The potential to discover equivalent effects caused by different genes in a model by their dysregulation of overlapping or congruent pathways holds a key for our understanding of both normal and perturbed immune functions.

CONCLUSIONS REGARDING IMPORTANT GENES IN SLE
The susceptibility genes identified thus far for SLE implicate a diverse array of pathways, including lymphocyte signalling, interferon response, clearance of complement and immune complexes, apoptosis, and DNA methylation. Although polymorphisms in ITGAM, IRF5 and PTEN22 offer mechanisms that provide plausible contributions to the pathogenesis of SLE, direct functional effects of many associated SNP and complete characterisation of risk haplotypes remain to be elucidated for most of the known genetic associations. Even as this characterisation proceeds, the knowledge derived from the genetic studies to date points to new avenues of therapy. When the mechanism of action for each risk polymorphism is better understood, new strategies for intervention will emerge. It should also be appreciated that whole genome scanning methods may fail to detect a number of potentially important genetic effects, and that some polymorphisms may have little impact alone but powerful disease consequences in combination.

USING GENETIC INFORMATION IN THE TREATMENT OF SLE: IMPLICATIONS FOR CURRENT THERAPIES
Cyclophosphamide
The best characterised use of pharmacogenomics in SLE has been the discovery of the impact of the cytochrome P450 system on cyclophosphamide therapy. Cyclophosphamide is a prodrug that requires activation by cytochrome P450 to 4-hydroxy-cyclophosphamide. There are many isoenzymes in P450 complex important for this bioactivation step, including CYP2B6, 2C9, 2C19, 3A4 and 3A5.61 Allelic variants in CYP2B6 have been reported to influence enzyme hydroxylation activity.62 At the other end of the pathway, detoxification of activated cyclophosphamide metabolites is mediated by aldehyde dehydrogenase and the glutathione S-transferase (GST) enzyme system. It has recently been reported that aldehyde dehydrogenase alleles strongly influence the level of cyclophosphamide cell toxicity and therefore the risk of haemorrhagic cystitis and liver toxicity (OR 11.95).63 In another study, the presence of at least one and therefore the risk of haemorrhagic cystitis and liver toxicity strongly influence the level of cyclophosphamide cell toxicity is mediated by aldehyde dehydrogenase alleles.

Mycophenolate mofetil
MMF is a potent immunosuppressive agent used for the prevention of allograft rejection. Several studies have reported that MMF can be effective in the treatment of lupus nephritis and may have fewer side-effects than cyclophosphamide.67–69 MMF is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), which is essential in the de novo pathway of purine biosynthesis. Although the purine salvage pathway is used in many cell types, activated lymphocytes are dependent on de novo purine synthesis.70 MMF is rapidly hydrolysed to an active metabolite (mycophenolic acid) with more than 90% bioavailability by the oral route. Although not yet studied in lupus, polymorphisms in genes of the MMF metabolic pathway, such as IMPDH1 and IMPDH2, can affect the gastrointestinal tolerance profile and drug-associated neutropenia in heart transplant patients.71 Genetic profiling, therefore, also holds promise for predicting adverse responses in SLE.

Azathioprine
Azathioprine is also a prodrug, and it is metabolised to its active forms, 6-mercaptopurine (6MP) and 6-thionosinic acid by a series of enzymatic steps.72 Thiopurine S-methyltransferase (TPMT) deactivates 6MP, and TPMT deficiency is inherited as an autosomal recessive trait and is correlated with the risk of severe neutropenia, due to excessive accumulation of intracellular 6MP.72 Following description of the enzyme defect, the low TPMT enzyme activity was found to be predominantly due to three common variants in the TPMT gene.73–74 Inosine triphosphate pyrophosphatase (ITPA) is an enzyme that prevents accumulation of thioinosine metabolites by converting them to 6-thioninosine monophosphate, and deficiency of this enzyme has also been reported in patients with adverse reactions to thiopurine compounds.75–77 ITPA deficiency is usually due to a polymorphism of ITPA (Pro52Thr) more common in Asian populations (11–19%), than in other ethnic groups such as Caucasians, Hispanics and Africans (1–7%). It has been reported that Asians require lower doses of azathioprine compared with Caucasian patients to achieve the same concentration of active metabolites, possibly due to this polymorphism.77 Although it has been proposed that TPMT and/or ITPA screening be initiated to prevent toxic responses to azathioprine, this theoretical application of pharmacogenetics is not currently used in clinical practice, in which a much cheaper trial and error approach, closely following blood counts and liver enzymes at the initiation of therapy, seems just as effective.

GENETIC INFORMATION FROM CLINICAL TRIALS
In the past 20 years a number of targeted biological agents have been developed, including monoclonal antibodies, protein and cytokine inhibitors, and many signalling modulators have entered preclinical development for lupus, some advancing quite far into phase III trials. The ability to target nearly any protein or chemical and either imitate or block its function, sometimes with unexpected results, is bound to shed additional light on disease pathology. There are over a dozen agents in development targeting the 10 receptors and cytokines shown in the table 2, and there are dozens more currently in preclinical and clinical development. The recent discovery of new genes and genetic pathways contributing to SLE is likely to lead to the development of even more such targeted agents. The ongoing clinical trials incorporate genotyping of their subjects, such that there is the potential to correlate specific genetic polymorphisms with clinical manifestations, response to specific therapeutic interventions and adverse events. It will be fascinating to watch this field of study unfold over the next few years and to discover if these parameters are associated with known SLE genetic risk factors. In light of this potential and the ongoing efforts to generate pharmacogenomic data, the biological agents in SLE clinical trials are briefly reviewed here.
**Supplement**

Table 2  Some targeted biological treatments in development for SLE

<table>
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<th>Target</th>
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<th>Results</th>
<th>Reference</th>
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**BIOLOGICAL AGENTS TARGETING B CELLS**

Autoreactive B cells in SLE play a key role in disease pathogenesis, which leads to an increase in antibody-secreting plasma cells, hypergammaglobulinemia and immune complex formation. This may be due to alterations in cytokine balance, either potentiated by or leading to IFNα hypersecretion in SLE. Therefore, targeting B cells has been considered a promising therapeutic approach for lupus.

**Anti-CD20 (rituximab)**

CD20 is a B-cell-specific antigen marker that is expressed on pre-B cells, naive and memory B cells, as well as on some B cells that enter the germinal centre, but not on mature plasma cells. Although first approved for the treatment of refractory non-Hodgkin’s lymphoma,94 it has since been shown to be effective for the treatment of RA.92 Two large phase III trials (Explorer and Lunar) recently failed to demonstrate the efficacy of rituximab in SLE, but the data suggested that this agent may have been effective in some subsets of patients. Pharmacogenomic studies could provide insights into differences between those who responded and those who did not.

**Anti-CD22**

CD22 is a transmembrane protein that appears on the cell surface at the pre-B-cell stage and is a critical regulator of B-cell receptor signalling. Epratuzumab is a humanised monoclonal antibody that binds to the third immunoglobulin domain of CD22 and it has encouraging initial findings in lupus, with 93% of patients in one series experiencing clinical improvement on the British Isles Lupus Assessment Group (BILAG) scale.90

**BLyS monoclonal antibody**

Anti-B lymphocyte stimulator protein (BLyS) is a member of the TNF family. It has been reported that serum levels and gene expression of BLyS are increased in patients with SLE and correlate with disease activity.93 94 Belimumab (also called lymphostat-B or benlysta), is a fully human monoclonal antibody that inhibits the binding of BLyS to its three receptors, resulting in reduced BLyS-induced B-cell proliferation. This drug was promising for SLE treatment in phase III trials,79 and studies on other BLyS antagonists such as BAFFR-Ig and TACI-Ig (atacicept) are currently underway.92 95 Variations in response to these agents might someday be predicted by subtle genetic variability.

**BIOLOGICAL AGENTS TARGETING T CELLS**

An early target for the reduction of T-cell populations was the membrane bound form of CD40 ligand, which is overexpressed in the peripheral lymphocytes of patients with active SLE.96–98 Hu5c, IDEC-131 and BG9358 are anti-CD40 monoclonal antibodies that were promising in experimental studies but failed in clinical trials, mostly because of thrombotic complications.83 99 The thrombotic complications are thought to result from the presence of CD40L on platelets, such that anti-CD40 reagents might avoid clotting side-effects.

Another agent targeting T cells is abatacept (CTLA4Ig), which is approved for use in RA. Primary results in a murine model of lupus showed a delay in disease progression.100 A phase II trial of abatacept failed to meet its primary endpoints and the data are currently under evaluation.101 Belatacept, a second-generation CTLA4Ig, may have greater affinity to the CD80/CD86 ligands and is in clinical trials for organ transplantation.94

**BIOLOGICAL AGENTS TARGETING CYTOKINES AND COMPLEMENT COMPONENTS**

**Tumour necrosis factor alpha**

TNFα is a proinflammatory cytokine that is essential for the production of many other cytokines and B and T-cell proliferation. Some reports suggest that agents that block TNFα (infliximab, etanercept and adalimumab) may cause disparate clinical outcomes, and the development of anti-double-stranded DNA and transient lupus-like syndrome makes use of these agents in lupus controversial.102

**Interleukin 6**

IL-6 is a potent proinflammatory cytokine produced by T cells and macrophages to stimulate B-cell proliferation, maturation and antibody secretion. It can also induce the proliferation of TH17 cells and therefore the production of IL-17, which was recently shown to play a key role in SLE and other autoimmune conditions.103 Tocilizumab (MRA, Actemra, RoActemra) is a humanised anti-IL-6R monoclonal antibody, which has been approved for RA. Recently, an open label phase I study of tocilizumab studied in 16 lupus patients was published, in which some clinical improvement was observed,104 and additional trials are underway.

There are numerous other monoclonal antibodies against cytokines implicated in autoimmune disease. Phase II trials are ongoing for two antagonists of IFNα, MEDI-54597 and

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RNP, ribonuclear protein; SLE, systemic lupus erythematosus; TMHA, thrombotic microangiopathic haemolytic anaemia; TTP, thrombotic thrombocytopenic purpura.
rortalizumab. Monoclonal antibodies against other cytokines, such as IL-10 (B-N10) and IL-18 (ABT-325) are also in development for SLE. As better genetic models of disease pathology develop in SLE, new agents brought to trial and strategic combinations of these agents could perhaps be personalised to a given patient.

Complement component C5

In 2007, the US Food and Drug Administration approved eculizumab, a monoclonal antibody against complement component C5, for the treatment of paroxysmal nocturnal haemoglobinuria. This monoclonal antibody binds specifically to complement protein C5 and inhibits cleavage to C5a and C5b; therefore, this prevents the formation of terminal complement complex C5b-9 to induce haemolytic activity. This drug has been in early development for lupus.

THE FUTURE OF LUPUS GENETICS

New technologies are providing tools to make rapid advances in the genetics of very complicated diseases. SLE is a complicated disorder, with many new genetic associations to consider in the evolving conceptual organisation of its pathogenesis. Genes that influence disease as well as those that influence therapeutic delivery are potentially of equal importance in optimal treatment selection and dosing. There is significant morbidity and mortality from current therapies, either because of immediate toxicities, risks from long-term, global immune suppression, or chronic progressive damage in patients who cannot always tolerate disease-ameliorating therapies. In this heterogenous population it is also well known that there is significant variation in individual patient responsiveness to treatments, but the science of using biomarkers to select optimal treatments and guide their dosing is in its infancy. Attempts to correlate the clinical course of disease with the genetic profile of the patient are currently underway. The next phase of genetic discovery will be to explore how the many genes that might be associated with disease risk may contribute to pathology, as well as how they work together or against each other. It could be that much of the variation in the presentation of SLE could be explained and predicted by genetic factors. The currently evolving information and technology has the potential to permit significant strides towards unravelling this complicated and previously unpredictable disease.

Competing interests JTM serves as a consultant for Genentech/Roche, UCB, Immunomedics, Human Genome Sciences/Glaxo Smith Kline, Bristol Myers Squibb, Cephalon and MedImmune/Astra Zeneca; all other authors have no competing interests.

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metabolizing enzymes and toxicity of chemotherapy with cyclophosphamide, thiopeta and carboplatin.


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