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Recent acquisitions on the genetic basis of autoimmune disease

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1. ABSTRACT

In this review we will discuss recent progress from studies on the genetic basis of autoimmune disease and how this has advanced our understanding of the processes behind disease susceptibility and pathogenesis. We review the genetic associations with autoimmune and inflammatory disease discovered in the latest genome-wide association (GWA) scans, and discuss the importance of animal models both for generating candidates and for mechanistic studies. Investigating the natural variants of key immune regulatory molecules can give us an additional level of insight into their function and physiological regulation over gene knockouts. New data showing the association of multiple genes involved in pathogen defense highlights the potential role of infection in autoimmunity, and a more complete understanding of the pathways defective in genetically susceptible individuals will also give us a handle on how environmental and epigenetic factors may be impacting disease.

2. INTRODUCTION

Susceptibility to autoimmune disease has a defined genetic component, and recent progress in identifying the genes involved is changing our understanding of disease etiology. Variation in the DNA sequence is clearly not the whole story since concordance in genetically identical twins is less than complete (1), even though more recent follow-up studies suggest that concordance is considerably higher than previous estimates (2). The importance of environmental and stochastic effects may equal or exceed that of the genetic makeup in some cases. However, genetic and environmental influences are probably not independent, and the effect of an environmental event may depend on the context of an individual's genetic background. The growing field of epigenetics offers a further link between environmental events and genetics, and the idea that non-coding modifications of the genome induced by nutritional and infectious events during early life influence the

development of autoimmune disease at a later stage is an attractive hypothesis (3).

In this review we will discuss aspects of current knowledge with regard to the genetic variants that cause autoimmune disease, both from human studies and animal models, and how this is advancing our understanding of the processes underlying disease susceptibility and pathogenesis. We will focus in particular on the organ-specific autoimmune disease Type 1 diabetes (T1D), as well as rheumatoid arthritis (RA) as an example of an organ-specific autoimmune disease with a strong inflammatory component, systemic autoimmunity in systemic lupus erythematosus (SLE), and the inflammatory disorder Crohn's disease (CD), for which there is a clear connection between microbial and host genetic factors. Besides being distinct examples from the spectrum of autoimmune and inflammatory disorders, the study of these diseases has also recently been boosted by the publication of comprehensive genome-wide association (GWA) studies in humans, and by the availability of relevant animal models.

3. APPROACHES TO THE GENETIC DISSECTION OF HUMAN AUTOIMMUNE DISEASE

3.1. Discovering human autoimmune susceptibility genes

Testing whether variants at a particular genetic locus influence susceptibility to disease typically involves comparing the frequency of each allele in affected and non-affected individuals (association), or its inheritance in families, for example by affected siblings (linkage). The resolution of linkage analysis for common diseases is low, but the recent development of new technologies and multi-centre collaborations to collate large numbers of samples with detailed phenotypic information in well-controlled experiments has made genome-wide association (GWA) studies a powerful tool for human genetics research. The recent Wellcome Trust Case Control Consortium (WTCCC), for example, scanned 17,000 individuals for 7 diseases, including T1D and CD, using high density single nucleotide polymorphism (SNP) genotyping arrays (4). The association of many key SNPs has been confirmed by replication, and although exhaustive sequencing will be required to identify causal variants (5), strong candidate genes arising from these and other studies have been identified.

While highly significant p values have been achieved in recent GWA studies, the odds ratios, reflecting the size of the contribution of a particular SNP to disease susceptibility, are generally very low (4). The remaining genetic component of autoimmune diseases such as T1D for which extensive GWA scans have been performed is likely to be caused by a large number of genes with even smaller effects in the general population. The power of such genes to predict disease susceptibility will be low, although potentially increased in combination, but what we can hope from the identification of such genes by both GWA and candidate screens is the identification of novel pathways that play a role in the pathogenesis of autoimmune disease, and that may offer new approaches to disease therapy.

3.2. The use of rodent models

Models of human autoimmune disease in rodents include both spontaneous models, such as the non-obese diabetic (NOD) mouse model of T1D, and experimentally induced models such as collagen-induced arthritis (CIA). The mapping of susceptibility genes in rodents is useful both for generating hypotheses for human disease and for mechanistic studies, and the use of targeted knockout mice can provide good support for the role of a candidate human gene in disease etiology. Despite some important differences from human physiology, cross-fertilization between the study of human and rodent disease genetics accelerates our understanding of autoimmune etiology.

Congenic strains have been the cornerstone of the success of mouse genetic studies to date. A genetic interval identified from linkage studies to contain gene/s influencing disease susceptibility is replaced with the corresponding interval from the resistant strain by selection of appropriate homologous recombination events during breeding, followed by serial backcross. By creating strains with successively smaller congenic intervals the locus can be fine mapped, and the physiological function in disease pathogenesis of candidate genes within the interval can be investigated. As with human disease, identification of the causative variant can still prove challenging, particularly when multiple closely linked genes that function in the immune system are present, since it is also almost impossible to create a congenic strain containing a single gene. However, detailed examination of the biological effects of genes and their variants, in combination with targeted mutagenesis and complementation where appropriate, should ultimately be able to resolve the question.

The intensive development of a large number of congenic strains to fine map diabetes susceptibility genes in the NOD mouse by Wicker et al (6) is a good illustration of the power of the congenic strategy (see also section 5.1.), but also highlights the difficulties with this approach that have become apparent. The main stumbling block is the density of genes variant between strains that influence the autoimmune phenotype. Protection against disease in the initial congenic strain frequently fragments into minor effects when smaller congenic strains are developed. Systematic fine mapping is complicated by the fact that any particular interval may contain a combination of protective and susceptible alleles, making the arithmetic of analyzing these strains difficult to interpret, and with the implication that it is not always possible to conclusively exclude any part of the interval as having no effect on phenotype. However, as demonstrated by the recent report on the *Idd5* locus in the NOD mouse, congenic strains can be used to successfully fine map such genes, and are an incisive tool for examining the effect of interactions between genes on affected pathways and disease phenotype (7, 8).

Alternative approaches are now also being explored, in part to circumvent these problems and to try to

speed up the discovery of genes behind known loci affecting disease phenotypes. Genome-wide studies of quantitative trait loci (QTL) affecting multiple complex traits, including inflammatory phenotypes, have been undertaken in panels of different mouse strains (9). These are, in effect, a parallel of the WTCCC studies in human disease, and the major challenge in both cases is the ability to detect small genetic effects (10). In a complementary approach to traditional mouse genetics, mutagenesis studies aim not to discover natural genetic variants but to create random new mutations, often with more moderate disturbances than a functional knockout, and then map these mutants to discover genes that function in the regulation of autoimmunity and other traits (11). Using ENU (N-ethyl-N-nitrosourea) mutagenesis, a mutation causing lymphadenopathy and lupus-like symptoms led to the discovery of a novel ubiquitin ligase, Roquin, that is an essential negative regulator of the costimulatory molecule ICOS affecting the generation of follicular helper T cells and autoantibody responses (12). In combination, the use of new and traditional tools for analyzing autoimmunity in animal models is increasing our understanding of the regulation of immune function in autoimmune disease.

4. GENETIC INFLUENCES IN HUMAN AUTOIMMUNE AND INFLAMMATORY DISEASE

4.1. Type 1 diabetes (T1D)

In Type 1 diabetes the immune system specifically destroys the insulin-producing cells of the pancreas. This leads to insulin deficiency and an inability to take up glucose from the blood. Even with insulin treatment the inherent difficulty in maintaining a balance between insulin and blood glucose is associated with severe secondary complications that profoundly reduce life expectancy and quality of life. It has been known for many years that the most important genetic determinant of T1D susceptibility is the MHC locus on chromosome 6p21, and it has now been conclusively shown that there are distinct contributions from Class II and Class I genes (13). The protein products of these genes are responsible for presenting antigen to T cells, and changes in the amino acid sequence of the peptide-binding pocket are thought to alter the developing T cell repertoire in the thymus (14). The VNTR in the insulin (INS) gene promoter on chromosome 11p15 determines thymic expression levels of insulin. Low thymic insulin levels associated with the susceptible allele are thought to be insufficient to induce adequate thymic tolerance to insulin, which is a known autoantigen in T1D (15). In addition to these two established loci, a combination of candidate analyses and the recent GWA screens have now brought the number of confirmed diabetes susceptibility genes up to ten: CTLA4 on 2q33, PTPN22 on 1p13, IL2RA/CD25 on 10p15 and IFIH1 on 2q24, plus four other loci at 12q24, 12q13, 18p11 (PTPN2), and 16p13 (KIAA0350-SOCS1) (16-21).

Variants in the 3'UTR region of CTLA4 are associated with susceptibility to both T1D and Graves disease, and correlate with decreased expression of a particular soluble splice variant of CTLA4 in peripheral T cells (21). CTLA4 is a negative costimulatory molecule that inhibits T cell activation, and although the causal variant is not yet firmly established, unraveling the role of the soluble splice variant in the control of diabetes is likely to be important for a much more complete understanding of CTLA4 function in the regulation of T cell responses (22).

PTPN22 encodes the LYP tyrosine phosphate protein, also involved in the regulation of T cell activation. PTPN22 is associated with other autoimmune disorders such as RA, SLE and Graves disease (16, 23). Unexpectedly, a recent study by Vang *et al* suggests that the associated Trp620 variant has increased phosphatase activity and more potently inhibits T cell activation. The authors propose that increased LYP activity could increase the threshold for TCR activation, affecting either the T cell repertoire by allowing positive thymic selection of potentially self-reactive TCR that would otherwise be deleted, or by increasing the threshold for regulatory T cell (Treg) activation resulting in deficient T cell regulation in the periphery (24).

The IL2RA/CD25 locus was originally tested as a candidate gene based on the association of the IL2/IL21 locus in the NOD mouse model of T1D (25), and the association has been replicated in GWA studies (20). In the NOD mouse, the IL2/IL21 pathway/s play an important role in T cell homeostasis (26, 27) (see section 5.1.). There is also some support for association of the IL2/IL21 region on human chromosome 4q27 with T1D (20), strengthened by a recent study in both T1D and RA patients (28). This interval was also found to be the strongest association in a recent GWA study of Celiac Disease (29).

The association of IFIH1 with T1D (19) raises some interesting questions. IFIH1 (or Mda-5) is involved in viral recognition and plays a role in inducing type-I interferon (IFN) and the apoptosis of infected cells (30-33). Human islet cells express IFIH1, and expression is further induced by exposure to IFN-alpha. The regulation of IFIH1 in response to IFN-alpha early during infection may be an important mechanism by which islets are able to control viral replication. The effect of the associated variant (A946T) on IFIH1 function and anti-viral responses is not known, but given the long history of posited links between viral infection and T1D, it is tempting to speculate that this gene may provide a link between host permissiveness to viral infection and susceptibility to T1D (34).

Genetic association studies therefore support the importance of both thymic and peripheral T cell tolerance, the control of immune homeostasis, and also viral defense mechanisms in the control of T1D susceptibility.

4.2. Systemic lupus erythematosus (SLE)

SLE is a systemic autoimmune disease characterized by the presence of autoantibodies against components of the nucleus. It results in a multi-organ disease of which glomerulonephritis (GN), in some cases leading to kidney failure, is one of the most severe symptoms. The HLA region is also linked to SLE, and specific DRB1/DQB1 haplotypes have been shown to be associated with susceptibility (35). Complement genes also

map to the HLA region (HLA III), and there is a long-standing association between rare deficiencies in early classical complement components and the development of SLE (reviewed in (36)). Complement is thought to be important in the clearance of apoptotic cells.

Based on studies in rat models (see section 5.2.), association with altered copy number of the FCGR3B gene was tested for, and found, in SLE patients (37). Copy number variants, in addition to the effect of rare polymorphisms, are not detectable by GWA scans so candidate approaches based on animal models play an even more important role in detecting association with this type of variant. FCGR3B is expressed in neutrophils and eosinophils and is important for the uptake and clearance of immune complexes. Low FCGR3B copy number is associated with increased risk of disease, and may therefore promote a pathogenic build up of autoantibodies in key sites (37).

An association with PDCD1 (or PD-1) has been replicated in a large number of individuals (38). PDCD1 (or PD-1) is critical for peripheral tolerance. It is upregulated in T cells upon activation and inhibits TCR signaling and T/B cell survival, and mice deficient in PDCD1 are known to develop a lupus like disease (39, 40). The associated variant is intronic and within the binding site for the RUNX1 transcription factor, and it is therefore hypothesized that regulation of PDCD1 expression may be impaired in susceptible individuals (38).

SLE is also strongly associated with variants in the IRF5 (interferon regulatory factor-5) gene. Multiple SNPs in the IRF5 gene were detected by re-sequencing and analyzed to define haplotypes of 3 functional variants associated with susceptibility and protection. The highest risk is associated with a haplotype predicted to result in high level expression of the alternative exon 1B and an insertion in exon 6 (41). IRF5 is activated downstream of toll-like receptors (TLR) and IFN-alpha, and induces IFN-alpha production. From studies using IRF5-deficient mice, it is known that IRF5 is important for the control of viral infection (42). In addition, based on the proposed mechanism behind the association of TLR7 in a mouse model of SLE (43) (see section 5.2.) IRF5 could potentially play a role in the amplification of TLR signaling aberrantly induced by self-antigens.

Pathways involved in the removal of dying cells and immune complexes appear to be impacted by multiple susceptibility genes in SLE (complement, FCGR3B), and it is thought that defective clearance may act as a stimulus to further immune responses. Responsiveness to self antigens may also be enhanced by increased TLR signaling (IRF5), and by inadequate regulation of T and B cell activation/survival in the periphery (PDCD1).

4.3. Crohn's disease (CD)

Crohn's disease is a chronic intestinal inflammatory disorder that causes diarrhea, bleeding, abdominal pain and weight loss, and treatment often requires the long-term use of anti-inflammatory drugs or surgery to remove severely affected parts of the gut. CD is triggered by the microflora of the gut but there is also a strong genetic component determining susceptibility to disease (44). There have been many recent GWA scans in CD, including the WTCCC scan, and they have been very effective in identifying new genes associated with CD susceptibility and in generating a new working hypothesis for disease pathogenesis (45-49). In particular, new pathways potentially important for the host immune response to gut bacteria and in maintaining epithelial barrier function have been identified. Replicated loci associated with CD susceptibility now include NOD2/CARD15, IBD5, IL23R, ATG16L1, 5p13.1., 5q33.1. (IRGM) and 10q21.1. Additionally, NCF4, PHOX2B, PTPN2, TNFSF15 and 16q24.1. (FAM92B) are also associated but await additional replication (50).

NOD2 is a pathogen recognition receptor that recognizes bacterial components and triggers an antimicrobial response via NFkB activation. In intestinal epithelial and Paneth cells NOD2 induces defensin production, and in antigen presenting cells (APC) NOD2 integrates with TLR signaling pathway to activate pro-inflammatory cytokines, including IL23 (50). IL23 is an essential driver of innate and adaptive gut inflammation in mouse models (51), and the association of the IL23R locus with CD susceptibility confirms the importance of this pathway. IL23 can promote intestinal inflammation by inducing the expression of IL17 and other cytokines. Production of IL23 by macrophages and dendritic cells (DC) is thought to be particularly important, and macrophages and DC, as well as eosinophils, can generate reactive oxygen molecules that are not only key effector mechanisms of host defense, they can also mediate inflammatory damage and compromise epithelial barrier function (50).

The association with ATG16L1 and IRGM flagged the potential importance of autophagy in the pathogenesis of CD (47). Autophagy has traditionally been seen as a pathway involved in the control of cell survival/death, but it now has an emerging role in innate immunity and the removal of intracellular pathogens downstream of TLR4 signaling, and involving regulation of Type-1 IFNs (52, 53). The importance of host defense pathways is further suggested by the association between low copy number of beta-defensin 2 and CD (54), and defective antimicrobial production may contribute to disease in patients with NOD2 mutations (55).

The locus at 5p13.1. is within a gene desert (an interval lacking evident gene coding regions), but the associated alleles correlate with expression of the prostaglandin E2 receptor PTGER4 (46). PTGER4 is a G protein coupled receptor and studies in the mouse have shown that PTGER4 promotes epithelial barrier function and inhibits immune responses to protect against DSS-induced colitis (56).

Inhibiting immune responses and promoting epithelial barrier integrity seem to be two sides of the same coin. Intestinal epithelial cells are no longer considered a

passive mechanical barrier (57), and studies in the mouse suggest that epithelial cell NFkB activation is the 'gate-keeper' of gut immune responses, determining the suppression or enhancement of immune responses, epithelial barrier integrity and also the release of microbial peptides (58). The picture that emerges from these studies is that in genetically susceptible individuals gut microbes cause loss of epithelial barrier integrity and activation of innate and adaptive immune responses and a pathological state of inflammation (50).

The importance of genes with potential roles in host defense (NOD2, NCF4) is particularly evident in CD, and the identification of two further potential host defense genes that are involved in autophagy (ATG16L1, IRGM) is a good example of how genome scans have highlighted novel cellular process in CD pathogenesis (47). Interestingly, despite the apparent differences in etiology, there is some overlap between genes associated with CD and with autoimmune disorders. In both CD and autoimmune disease, the regulation of TLR signaling and IFN responses, whether activated by infection or self-antigens, appears to play a major role in determining susceptibility. There is further potential for overlap since pathways involved in anti-microbial control (NCF4) may also be important for the regulation of autoimmune responses, either by a failure to control infection or ineffective control of damaging activated T cell responses (see also role of Ncf1 in mouse models of RA in section 5.4.). Much interesting work remains to be done testing the proposed mechanistic hypotheses to unravel the roles of dysregulated anti-microbial responses, inflammation and tissue damage that occurs in CD.

4.4. Rheumatoid arthritis (RA)

RA is an autoimmune chronic inflammatory disease affecting primarily peripheral joints, it leads to joint destruction and deformation and results in severe pain and loss of mobility. As in other autoimmune diseases the HLA Class II locus plays a major role, and in RA HLA-DRB1 alleles are associated with susceptibility. Association with PTPN22, CTLA4 and PADI4 has also been replicated (59). PTPN22 and CTLA4 are both also linked to T1D susceptibility and, as discussed above, have the capacity to regulate T cell activation. PADI4 encodes pepdidylarginine deiminase 4 that catalyses the citrullination of proteins (in which arginine is deiminated to citrulline), a post-translational modification present on epitopes recognized by autoantibodies in some RA patients (60, 61).

A recent GWA scan confirmed association of HLA and PTPN22, and in addition identified a new locus in the TRAF1-C5 region on chromosome 8 (62). C5 is a component of the complement cascade, and C5-deficient mice are resistant to CIA. TRAF1 is an adaptor protein that mediates signaling through TNFR1, TNFR2 and CD40, and TRAF1-deficient mice have exaggerated T cell responses to TCR and TNF signaling (62).

Two further GWA scans identified the association of two apparently independent alleles at the TNFAIP3-OLIG3 region on chromosome 6q23 (63, 64), although it was noted that additional genes within 1Mb, IL22RA and IFNGR1, are also involved in immune function (63). TNFAIP3 encodes TNF-induced protein 3, or A20, an inhibitor of NFkB activation important for termination of TNF and TLR signaling. TNFAIP3 can also bind TRAF1 (62). TNF is known to play an essential role in RA pathogenesis, and TNF blockers are an effective treatment for the symptoms of RA. Although the causal variants have not been identified, and additional functional data is still lacking, the association of two genes involved in TNF signaling, TRAF1 and TNFAIP3, may represent new important regulatory checkpoints for the TNF pathway in RA.

These studies indicate that RA and T1D contain many overlapping susceptibility genes (HLA, CTLA4, PTPN22), although genes specific to RA pathogenesis (PADI4) are also involved, and the TNF pathway in particular seems to have potential importance in RA pathogenesis.

5. LESSONS FROM ANIMAL MODELS

5.1. Type 1 Diabetes in the NOD mouse

The non-obese diabetic (NOD) mouse spontaneously develops a high incidence of a disease that closely resembles many aspects of human T1D. Human autoimmune diabetes is likely to exhibit a greater degree of heterogeneity than the NOD mouse, and treatments that work in the mouse model are not guaranteed to work in human patients. However, to date it has proved a remarkably faithful model in terms of genetic susceptibility. The human MHC Class II susceptibility alleles are mirrored by the NOD susceptibility variant, and are thought to act in similar ways to affect antigen presentation and selection of the immune repertoire. Furthermore, as in human diabetes, genes in the Class I region are also associated with disease susceptibility (65).

The *Idd3* locus on mouse chromosome 3 has been successfully mapped to 780 kb interval containing the IL2 and IL21 genes (66), and functional studies have shown that genes in the *Idd3* interval control T cell homeostasis. Protective *Idd3* genes correct the destructive cytotoxicity of CD8 T cells in the NOD mouse (26), and overcome the deficiency in Treg function (27). There are established links between IL2-deficiency, lymphopenia, defective Treg function and the development of autoimmune disease (67, 68). *Idd3* congenic mice have increased IL2 expression compared to NOD mice, and reducing IL2 copy number in *Idd3* congenic mice overcomes diabetes protection (27). IL21 and IL21R expression are reduced in *Idd3* congenic mice and have demonstrated importance in immune homeostasis (26). It is therefore likely that dysregulated expression of both of the closely linked IL2 and IL21 genes is important in causing the pathogenic disturbances in T cell homeostasis driving autoimmunity and diabetes in the NOD mouse.

The *Idd5* locus on chromosome 1 was initially divided by congenic mapping into two loci known as *Idd5.1.* and *Idd5.2.* (69), and a recent report demonstrates

the deeper complexity of this locus and describes the additional loci *Idd5.3.* and *Idd5.4.* (7). These studies demonstrate that, given sufficient resources, congenic mapping is possible even in chromosomal regions where there is a high density of genes affecting phenotype, and with alleles from the susceptible strain having both positive and negative effects. Fine mapping strongly supports the role of an SNP variant in exon 2 of *Ctla4* as the *Idd5.1.* genetic variant, and suggests *Nramp1* as a candidate for *Idd5.2.* (69, 70). In human T1D, susceptibility at the CTLA4 locus is associated with reduced expression of a soluble splice variant (21). In NOD mice the susceptible *Ctla4* variant is associated with reduced expression of a splice variant lacking the CD80/CD86 ligand-binding domain, known as *liCtla4* (21, 70). The *liCtla4* protein product is expressed in T cells, and inhibits T cell responses by binding and dephosphorylating the TCRzeta chain (71). The larger *Idd5* interval is associated with lymphocyte resistance to apoptosis (72), and decreased levels of full length *Ctla4* are reported by this group in recently activated T cells following stimulation with anti-CD3. Interestingly, the NOD defect in *Ctla4* expression in this assay is controlled by a chromosome 1 interval distal to *Idd5.1.*, and also by *Idd3* (73). Although the exact mechanism by which *Ctla4* variants control diabetes susceptibility in mouse models and humans is not fully determined, this is a good example of the additional level of understanding with regard to molecular function that can be gained from looking at the effects of gene variants with milder effects on phenotype rather than gene knockouts.

There are also multiple loci on mouse chromosome 6 associated with diabetes susceptibility in the NOD mouse: *Idd19*, *Idd20*, and *Idd6* which has been further broken down into 3 loci. The *Idd6* loci influence T cell proliferation and the function of CD4+CD25+ Treg, and protection correlates with reduced Tlr1 expression in macrophages (74).

The *Idd9/11* loci on mouse chromosome 4 has been linked to a range of different phenotypes associated with diabetes susceptibility, presumably because of the size of the interval and the large number of genes within it. The *Idd9* locus consists of *Idd9.1.* (which overlaps *Idd11*) *Idd9.2.* and *Idd9.3.* (75). *Idd9.3.* has been mapped to the smallest interval, a 1.2. Mb region containing the candidate gene *CD137/4-1BB*. CD137 is a costimulatory molecule, and T cell proliferation induced by anti-CD137/anti-CD3 *in vitro* is increased by the presence of resistance *Idd9.3.* alleles (76). A number of defects in B cell subsets present in the NOD mouse are linked to the *Idd9/11* interval (77, 78), and an interval containing *Idd9.3.* is associated with aberrant autoantibody production (79). Changes in the homing of islet-specific CD4 T cells have also been reported to occur in *Idd9* congenic mice (80). The *Idd9.1.* region is associated with protection from diabetes in a TNF-accelerated model of diabetes, in which TNF is expressed in the islets of NOD mice. Protective genes in this interval inhibit the proliferation of CD8 T cells to islet-derived APC (81). A component of the protective effect of *Idd9* resistance genes is also exerted within islet cells. Most autoimmune susceptibility genes appear to act within the immune system, but isolated islets from *Idd9* congenic mice are able to resist CD8 T cell mediated destruction following transplantation. Compared to NOD islets, they also exhibit hypo-responsiveness to inflammatory cytokines as measured by Fas upregulation. This response is also suppressed in islets lacking TNFR2 expression, and colocalization of the adaptor protein TRAF2 with TNFR2 in *Idd9* islet beta cells is altered compared to NOD islets (82). TNFR2 maps within the *Idd9.2.* interval, and the NOD isoform is known to have coding variants that could affect function (75) suggesting that *TNFR2* is a candidate for the control of islet-intrinsic resistance to autoimmune destruction mediated by *Idd9* gene/s.

The importance of pancreas-intrinsic factors in determining diabetes susceptibility is also supported by work on the *Idd4* locus, which demonstrates a role for pancreatic sensory neurons in the development of islet autoimmunity (83). Many T cell and autoantibody responses in diabetes patients and in the NOD mouse are directed at neural cell antigens, often those shared with islets (reviewed in (84)). Neurons expressing the capsaicin receptor TRPV1 are associated in the pancreas with islets, and capsaicin treatment to deplete these cells protects NOD mice against diabetes. The TRPV1 gene is polymorphic and maps to the *Idd4.1.* locus, and the congenic strain has increased TRPV1 cell function. Both increased TRPV1 function and the lack of these cells are therefore associated with diabetes protection, and the authors propose a role for neuronal control of inflammation and beta cell stress in diabetes pathogenesis (83).

Finally, in the Komeda diabetes-prone (KDP) rat model, a nonsense mutation in Cblb was shown by transgenic rescue experiments to be a strong candidate for the Kdp1 locus on chromosome 11 (85). Cblb is an ubiquitin ligase that confers dependency on CD28 costimulation for T cell activation. Cblb-deficiency in mice causes autoimmune symptoms and increased susceptibility to induced autoimmune disease due to excessive T cell activation (86, 87).

There are many overlapping genes/pathways involved in susceptibility between human T1D and the NOD mouse, in particular MHC genes, the IL2 pathways and Ctla4, and the additional pathways identified in the NOD mouse generate interesting new hypotheses and candidates to be tested in human diabetes.

5.2. SLE models

SLE-like phenotypes occur spontaneously in a number of mouse strains, and the most commonly used include the BXSB hybrid line, and hybrids of the New Zealand Black (NZB) and White (NZW) strains. (NZB x NZW)F1 mice have anti-nuclear antibodies (ANA) and immune-complex associated kidney disease (GN) similar to human SLE. Congenic mice derived from this strain show that specific loci seem to control distinct aspects of disease, such as the level of ANA, or B and T cell defects (88).

The complement component *C1qa*, involved in clearance of immune complexes, is a candidate for the

Nba1 locus on chromosome 4 (89), and complement components are also potentially involved in human SLE (36).

There is a cluster of susceptibility loci on mouse chromosome 1, including *Nba2*. The major candidate for *Nba2*, based on expression microarray analysis of a congenic strain, is *Ifi202*. Increased expression of *Ifi202* in the susceptible congenic strain is associated with inhibition of lymphocyte apoptosis, and increased lymphocyte survival may cause exaggerated antibody production (90).

The *Sle1b* chromosome 1 susceptibility locus is associated with increased expression of *Ly108* (91), a member of the SLAM costimulatory family that was recently shown to control B cell tolerance through its effect on B cell anergy, receptor revision and deletion (92).

A novel mechanism in SLE pathogenesis that has come to light in mouse models recently involves TLR signaling and the regulation of B cell tolerance to nucleolar antigens. The *Yaa* locus accelerates SLE on susceptible backgrounds, and biases B cells towards the production of antibodies to particular nuclear antigens. The phenotype is due to a duplication of part of the pseudoautosomal region. Only a small number of genes are present in the duplicated region, including *TLR7* (43, 93), and reduction of TLR7 gene dosage abolishes the effect of *Yaa* (94). TLR7 is a pathogen recognition receptor activated by single-stranded RNA. RNA is likely to be a component of nucleolar antigens, and increased expression of TLR7 by the *Yaa* accelerator could increase sensitivity and promote loss of tolerance to nucleolar antigens (43).

Gene copy number variation in Fcgr3 predisposes to GN in the experimentally-induced Wistar Kyoto rat model (95). Fcgr3 is the activating Fc receptor for IgG, and loss of the rat Fcgr3 paralogue, Fcgr3-related sequence (Fcgr3-rs), causes macrophage overactivity, potentially through decreased clearance of immune complexes (95). This study led to the identification of copy number variation of the orthologous FCGR3B gene in human SLE susceptibility (37).

Susceptibility to SLE in mouse models is therefore strongly linked to defects in B cell tolerance affecting B cell deletion and tuning of BCR signals (*Ly108*) (43), defects in immune-complex clearance that could be responsible for triggering loss of tolerance to nuclear components (*Fcgr3*, *C1q*) (88), in sensitivity to these triggers (*TLR7*), and in lymphocyte activation/survival that could exaggerate lymphocyte responses and antibody production (*Ifi202*). These affected pathways mirror the human disease, and suggest that these models will be useful tools for dissecting the mechanism and interaction of susceptibility genes in SLE pathogenesis.

5.3. Colitis

While there are many experimental models of CD, or inflammatory bowel disease (IBD) more generally, less is known about how genetic factors control susceptibility. However, susceptibility to colitis caused by IL10-deficiency is, like human CD, dependent not only on the microbial environment, but also on the genetic background. C3H/HeJBir and C57BL/6 mice are commonly used as susceptible and resistant strains, respectively. The major locus controlling susceptibility is on chromosome 3, and has been mapped using congenic strains to a 7Mb interval containing the *NFkB1* gene encoding the NFkB p50 subunit (96). This region is also linked to genetic susceptibility in another model of IBD caused by *Gnai2* (G-protein alpha inhibitory 2 chain) deficiency (97). Increased macrophage NFkB expression was observed in the susceptible strain, correlating with hyporesponsiveness to bacterial stimuli. It is proposed that vigorous innate responses and clearance of invasive gut pathogens would prevent activation of adaptive immune responses that mediate chronic inflammation and IBD (96). Therefore, mouse models support the idea that genetic regulation of the immune response to gut bacteria influences susceptibility to IBD and that NFkB may be an important regulator of this process. Additional loci in the *Gnai2-/-* model (97), and in the DSS-induced model of colitis have been identified (98), although the genes underlying these effects are not yet known.

5.4. Models of RA

There are many different animal models of RA, most of them requiring disease to be experimentally induced by immunization (99). Again, clear differences between strains exist in their susceptibility to experimental RA. The most commonly used models are pristine-induced arthritis (PIA) in rats, and Collagen II arthritis (CIA) in mice (and also rats). In the mouse CIA model disease is induced by immunization with collagen, a defined antigen, emulsified in adjuvant. In the DBA/1 strain this results in a severe and acute arthritis, whereas in C57Bl/10-derived strains the disease is mild, although later develops into chronic-relapsing form, and the control of disease susceptibility is polygenic. As in the NOD mouse, the MHC locus plays a major role in determining CIA susceptibility, and again there is a striking conservation of the properties of the class II peptide binding pocket encoded by the susceptibility alleles in mouse (Aq beta) and human disease (DR4B1*0401/DRA) (99). In rats, pristine induces a chronic relapsing arthritis in peripheral joints in susceptible strains such as the DA rat. Pristane, an adjuvant oil, is thought to trigger innate immunity and activate self antigen specific T cells, but the mechanism is not yet known (99). Like CIA, susceptibility is again polygenic and at least 20 QTL controlling different stages of PIA, plus many more in different rat models have been identified (reviewed in (100)).

The first gene associated with the regulation of PIA susceptibility has been discovered (101), and recent studies have elegantly delineated the mechanism by which it acts to modulate disease pathogenesis (102, 103). The Pia4 locus on chromosome 12 was identified originally by linkage analysis using the susceptible PA and resistant E3 rat strains, and then fine mapped using a congenic strategy that reduced the interval to a 150 kb segment containing the *Ncf1* gene (101). The Ncf1 protein is part of the NADPH oxidase complex responsible for generating the oxidative

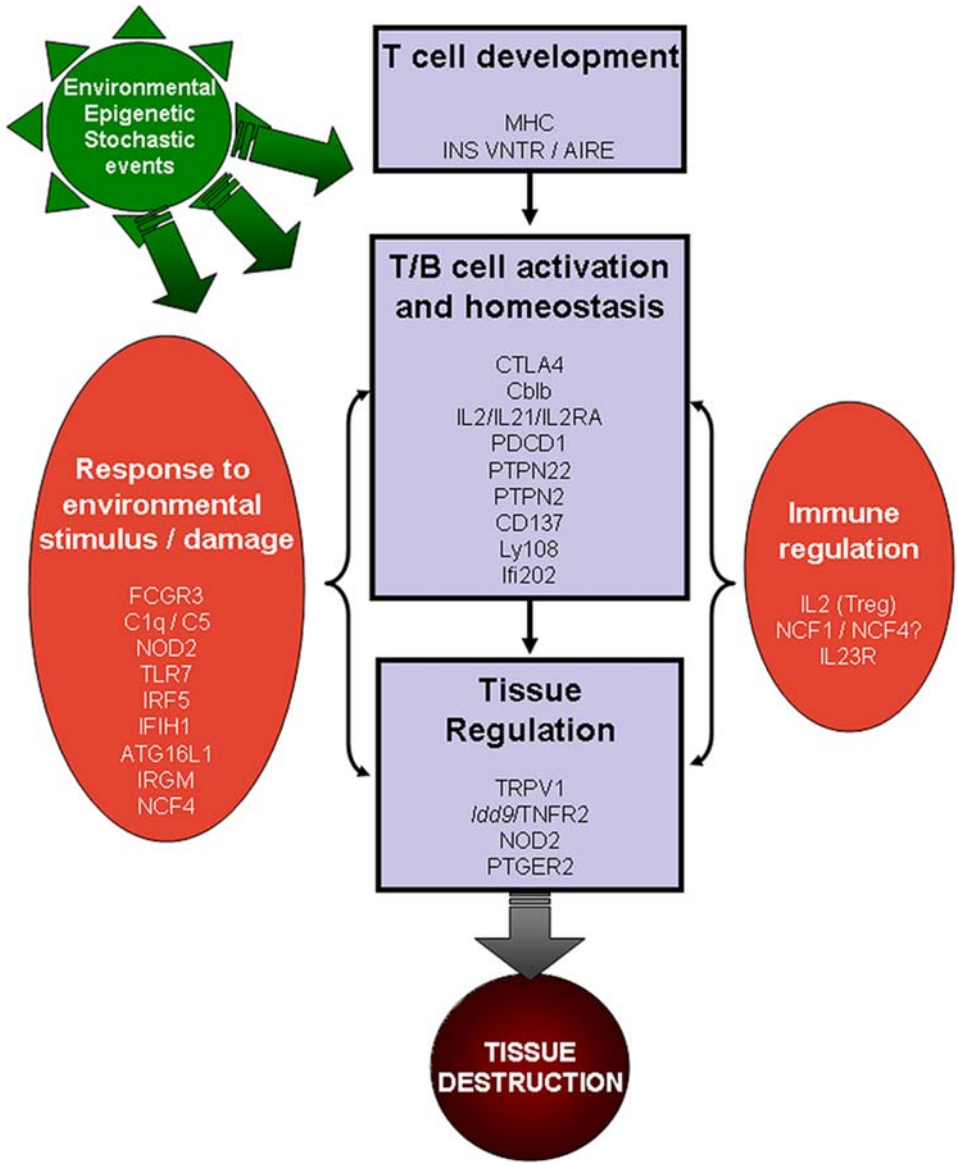

Figure 1. Genes associated with susceptibility to autoimmune and inflammatory disease act at many levels to promote or allow the development of tissue destruction. Understanding the mechanisms by which gene variants affect disease pathogenesis will give us much greater insight into how autoimmune disease can be regulated.

burst that leads to formation of reactive oxygen species. In the resting state Ncf1 is cytoplasmic, but upon activation and phosphorylation Ncf1, along with additional regulatory subunits Ncf2 and Ncf4, translocates to the membrane to form an activated complex with Cybb and Cyba. In neutrophils, macrophages, eosinophils and DC free radicals can then be generated either in phagosomes to kill intracellular pathogens, or extracellularly by fusion with the plasma membrane (104). Although ROS are generally regarded as pro-inflammatory, susceptible DA rats have lower oxidative burst than resistant congenic strain, and NADPH oxidase activation can prevent or reduce disease (101). In mice, an Ncf-1 variant that results in reduced oxidative burst is also associated with increased severity of CIA, as well as enhancing susceptibility to EAE (105). It has now been shown using transgenic mice expressing functional Ncf1 specifically in macrophages that macrophage-derived ROS can suppress T cell activation and expansion to protect against CIA (103).

Human NCF1 deficiency is associated with chronic granulomatous inflammation of the intestine (99), and intestinal granuloma is a hallmark of CD (50). It is therefore interesting that CD susceptibility in humans was recently associated with the NCF4 locus (see section 4.3.). Although the association of NCF4 with CD is thought to be involved in the control of intracellular pathogens, NCF4 variants may also be important for T cell regulation and associated tissue damage. The effects of reduced oxidative burst are presumably complicated during infection or

exposure to intestinal microbes because of the requirement for host defense for pathogen clearance in addition to T cell regulation.

Recent progress in RA animal models has therefore highlighted a new mechanistic pathway involved in the disease that has interesting application for other inflammatory diseases.

6. CONCLUDING REMARKS

There are now multiple loci for which there is strong evidence that the function or expression of a particular gene is affected in autoimmune and inflammatory disease, and this is adding new dimensions to our understanding of the disease pathogenesis. Even though the causative variant has not yet been identified for most loci, strong evidence of association and additional biological information has now enabled solid cases to be made for the association of many genes with autoimmune disease. It is important to bear in mind, particularly for SNPs in gene regulatory regions thought to control gene expression, that the gene affected may not necessarily be the closest, and that expression of multiple genes may be affected. Re-sequencing to define detailed haplotypes, as for the association of IRF5 with SLE, is essential since there may be multiple functional variants, and the original association may just be a proxy (41).

While many susceptibility genes are therefore still only candidates, consistent themes are starting to emerge from the current crop of genetic associations that have interesting, and often novel, implications for the physiological regulation of inflammation and the pathogenesis of autoimmunity. Figure 1 shows the stage of autoimmune pathogenesis at which some of the genes discussed here are thought to act. The identification of pathways common across the board of autoimmune and also inflammatory disease is gaining momentum. HLA genes clearly play a vital role, and genes important for the regulation of T cell activation and homeostasis, such as CTLA4, PTPN22, IL2 and IL21 are also involved in multiple autoimmune diseases. IFN responses and pathogen-recognition pathways are also a newly emerging theme, and may reflect either a causative role of infection or aberrant activation of these pathways by self-antigens. Interestingly, these genes may be acting within cells of the organ targeted by the immune system, such as IFIH1 in T1D and NOD2 in CD gut epithelial cells, either exclusively or together with their role in immune cells. Pathways linked to the control of microbial infection may also play a direct role in controlling T cell responses, such as macrophage Ncf1, in addition to the removal of a pathogen-stimulus.

The vital role of mouse genetic and functional studies is evident from the examples discussed here, and is highlighted by the discovery of the association of FCGRIIII copy number variants with SLE based on findings in a rat model, since this type of genetic variation is not detected by current GWA approaches. Much interesting work can now be done to form an integrated picture of how gene variants affect phenotype, and how they interact to cause autoimmunity, much of which will be helped by the study of animal models.

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8. REFERENCES

1. Salvetti, M., G. Ristori, R. Bomprezzi, P. Pozzilli & R. D. Leslie: Twins: mirrors of the immune system. *Immunol Today*, 21, 342-7 (2000)
2. Babu, S. R., M. J. Redondo, R. V. Wood, M. S. Fernando, L. Yu, T. Orban, J. Barker, P. R. Fain & G. S. Eisenbarth: Progressively increasing concordance for anti-islet autoimmunity and diabetes with long term follow-up in monozygotic twins of patients with type 1 diabetes. *9th International Congress of the Immunology of Diabetes Society and American Diabetes Association Research Symposium (Miami 2007)* (2007)
3. Ballestar, E., M. Esteller & B. C. Richardson: The epigenetic face of systemic lupus erythematosus. *J Immunol*, 176, 7143-7 (2006)
4. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*, 447, 661-78 (2007)
5. Altshuler, D. & M. Daly: Guilt beyond a reasonable doubt. *Nat Genet*, 39, 813-5 (2007)
6. Wicker, L. S., J. Clark, H. I. Fraser, V. E. Garner, A. Gonzalez-Munoz, B. Healy, S. Howlett, K. Hunter, D. Rainbow, R. L. Rosa, L. J. Smink, J. A. Todd & L. B. Peterson: Type 1 diabetes genes and pathways shared by humans and NOD mice. *J Autoimmun*, 25 Suppl, 29-33 (2005)
7. Hunter, K., D. Rainbow, V. Plagnol, J. A. Todd, L. B. Peterson & L. S. Wicker: Interactions between Idd5.1./Ctla4 and Other Type 1 Diabetes Genes. *J Immunol*, 179, 8341-9 (2007)
8. Cordell, H. J., J. A. Todd, N. J. Hill, C. J. Lord, P. A. Lyons, L. B. Peterson, L. S. Wicker & D. G. Clayton: Statistical modeling of interlocus interactions in a complex disease: rejection of the multiplicative model of epistasis in type 1 diabetes. *Genetics*, 158, 357-67 (2001)
9. Valdar, W., L. C. Solberg, D. Gauguier, S. Burnett, P. Klenerman, W. O. Cookson, M. S. Taylor, J. N. Rawlins, R. Mott & J. Flint: Genome-wide genetic association of complex traits in heterogeneous stock mice. *Nat Genet*, 38, 879-87 (2006)
10. Flint, J., W. Valdar, S. Shifman & R. Mott: Strategies for mapping and cloning quantitative trait genes in rodents. *Nat Rev Genet*, 6, 271-86 (2005)
11. Hoyne, G. F. & C. C. Goodnow: The use of genomewide ENU mutagenesis screens to unravel complex mammalian traits: identifying genes that regulate organ-specific and systemic autoimmunity. *Immunol Rev*, 210, 27-39 (2006)
12. Vinuesa, C. G., M. C. Cook, C. Angelucci, V. Athanasopoulos, L. Rui, K. M. Hill, D. Yu, H.

Domaschenz, B. Whittle, T. Lambe, I. S. Roberts, R. R. Copley, J. I. Bell, R. J. Cornall & C. C. Goodnow: A RING-type ubiquitin ligase family member required to repress follicular helper T cells and autoimmunity. *Nature*, 435, 452-8 (2005)
13. Nejentsev, S., J. M. Howson, N. M. Walker, J. Szeszko, S. F. Field, H. E. Stevens, P. Reynolds, M. Hardy, E. King, J. Masters, J. Hulme, L. M. Maier, D. Smyth, R. Bailey, J. D. Cooper, G. Ribas, R. D. Campbell, D. G. Clayton & J. A. Todd: Localization of type 1 diabetes susceptibility to the MHC class I genes HLA-B and HLA-A. *Nature*, 450, 887-92 (2007)
14. Roep, B. O.: Diabetes: missing links. *Nature*, 450, 799-800 (2007)
15. Vafiadis, P., S. T. Bennett, J. A. Todd, J. Nadeau, R. Grabs, C. G. Goodyer, S. Wickramasinghe, E. Colle & C. Polychronakos: Insulin expression in human thymus is modulated by INS VNTR alleles at the IDDM2 locus. *Nat Genet*, 15, 289-92 (1997)
16. Bottini, N., L. Musumeci, A. Alonso, S. Rahmouni, K. Nika, M. Rostamkhani, J. MacMurray, G. F. Meloni, P. Lucarelli, M. Pellecchia, G. S. Eisenbarth, D. Comings & T. Mustelin: A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. *Nat Genet*, 36, 337-8 (2004)
17. Hakonarson, H., S. F. Grant, J. P. Bradfield, L. Marchand, C. E. Kim, J. T. Glessner, R. Grabs, T. Casalunovo, S. P. Taback, E. C. Frackelton, M. L. Lawson, L. J. Robinson, R. Skraban, Y. Lu, R. M. Chiavacci, C. A. Stanley, S. E. Kirsch, E. F. Rappaport, J. S. Orange, D. S. Monos, M. Devoto, H. Q. Qu & C. Polychronakos: A genome-wide association study identifies KIAA0350 as a type 1 diabetes gene. *Nature*, 448, 591-4 (2007)
18. Lowe, C. E., J. D. Cooper, T. Brusko, N. M. Walker, D. J. Smyth, R. Bailey, K. Bourget, V. Plagnol, S. Field, M. Atkinson, D. G. Clayton, L. S. Wicker & J. A. Todd: Large-scale genetic fine mapping and genotype-phenotype associations implicate polymorphism in the IL2RA region in type 1 diabetes. *Nat Genet*, 39, 1074-82 (2007)
19. Smyth, D. J., J. D. Cooper, R. Bailey, S. Field, O. Burren, L. J. Smink, C. Guja, C. Ionescu-Tirgoviste, B. Widmer, D. B. Dunger, D. A. Savage, N. M. Walker, D. G. Clayton & J. A. Todd: A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. *Nat Genet*, 38, 617-9 (2006)
20. Todd, J. A., N. M. Walker, J. D. Cooper, D. J. Smyth, K. Downes, V. Plagnol, R. Bailey, S. Nejentsev, S. F. Field, F. Payne, C. E. Lowe, J. S. Szeszko, J. P. Hafler, L. Zeitels, J. H. Yang, A. Vella, S. Nutland, H. E. Stevens, H. Schuilenburg, G. Coleman, M. Maisuria, W. Meadows, L. J. Smink, B. Healy, O. S. Burren, A. A. Lam, N. R. Ovington, J. Allen, E. Adlem, H. T. Leung, C. Wallace, J. M. Howson, C. Guja, C. Ionescu-Tirgoviste, M. J. Simmonds, J. M. Heward, S. C. Gough, D. B. Dunger, L. S. Wicker & D. G. Clayton: Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. *Nat Genet*, 39, 857-64 (2007)
21. Ueda, H., J. M. Howson, L. Esposito, J. Heward, H. Snook, G. Chamberlain, D. B. Rainbow, K. M. Hunter, A. N. Smith, G. Di Genova, M. H. Herr, I. Dahlman, F. Payne, D. Smyth, C. Lowe, R. C. Twells, S. Howlett, B. Healy, S. Nutland, H. E. Rance, V. Everett, L. J. Smink, A. C. Lam, H. J. Cordell, N. M. Walker, C. Bordin, J. Hulme, C. Motzo, F. Cucca, J. F. Hess, M. L. Metzker, J. Rogers, S. Gregory, A. Allahabadia, R. Nithiyananthan, E. Tuomilehto-Wolf, J. Tuomilehto, P. Bingley, K. M. Gillespie, D. E. Undlien, K. S. Ronningen, C. Guja, C. Ionescu-Tirgoviste, D. A. Savage, A. P. Maxwell, D. J. Carson, C. C. Patterson, J. A. Franklyn, D. G. Clayton, L. B. Peterson, L. S. Wicker, J. A. Todd & S. C. Gough: Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature*, 423, 506-11 (2003)
22. Gough, S. C., L. S. Walker & D. M. Sansom: CTLA4 gene polymorphism and autoimmunity. *Immunol Rev*, 204, 102-15 (2005)
23. Bottini, N., T. Vang, F. Cucca & T. Mustelin: Role of PTPN22 in type 1 diabetes and other autoimmune diseases. *Semin Immunol*, 18, 207-13 (2006)
24. Vang, T., M. Congia, M. D. Macis, L. Musumeci, V. Orru, P. Zavattari, K. Nika, L. Tautz, K. Tasken, F. Cucca, T. Mustelin & N. Bottini: Autoimmune-associated lymphoid tyrosine phosphatase is a gain-of-function variant. *Nat Genet*, 37, 1317-9 (2005)
25. Vella, A., J. D. Cooper, C. E. Lowe, N. Walker, S. Nutland, B. Widmer, R. Jones, S. M. Ring, W. McArdle, M. E. Pembrey, D. P. Strachan, D. B. Dunger, R. C. Twells, D. G. Clayton & J. A. Todd: Localization of a type 1 diabetes locus in the IL2RA/CD25 region by use of tag single-nucleotide polymorphisms. *Am J Hum Genet*, 76, 773-9 (2005)
26. King, C., A. Ilic, K. Koelsch & N. Sarvetnick: Homeostatic expansion of T cells during immune insufficiency generates autoimmunity. *Cell*, 117, 265-77 (2004)
27. Yamanouchi, J., D. Rainbow, P. Serra, S. Howlett, K. Hunter, V. E. Garner, A. Gonzalez-Munoz, J. Clark, R. Veijola, R. Cubbon, S. L. Chen, R. Rosa, A. M. Cumiskey, D. V. Serreze, S. Gregory, J. Rogers, P. A. Lyons, B. Healy, L. J. Smink, J. A. Todd, L. B. Peterson, L. S. Wicker & P. Santamaria: Interleukin-2 gene variation impairs regulatory T cell function and causes autoimmunity. *Nat Genet*, 39, 329-37 (2007)
28. Zhernakova, A., B. Z. Alizadeh, M. Bevova, M. A. van Leeuwen, M. J. Coenen, B. Franke, L. Franke, M. D. Posthumus, D. A. van Heel, G. van der Steege, T. R. Radstake, P. Barrera, B. O. Roep, B. P. Koeleman & C. Wijmenga: Novel association in chromosome 4q27 region with rheumatoid arthritis and confirmation of type 1 diabetes point to a general risk locus for autoimmune diseases. *Am J Hum Genet*, 81, 1284-8 (2007)
29. van Heel, D. A., L. Franke, K. A. Hunt, R. Gwilliam, A. Zhernakova, M. Inouye, M. C. Wapenaar, M. C. Barnardo, G. Bethel, G. K. Holmes, C. Feighery, D. Jewell, D. Kelleher, P. Kumar, S. Travis, J. R. Walters, D. S. Sanders, P. Howdle, J. Swift, R. J. Playford, W. M. McLaren, M. L. Mearin, C. J. Mulder, R. McManus, R. McGinnis, L. R. Cardon, P. Deloukas & C. Wijmenga: A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. *Nat Genet*, 39, 827-9 (2007)
30. Gitlin, L., W. Barchet, S. Gilfillan, M. Cella, B. Beutler, R. A. Flavell, M. S. Diamond & M. Colonna:

Essential role of mda-5 in type I IFN responses to polyriboinosinic:polyribocytidylic acid and encephalomyocarditis picornavirus. *Proc Natl Acad Sci U S A*, 103, 8459-64 (2006)
31. Hornung, V., J. Ellegast, S. Kim, K. Brzozka, A. Jung, H. Kato, H. Poeck, S. Akira, K. K. Conzelmann, M. Schlee, S. Endres & G. Hartmann: 5'-Triphosphate RNA is the ligand for RIG-I. *Science*, 314, 994-7 (2006)
32. Kato, H., O. Takeuchi, S. Sato, M. Yoneyama, M. Yamamoto, K. Matsui, S. Uematsu, A. Jung, T. Kawai, K. J. Ishii, O. Yamaguchi, K. Otsu, T. Tsujimura, C. S. Koh, C. Reis e Sousa, Y. Matsuura, T. Fujita & S. Akira: Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. *Nature*, 441, 101-5 (2006)
33. Pichlmair, A., O. Schulz, C. P. Tan, T. I. Naslund, P. Liljestrom, F. Weber & C. Reis e Sousa: RIG-I-mediated antiviral responses to single-stranded RNA bearing 5'-phosphates. *Science*, 314, 997-1001 (2006)
34. Hultcrantz, M., M. H. Huhn, M. Wolf, A. Olsson, S. Jacobson, B. R. Williams, O. Korsgren & M. Flodstrom-Tullberg: Interferons induce an antiviral state in human pancreatic islet cells. *Virology*, 367, 92-101 (2007)
35. Graham, R. R., W. A. Ortmann, C. D. Langefeld, D. Jawaheer, S. A. Selby, P. R. Rodine, E. C. Baechler, K. E. Rohlf, K. B. Shark, K. J. Espe, L. E. Green, R. P. Nair, P. E. Stuart, J. T. Elder, R. A. King, K. L. Moser, P. M. Gaffney, T. L. Bugawan, H. A. Erlich, S. S. Rich, P. K. Gregersen & T. W. Behrens: Visualizing human leukocyte antigen class II risk haplotypes in human systemic lupus erythematosus. *Am J Hum Genet*, 71, 543-53 (2002)
36. Harley, J. B., J. A. Kelly & K. M. Kaufman: Unraveling the genetics of systemic lupus erythematosus. *Springer Semin Immunopathol*, 28, 119-30 (2006)
37. Fanciulli, M., P. J. Norsworthy, E. Petretto, R. Dong, L. Harper, L. Kamesh, J. M. Heward, S. C. Gough, A. de Smith, A. I. Blakemore, P. Froguel, C. J. Owen, S. H. Pearce, L. Teixeira, L. Guillevin, D. S. Graham, C. D. Pusey, H. T. Cook, T. J. Vyse & T. J. Aitman: FCGR3B copy number variation is associated with susceptibility to systemic, but not organ-specific, autoimmunity. *Nat Genet*, 39, 721-3 (2007)
38. Prokunina, L., C. Castillejo-Lopez, F. Oberg, I. Gunnarsson, L. Berg, V. Magnusson, A. J. Brookes, D. Tentler, H. Kristjansdottir, G. Grondal, A. I. Bolstad, E. Svenungsson, I. Lundberg, G. Sturfelt, A. Jonssen, L. Truedsson, G. Lima, J. Alcocer-Varela, R. Jonsson, U. B. Gyllensten, J. B. Harley, D. Alarcon-Segovia, K. Steinsson & M. E. Alarcon-Riquelme: A regulatory polymorphism in PDCD1 is associated with susceptibility to systemic lupus erythematosus in humans. *Nat Genet*, 32, 666-9 (2002)
39. Nishimura, H., M. Nose, H. Hiai, N. Minato & T. Honjo: Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity*, 11, 141-51 (1999)
40. Okazaki, T., A. Maeda, H. Nishimura, T. Kurosaki & T. Honjo: PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *Proc Natl Acad Sci U S A*, 98, 13866-71 (2001)
41. Graham, R. R., C. Kyogoku, S. Sigurdsson, I. A. Vlasova, L. R. Davies, E. C. Baechler, R. M. Plenge, T. Koeuth, W. A. Ortmann, G. Hom, J. W. Bauer, C. Gillett, N. Burtt, D. S. Cunninghame Graham, R. Onofrio, M. Petri, I. Gunnarsson, E. Svenungsson, L. Ronnblom, G. Nordmark, P. K. Gregersen, K. Moser, P. M. Gaffney, L. A. Criswell, T. J. Vyse, A. C. Syvanen, P. R. Bohjanen, M. J. Daly, T. W. Behrens & D. Altshuler: Three functional variants of IFN regulatory factor 5 (IRF5) define risk and protective haplotypes for human lupus. *Proc Natl Acad Sci U S A*, 104, 6758-63 (2007)
42. Yanai, H., H. M. Chen, T. Inuzuka, S. Kondo, T. W. Mak, A. Takaoka, K. Honda & T. Taniguchi: Role of IFN regulatory factor 5 transcription factor in antiviral immunity and tumor suppression. *Proc Natl Acad Sci U S A*, 104, 3402-7 (2007)
43. Pisitkun, P., J. A. Deane, M. J. Difilippantonio, T. Tarasenko, A. B. Satterthwaite & S. Bolland: Autoreactive B cell responses to RNA-related antigens due to TLR7 gene duplication. *Science*, 312, 1669-72 (2006)
44. Mathew, C. G.: New links to the pathogenesis of Crohn disease provided by genome-wide association scans. *Nat Rev Genet* (2007)
45. Hampe, J., A. Franke, P. Rosenstiel, A. Till, M. Teuber, K. Huse, M. Albrecht, G. Mayr, F. M. De La Vega, J. Briggs, S. Gunther, N. J. Prescott, C. M. Onnie, R. Hasler, B. Sipos, U. R. Folsch, T. Lengauer, M. Platzer, C. G. Mathew, M. Krawczak & S. Schreiber: A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. *Nat Genet*, 39, 207-11 (2007)
46. Libioulle, C., E. Louis, S. Hansoul, C. Sandor, F. Farnir, D. Franchimont, S. Vermeire, O. Dewit, M. de Vos, A. Dixon, B. Demarche, I. Gut, S. Heath, M. Foglio, L. Liang, D. Laukens, M. Mni, D. Zelenika, A. Van Gossum, P. Rutgeerts, J. Belaiche, M. Lathrop & M. Georges: Novel Crohn disease locus identified by genome-wide association maps to a gene desert on 5p13.1. and modulates expression of PTGER4. *PLoS Genet*, 3, e58 (2007)
47. Parkes, M., J. C. Barrett, N. J. Prescott, M. Tremelling, C. A. Anderson, S. A. Fisher, R. G. Roberts, E. R. Nimmo, F. R. Cummings, D. Soars, H. Drummond, C. W. Lees, S. A. Khawaja, R. Bagnall, D. A. Burke, C. E. Todhunter, T. Ahmad, C. M. Onnie, W. McArdle, D. Strachan, G. Bethel, C. Bryan, C. M. Lewis, P. Deloukas, A. Forbes, J. Sanderson, D. P. Jewell, J. Satsangi, J. C. Mansfield, L. Cardon & C. G. Mathew: Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility. *Nat Genet*, 39, 830-2 (2007)
48. Raelson, J. V., R. D. Little, A. Ruether, H. Fournier, B. Paquin, P. Van Eerdewegh, W. E. Bradley, P. Croteau, Q. Nguyen-Huu, J. Segal, S. Debrus, R. Allard, P. Rosenstiel, A. Franke, G. Jacobs, S. Nikolaus, J. M. Vidal, P. Szego, N. Laplante, H. F. Clark, R. J. Paulussen, J. W. Hooper, T. P. Keith, A. Belouchi & S. Schreiber: Genome-wide association study for Crohn's disease in the Quebec Founder Population identifies multiple validated disease loci. *Proc Natl Acad Sci U S A*, 104, 14747-52 (2007)
49. Rioux, J. D., R. J. Xavier, K. D. Taylor, M. S. Silverberg, P. Goyette, A. Huett, T. Green, P. Kuballa, M. M. Barmada, L. W. Datta, Y. Y. Shugart, A. M. Griffiths, S. R. Targan, A. F. Ippoliti, E. J. Bernard, L. Mei, D. L. Nicolae, M. Regueiro, L. P. Schumm, A. H. Steinhart, J. I. Rotter, R. H. Duerr, J. H. Cho, M. J. Daly & S. R. Brant:

Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. *Nat Genet*, 39, 596-604 (2007)
50. Xavier, R. J. & D. K. Podolsky: Unravelling the pathogenesis of inflammatory bowel disease. *Nature*, 448, 427-34 (2007)
51. Hue, S., P. Ahern, S. Buonocore, M. C. Kullberg, D. J. Cua, B. S. McKenzie, F. Powrie & K. J. Maloy: Interleukin-23 drives innate and T cell-mediated intestinal inflammation. *J Exp Med*, 203, 2473-83 (2006)
52. Jounai, N., F. Takeshita, K. Kobiyama, A. Sawano, A. Miyawaki, K. Q. Xin, K. J. Ishii, T. Kawai, S. Akira, K. Suzuki & K. Okuda: The Atg5 Atg12 conjugate associates with innate antiviral immune responses. *Proc Natl Acad Sci U S A*, 104, 14050-5 (2007)
53. Xu, Y., C. Jagannath, X. D. Liu, A. Sharafkhaneh, K. E. Kolodziejska & N. T. Eissa: Toll-like receptor 4 is a sensor for autophagy associated with innate immunity. *Immunity*, 27, 135-44 (2007)
54. Fellermann, K., D. E. Stange, E. Schaeffeler, H. Schmalzl, J. Wehkamp, C. L. Bevins, W. Reinisch, A. Teml, M. Schwab, P. Lichter, B. Radlwimmer & E. F. Stange: A chromosome 8 gene-cluster polymorphism with low human beta-defensin 2 gene copy number predisposes to Crohn disease of the colon. *Am J Hum Genet*, 79, 439-48 (2006)
55. Wehkamp, J., N. H. Salzman, E. Porter, S. Nuding, M. Weichenthal, R. E. Petras, B. Shen, E. Schaeffeler, M. Schwab, R. Linzmeier, R. W. Feathers, H. Chu, H. Lima, Jr., K. Fellermann, T. Ganz, E. F. Stange & C. L. Bevins: Reduced Paneth cell alpha-defensins in ileal Crohn's disease. *Proc Natl Acad Sci U S A*, 102, 18129-34 (2005)
56. Kabashima, K., T. Saji, T. Murata, M. Nagamachi, T. Matsuoka, E. Segi, K. Tsuboi, Y. Sugimoto, T. Kobayashi, Y. Miyachi, A. Ichikawa & S. Narumiya: The prostaglandin receptor EP4 suppresses colitis, mucosal damage and CD4 cell activation in the gut. *J Clin Invest*, 109, 883-93 (2002)
57. Van Limbergen, J., R. K. Russell, E. R. Nimmo, G. T. Ho, I. D. Arnott, D. C. Wilson & J. Satsangi: Genetics of the innate immune response in inflammatory bowel disease. *Inflamm Bowel Dis*, 13, 338-55 (2007)
58. Nenci, A., C. Becker, A. Wullaert, R. Gareus, G. van Loo, S. Danese, M. Huth, A. Nikolaev, C. Neufert, B. Madison, D. Gumucio, M. F. Neurath & M. Pasparakis: Epithelial NEMO links innate immunity to chronic intestinal inflammation. *Nature*, 446, 557-61 (2007)
59. Plenge, R. M., L. Padyukov, E. F. Remmers, S. Purcell, A. T. Lee, E. W. Karlson, F. Wolfe, D. L. Kastner, L. Alfredsson, D. Altshuler, P. K. Gregersen, L. Klareskog & J. D. Rioux: Replication of putative candidate-gene associations with rheumatoid arthritis in >4,000 samples from North America and Sweden: association of susceptibility with PTPN22, CTLA4, and PADI4. *Am J Hum Genet*, 77, 1044-60 (2005)
60. Suzuki, A., R. Yamada, X. Chang, S. Tokuhiro, T. Sawada, M. Suzuki, M. Nagasaki, M. Nakayama-Hamada, R. Kawaida, M. Ono, M. Ohtsuki, H. Furukawa, S. Yoshino, M. Yukioka, S. Tohma, T. Matsubara, S. Wakitani, R. Teshima, Y. Nishioka, A. Sekine, A. Iida, A. Takahashi, T. Tsunoda, Y. Nakamura & K. Yamamoto: Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis. *Nat Genet*, 34, 395-402 (2003)
61. Yamada, R., A. Suzuki, X. Chang & K. Yamamoto: Peptidylarginine deiminase type 4: identification of a rheumatoid arthritis-susceptible gene. *Trends Mol Med*, 9, 503-8 (2003)
62. Plenge, R. M., M. Seielstad, L. Padyukov, A. T. Lee, E. F. Remmers, B. Ding, A. Liew, H. Khalili, A. Chandrasekaran, L. R. Davies, W. Li, A. K. Tan, C. Bonnard, R. T. Ong, A. Thalamuthu, S. Pettersson, C. Liu, C. Tian, W. V. Chen, J. P. Carulli, E. M. Beckman, D. Altshuler, L. Alfredsson, L. A. Criswell, C. I. Amos, M. F. Seldin, D. L. Kastner, L. Klareskog & P. K. Gregersen: TRAF1-C5 as a risk locus for rheumatoid arthritis--a genomewide study. *N Engl J Med*, 357, 1199-209 (2007)
63. Plenge, R. M., C. Cotsapas, L. Davies, A. L. Price, P. I. de Bakker, J. Maller, I. Pe'er, N. P. Burtt, B. Blumenstiel, M. DeFelice, M. Parkin, R. Barry, W. Winslow, C. Healy, R. R. Graham, B. M. Neale, E. Izmailova, R. Roubenoff, A. N. Parker, R. Glass, E. W. Karlson, N. Maher, D. A. Hafler, D. M. Lee, M. F. Seldin, E. F. Remmers, A. T. Lee, L. Padyukov, L. Alfredsson, J. Coblyn, M. E. Weinblatt, S. B. Gabriel, S. Purcell, L. Klareskog, P. K. Gregersen, N. A. Shadick, M. J. Daly & D. Altshuler: Two independent alleles at 6q23 associated with risk of rheumatoid arthritis. *Nat Genet*, 39, 1477-82 (2007)
64. Thomson, W., A. Barton, X. Ke, S. Eyre, A. Hinks, J. Bowes, R. Donn, D. Symmons, S. Hider, I. N. Bruce, A. G. Wilson, I. Marinou, A. Morgan, P. Emery, A. Carter, S. Steer, L. Hocking, D. M. Reid, P. Wordsworth, P. Harrison, D. Strachan & J. Worthington: Rheumatoid arthritis association at 6q23. *Nat Genet*, 39, 1431-3 (2007)
65. Pomerleau, D. P., R. J. Bagley, D. V. Serreze, C. E. Mathews & E. H. Leiter: Major histocompatibility complex-linked diabetes susceptibility in NOD/Lt mice: subcongenic analysis localizes a component of Idd16 at the H2-D end of the diabetogenic H2 (g7) complex. *Diabetes*, 54, 1603-6 (2005)
66. Lyons, P. A., N. Armitage, F. Argentina, P. Denny, N. J. Hill, C. J. Lord, M. B. Wilusz, L. B. Peterson, L. S. Wicker & J. A. Todd: Congenic mapping of the type 1 diabetes locus, Idd3, to a 780-kb region of mouse chromosome 3: identification of a candidate segment of ancestral DNA by haplotype mapping. *Genome Res*, 10, 446-53 (2000)
67. Setoguchi, R., S. Hori, T. Takahashi & S. Sakaguchi: Homeostatic maintenance of natural Foxp3 (+) CD25 (+) CD4 (+) regulatory T cells by interleukin (IL)-2 and induction of autoimmune disease by IL-2 neutralization. *J Exp Med*, 201, 723-35 (2005)
68. Shen, S., Y. Ding, C. E. Tadokoro, D. Olivares-Villagomez, M. Camps-Ramirez, M. A. Curotto de Lafaille & J. J. Lafaille: Control of homeostatic proliferation by regulatory T cells. *J Clin Invest*, 115, 3517-26 (2005)
69. Hill, N. J., P. A. Lyons, N. Armitage, J. A. Todd, L. S. Wicker & L. B. Peterson: NOD Idd5 locus controls insulitis and diabetes and overlaps the orthologous CTLA4/IDDM12 and NRAMP1 loci in humans. *Diabetes*, 49, 1744-7 (2000)
70. Wicker, L. S., G. Chamberlain, K. Hunter, D. Rainbow, S. Howlett, P. Tiffen, J. Clark, A. Gonzalez-Munoz, A. M.

Cumiskey, R. L. Rosa, J. M. Howson, L. J. Smink, A. Kingsnorth, P. A. Lyons, S. Gregory, J. Rogers, J. A. Todd & L. B. Peterson: Fine mapping, gene content, comparative sequencing, and expression analyses support Ctla4 and Nramp1 as candidates for Idd5.1. and Idd5.2. in the nonobese diabetic mouse. *J Immunol*, 173, 164-73 (2004)
71. Vijayakrishnan, L., J. M. Slavik, Z. Illes, R. J. Greenwald, D. Rainbow, B. Greve, L. B. Peterson, D. A. Hafler, G. J. Freeman, A. H. Sharpe, L. S. Wicker & V. K. Kuchroo: An autoimmune disease-associated CTLA-4 splice variant lacking the B7 binding domain signals negatively in T cells. *Immunity*, 20, 563-75 (2004)
72. Colucci, F., M. L. Bergman, C. Penha-Goncalves, C. M. Cilio & D. Holmberg: Apoptosis resistance of nonobese diabetic peripheral lymphocytes linked to the Idd5 diabetes susceptibility region. *Proc Natl Acad Sci U S A*, 94, 8670-4 (1997)
73. Lundholm, M., V. Motta, A. Lofgren-Burstrom, N. Duarte, M. L. Bergman, S. Mayans & D. Holmberg: Defective induction of CTLA-4 in the NOD mouse is controlled by the NOD allele of Idd3/IL-2 and a novel locus (Ctex) telomeric on chromosome 1. *Diabetes*, 55, 538-44 (2006)
74. Vallois, D., C. H. Grimm, P. Avner, C. Boitard & U. C. Rogner: The type 1 diabetes locus Idd6 controls TLR1 expression. *J Immunol*, 179, 3896-903 (2007)
75. Lyons, P. A., W. W. Hancock, P. Denny, C. J. Lord, N. J. Hill, N. Armitage, T. Siegmund, J. A. Todd, M. S. Phillips, J. F. Hess, S. L. Chen, P. A. Fischer, L. B. Peterson & L. S. Wicker: The NOD Idd9 genetic interval influences the pathogenicity of insulitis and contains molecular variants of Cd30, Tnfr2, and Cd137. *Immunity*, 13, 107-15 (2000)
76. Cannons, J. L., G. Chamberlain, J. Howson, L. J. Smink, J. A. Todd, L. B. Peterson, L. S. Wicker & T. H. Watts: Genetic and functional association of the immune signaling molecule 4-1BB (CD137/TNFRSF9) with type 1 diabetes. *J Autoimmun*, 25, 13-20 (2005)
77. Rolf, J., V. Motta, N. Duarte, M. Lundholm, E. Berntman, M. L. Bergman, L. Sorokin, S. L. Cardell & D. Holmberg: The enlarged population of marginal zone/CD1d (high) B lymphocytes in nonobese diabetic mice maps to diabetes susceptibility region Idd11. *J Immunol*, 174, 4821-7 (2005)
78. Silveira, P. A., H. D. Chapman, J. Stolp, E. Johnson, S. L. Cox, K. Hunter, L. S. Wicker & D. V. Serreze: Genes within the Idd5 and Idd9/11 diabetes susceptibility loci affect the pathogenic activity of B cells in nonobese diabetic mice. *J Immunol*, 177, 7033-41 (2006)
79. Irie, J., Y. Wu, D. A. Sass & W. M. Ridgway: Genetic control of anti-Sm autoantibody production in NOD congenic mice narrowed to the Idd9.3. region. *Immunogenetics*, 58, 9-14 (2006)
80. Waldner, H., R. A. Sobel, N. Price & V. K. Kuchroo: The autoimmune diabetes locus Idd9 regulates development of type 1 diabetes by affecting the homing of islet-specific T cells. *J Immunol*, 176, 5455-62 (2006)
81. Chamberlain, G., M. Wallberg, D. Rainbow, K. Hunter, L. S. Wicker & E. A. Green: A 20-Mb region of chromosome 4 controls TNF-alpha-mediated CD8+ T cell aggression toward beta cells in type 1 diabetes. *J Immunol*, 177, 5105-14 (2006)
82. Hill, N. J., A. Stotland, M. Solomon, P. Secrest, E. Getzoff & N. Sarvetnick: Resistance of the target islet tissue to autoimmune destruction contributes to genetic susceptibility in Type 1 diabetes. *Biol Direct*, 2, 5 (2007)
83. Razavi, R., Y. Chan, F. N. Afifiyan, X. J. Liu, X. Wan, J. Yantha, H. Tsui, L. Tang, S. Tsai, P. Santamaria, J. P. Driver, D. Serreze, M. W. Salter & H. M. Dosch: TRPV1+ sensory neurons control beta cell stress and islet inflammation in autoimmune diabetes. *Cell*, 127, 1123-35 (2006)
84. Bour-Jordan, H. & J. A. Bluestone: Sensory neurons link the nervous system and autoimmune diabetes. *Cell*, 127, 1097-9 (2006)
85. Yokoi, N., K. Komeda, H. Y. Wang, H. Yano, K. Kitada, Y. Saitoh, Y. Seino, K. Yasuda, T. Serikawa & S. Seino: Cblb is a major susceptibility gene for rat type 1 diabetes mellitus. *Nat Genet*, 31, 391-4 (2002)
86. Bachmaier, K., C. Krawczyk, I. Kozieradzki, Y. Y. Kong, T. Sasaki, A. Oliveira-dos-Santos, S. Mariathasan, D. Bouchard, A. Wakeham, A. Itie, J. Le, P. S. Ohashi, I. Sarosi, H. Nishina, S. Lipkowitz & J. M. Penninger: Negative regulation of lymphocyte activation and autoimmunity by the molecular adaptor Cbl-b. *Nature*, 403, 211-6 (2000)
87. Chiang, Y. J., H. K. Kole, K. Brown, M. Naramura, S. Fukuhara, R. J. Hu, I. K. Jang, J. S. Gutkind, E. Shevach & H. Gu: Cbl-b regulates the CD28 dependence of T-cell activation. *Nature*, 403, 216-20 (2000)
88. Jorgensen, T. N., M. R. Gubbels & B. L. Kotzin: New insights into disease pathogenesis from mouse lupus genetics. *Curr Opin Immunol*, 16, 787-93 (2004)
89. Miura-Shimura, Y., K. Nakamura, M. Ohtsuji, H. Tomita, Y. Jiang, M. Abe, D. Zhang, Y. Hamano, H. Tsuda, H. Hashimoto, H. Nishimura, S. Taki, T. Shirai & S. Hirose: C1q regulatory region polymorphism down-regulating murine c1q protein levels with linkage to lupus nephritis. *J Immunol*, 169, 1334-9 (2002)
90. Rozzo, S. J., J. D. Allard, D. Choubey, T. J. Vyse, S. Izui, G. Peltz & B. L. Kotzin: Evidence for an interferon-inducible gene, Ifi202, in the susceptibility to systemic lupus. *Immunity*, 15, 435-43 (2001)
91. Wandstrat, A. E., C. Nguyen, N. Limaye, A. Y. Chan, S. Subramanian, X. H. Tian, Y. S. Yim, A. Pertsemlidis, H. R. Garner, Jr., L. Morel & E. K. Wakeland: Association of extensive polymorphisms in the SLAM/CD2 gene cluster with murine lupus. *Immunity*, 21, 769-80 (2004)
92. Kumar, K. R., L. Li, M. Yan, M. Bhaskarabhatla, A. B. Mobley, C. Nguyen, J. M. Mooney, J. D. Schatzle, E. K. Wakeland & C. Mohan: Regulation of B cell tolerance by the lupus susceptibility gene Ly108. *Science*, 312, 1665-9 (2006)
93. Subramanian, S., K. Tus, Q. Z. Li, A. Wang, X. H. Tian, J. Zhou, C. Liang, G. Bartov, L. D. McDaniel, X. J. Zhou, R. A. Schultz & E. K. Wakeland: A Tlr7 translocation accelerates systemic autoimmunity in murine lupus. *Proc Natl Acad Sci U S A*, 103, 9970-5 (2006)
94. Deane, J. A., P. Pisitkun, R. S. Barrett, L. Feigenbaum, T. Town, J. M. Ward, R. A. Flavell & S. Bolland: Control of Toll-like Receptor 7 Expression Is Essential to Restrict Autoimmunity and Dendritic Cell Proliferation. *Immunity*, 27, 801-10 (2007)
95. Aitman, T. J., R. Dong, T. J. Vyse, P. J. Norsworthy, M. D. Johnson, J. Smith, J. Mangion, C. Roberton-Lowe,

A. J. Marshall, E. Petretto, M. D. Hodges, G. Bhangal, S. G. Patel, K. Sheehan-Rooney, M. Duda, P. R. Cook, D. J. Evans, J. Domin, J. Flint, J. J. Boyle, C. D. Pusey & H. T. Cook: Copy number polymorphism in Fcgr3 predisposes to glomerulonephritis in rats and humans. *Nature*, 439, 851-5 (2006)
96. Beckwith, J., Y. Cong, J. P. Sundberg, C. O. Elson & E. H. Leiter: Cdcs1, a major colitogenic locus in mice, regulates innate and adaptive immune response to enteric bacterial antigens. *Gastroenterology*, 129, 1473-84 (2005)
97. Borm, M. E., J. He, B. Kelsall, A. S. Pena, W. Strober & G. Bouma: A major quantitative trait locus on mouse chromosome 3 is involved in disease susceptibility in different colitis models. *Gastroenterology*, 128, 74-85 (2005)
98. Mahler, M., I. J. Bristol, J. P. Sundberg, G. A. Churchill, E. H. Birkenmeier, C. O. Elson & E. H. Leiter: Genetic analysis of susceptibility to dextran sulfate sodium-induced colitis in mice. *Genomics*, 55, 147-56 (1999)
99. Holmdahl, R.: Dissection of the genetic complexity of arthritis using animal models. *Immunol Lett*, 103, 86-91 (2006)
100. Joe, B.: Quest for arthritis-causative genetic factors in the rat. *Physiol Genomics*, 27, 1-11 (2006)
101. Olofsson, P., J. Holmberg, J. Tordsson, S. Lu, B. Akerstrom & R. Holmdahl: Positional identification of Ncf1 as a gene that regulates arthritis severity in rats. *Nat Genet*, 33, 25-32 (2003)
102. Gelderman, K. A., M. Hultqvist, J. Holmberg, P. Olofsson & R. Holmdahl: T cell surface redox levels determine T cell reactivity and arthritis susceptibility. *Proc Natl Acad Sci U S A*, 103, 12831-6 (2006)
103. Gelderman, K. A., M. Hultqvist, A. Pizzolla, M. Zhao, K. S. Nandakumar, R. Mattsson & R. Holmdahl: Macrophages suppress T cell responses and arthritis development in mice by producing reactive oxygen species. *J Clin Invest*, 117, 3020-8 (2007)
104. Hultqvist, M. & R. Holmdahl: Ncf1 (p47phox) polymorphism determines oxidative burst and the severity of arthritis in rats and mice. *Cell Immunol*, 233, 97-101 (2005)
105. Hultqvist, M., P. Olofsson, J. Holmberg, B. T. Backstrom, J. Tordsson & R. Holmdahl: Enhanced autoimmunity, arthritis, and encephalomyelitis in mice with a reduced oxidative burst due to a mutation in the Ncf1 gene. *Proc Natl Acad Sci U S A*, 101, 12646-51 (2004)

Abbreviations: T1D: Type 1 diabetes, RA: Rheumatoid arthritis, CD: Crohns disease, SLE: Systemic lupus erythematosus, GWA: genome-wide association, WTCCC: Wellcome Trust Case Control Consortium, SNP: single nucleotide polymorphism, NOD: non-obese diabetic, CIA: collagen-induced arthritis, PIA: pristane-induced arthritis, QTL: quantitative trait loci, ENU: N-ethyl-N-nitrosourea, TCR: T cell receptor, IFN: interferon, DC: dendritic cell, TLR: toll-like receptor, APC: antigen presenting cell, Treg: regulatory T cell.

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