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Heterogeneity of autoimmune diseases: pathophysiologic insights from genetics and implications for new therapies

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Abstract

Recent advances in genome-wide association studies (GWAS) across autoimmune and immune-mediated diseases have augmented our understanding of pathogenic mechanisms underlying these diseases. This has further highlighted their heterogeneous nature, both within and between diseases. Furthermore, varying responses to therapy have also served to underline the importance of this heterogeneity in the manner in which these diseases are diagnosed and treated. Here we discuss our current understanding of the shared pathways of autoimmunity, including the tumor necrosis factor (TNF), major histocompatibility complex (MHC), interleukin 23 receptor (IL23R) and protein tyrosine phosphatase non-receptor type 22 (PTPN22) pathways. In addition, we summarize effective specific therapies tested across major autoimmune diseases, highlighting the insight they have provided into disease mechanisms and their implications for potential future improvements.

Although Paul Ehrlich proposed in 1901 that damaging self-reactivity or ‘horror autoxicus’ was impossible, this notion was soon contradicted by data from many sources. First, paroxysomal nocturnal hemoglobinuria was shown to be due to anti–red cell antibodies, and subsequently anti-thyroid antibodies were identified in individuals with thyroiditis. Sir Frank McFarlane Burnet’s ‘Clonal Selection Theory’ in 1957 suggested clear notions of how autoimmune diseases might arise from somatic mutations in antigen receptors, leading to ‘forbidden clones’ that were mistakenly not deleted during lymphocyte development.

GWASs for associations of genetic variants with various autoimmune diseases have informed our comparative understanding of disease mechanisms and revealed pathways that might yield potential drug targets. Furthermore, there has been a recent acceleration in the development of effective new therapies in autoimmune diseases by using knowledge that

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predates the recent advances in genetics. By helping advance knowledge of the molecular mechanisms of disease pathogenesis, genetics and genomics might help define novel therapeutic targets. Genetics and genomics might also be useful in some instances for clinical stratification.

Here we explore shared pathways of autoimmunity and recent advances in our molecular understanding of GWAS signals. We also summarize the effects of therapeutic agents tested across major autoimmune diseases and the pathophysiologic insights obtained from those tests, and we consider potential future therapeutic efforts.

Autoimmune disease phenotypes

It is now apparent that many chronic inflammatory and destructive diseases are autoimmune, including rheumatoid arthritis, Graves' disease, Hashimoto's thyroiditis, and Sjogren's syndrome, which each affect about 1% of the world's population. In addition, autoimmune diseases also comprise less-common diseases such as type 1 diabetes, multiple sclerosis, Crohn's disease, vitiligo, pernicious anemia, primary biliary cirrhosis, systemic lupus erythematosus, and ankylosing spondylitis. Over 80 autoimmune diseases have now been identified. These diseases are distinguished by their primary target organ (joints, skin—psoriasis; central nervous system—multiple sclerosis; intestine—inflammatory bowel disease (IBD); pancreas—type 1 diabetes mellitus), time course of disease presentation relative to tissue damage and major genetic associations (Table 1). For type 1 diabetes mellitus and autoimmune thyroid disease, extensive tissue destruction antedates disease presentation; therefore, for both of these diseases, the primary therapy remains hormone replacement, as opposed to anti-inflammatory agents (Fig. 1).

In autoimmune diseases, germline genetic variation accounts for only a fraction of disease trait variability, typically less than 20%. Most GWAS signals are driven by non-coding mutations that modulate gene expression (Box 1). Because autoimmunity most commonly presents in late childhood to early adulthood, additional phenotypic variability probably arises from factors that arise during development, such as autoantibody formation and epigenetic programming, as well as from environmental factors such as the intestinal microbiome and tobacco use. However, the integration of shared and distinguishing features of autoimmune diseases provides a conceptual framework within which to accelerate the development and application of novel therapeutic agents.

Box 1

Molecular understanding of non-coding associations

GWASs have defined the overall landscape of genetic polymorphisms in autoimmune diseases. However, in only a minority of disease-associated loci can a single, causal allele be identified that statistically accounts for the association signal in the region[110]. It is estimated that 90% of causal alleles are non-coding in nature, with a substantial fraction of these presumed to exert their pathogenic effects through modulation of gene expression. Early studies indicate that GWAS loci are indeed enriched for expression quantitative trait loci (eQTL)[111]. The potential value of mapping disease-associations

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with eQTLs is that it could provide more specific insight into disease mechanism. However eQTL are extraordinarily context specific, varying by cell and tissue type, time course and activation conditions. In a recent study in human macrophages stimulated by either lipopolysaccharide or IFN-γ, it was estimated that as many as 80% of transcripts are associated with eQTL[112]. Thus it is important to map disease-associated alleles with an eQTL observed in a relevant condition in order to provide pathophysiologic insights.

Related to gene expression changes, enrichment of GWAS signals has been observed for regions with specific regulatory chromatin states, cross-species conserved elements, DNA-accessible regions and histone marks. Generally, GWAS signal enrichment has been greater for cell-specific active enhancers (for example, H3K27ac peaks) than for promoter-associated peaks (for example, H3K4me3, H3K9ac). Disease and trait-associated polymorphisms are enriched in cell- and tissue-specific epigenetic marks, consistent with plausible mechanisms of disease pathogenesis. For example, autoimmune diseases have mapped to immune cell–specific marks, and metabolic diseases (for example, lipid regulation) have mapped with liver-specific histone marks, respectively. Of note, IBD GWAS signals enrich for both immune cell– and gastrointestinal-specific marks, indicating multiple contributing cell types in driving disease[113].

More precise cell subset definitions of the active enhancer landscape have provided additional insight into autoimmune disease pathogensis[95]. The greatest enrichment of GWAS signals is observed within active transcriptional regions for a variety of $CD4^+$ effector T cells (for example, T_H17, T_H1, T_H2) for numerous autoimmune diseases including multiple sclerosis, celiac disease, primary biliary cirrhosis, type 1 diabetes, rheumatoid arthritis and inflammatory bowel disease. Generally, enrichment scores of GWAS signals within epigenetic marks for T_{reg} cells were lower, with the greatest enrichment observed for multiple sclerosis. B cell enrichment scores were highest in multiple sclerosis, primary biliary cirrhosis, systemic lupus erythematosis, followed by rheumatoid arthritis, with lower B cell enrichment observed in classically seronegative diseases such as inflammatory bowel disease, psoriasis and ankylosing spondylitis. Interestingly, relatively low enrichment scores were observed in peripheral blood monocytes[95]. We speculate that this reflects the highly contextual and plastic nature of tissue macrophages and their enhancer landscape[114]. Whether more significant GWAS signal enrichment is observed with epigenetic and expression data from tissue-relevant macrophages should be the subject of future studies.

Within-disease heterogeneity

Many autoimmune diseases include the expression of autoantibodies, although autoantibodies are not a requirement. However, not all self-proteins are autoantigens, and not all potential epitopes are autoantigenic. What makes a self-protein autoantigenic is not clear. Sometimes autoantigens have additional properties; for example, they may interact with toll-like receptors (TLRs) or chemokine receptors[1,2], but usually these properties are not known. Equally unclear is why the presence of autoantibodies and the development of autoimmune disease are not more closely linked. Some autoantibodies, such as antibodies to the thyroid stimulating hormone (TSH) receptor, are agonistic, resulting in the excessive stimulation of

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the thyroid gland present in Graves' disease[3]. Others, such as anti-DNA antibodies, are mostly non-pathogenic. Clearly there are some important steps that need to be understood in the development of autoimmune disease aside from the generation of autoantibodies. One of these steps is immunoglobulin (Ig) class switching, because initially autoantibodies are IgM, but they mature into higher-affinity IgG autoantibodies. For example, IgM anti-dsDNA antibodies are less pathogenic than their IgG counterparts in systemic lupus erythematosus[4].

Within a single disease, there is considerable variation in clinical manifestations and severity. For example, in rheumatoid arthritis, there is marked heterogeneity in the age of onset. Furthermore, as a person with this disease ages, there is heterogeneity in the number of affected joints and their distribution; in some more severe cases, people develop extra-articular complications, such as nodules and lung fibrosis. There is considerable heterogeneity in the speed of progression and in the extent of joint damage, with the degree of cartilage and bone damage varying. Some, but not all, phenotypic heterogeneity is related to known factors, such as 'seropositivity', with rheumatoid factor (RF) and anti-citrullinated antibody (ACPA) often being associated with more severe disease than seronegative arthritis; seropositive disease also has different human leukocyte antigen (HLA) associations[5].

Related to disease heterogeneity, disease concordance rates in identical twins are surprisingly low, ranging from 15% in rheumatoid arthritis to 24% in systemic lupus erythematosus, and a bit higher in type 1 diabetes, with estimates averaging approximately 30% (refs. 6,7). Why this is is not understood, but it suggests an important role for subtle differences in the environment in the development of autoimmune disease. It is known that between twins, differences in epigenetic marks increase with age[8]. This discordance in disease development in identical twins also makes clear the difficulties of predicting disease; the popular concept that knowing a patient's DNA sequence will reveal their disease risk is thus clearly naive.

Heterogeneity of autoimmunity is also very apparent in inbred animal models; inbred mice within the same cage are analogous to identical twins reared together. In some animal models, such as in mouse models of collagen-induced arthritis, a minority of the mice might get the disease. Hence the issue of autoimmune disease being multi-factorial and not being just due to genetics is clear, and future studies should be designed to incorporate non-genetic factors in a longitudinal manner.

Shared pathways of autoimmunity

Genetic and non-genetic approaches have provided insights into the shared pathways of autoimmune and immune-mediated diseases and hence the identification of pathways that are likely to represent valid therapeutic targets. An important new insight from recent genetic studies is that loss-of-function alleles that decrease disease risk highlight potentially ideal therapeutic targets, as they represent a naturally occurring manner in which to validate a target. That these loss-of-function, disease-protective alleles exist in healthy individuals suggests that blocking a particular pathway might be both a safe and effective treatment at the earliest possible stages of disease pathogenesis. One example of the efficacy of this approach has involved the identification of loss-of-function alleles in proprotein convertase

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subtilisin/kexin type 9 (*PCSK9*), which is associated with both decreased LDL cholesterol levels and death from coronary artery disease[6,]. Soon after these genetic associations were identified, multiple agents to block PCSK9 expression were rapidly developed and demonstrated marked efficacy in phase 2 (ref. 9) and 3 (refs. 10–12) studies; however, rare neurocognitive events (less than 1% of cases) were observed more frequently in the treatment arm[10]. Other forms of cholesterol-lowering therapy such as statins may also predispose people to neuropsychiatric and cognitive problems[13].

MHC

The genetic associations within the MHC with autoimmune disease provided the first experimental evidence of genetic predisposition to autoimmune diseases in the 1970s (ref. 14). The relevance and mechanism of MHC as a major risk factor across all forms of autoimmunity in humans and mice became clear when it was elucidated that MHC molecules on antigen-presenting cells (APCs) bind peptides and present them to appropriate T cells.

GWAS that genotype a dense map of markers in case-control cohorts have highlighted a dominant role for the MHC region in autoimmune disease[15,16]. The MHC region includes genes with diverse immune function in addition to genes encoding the classical antigen-presenting molecules. It is the most genetically diverse region in the genome owing to the effects of natural selection. For most autoimmune diseases, genetic associations within the MHC region are the most significant, and there are multiple independent MHC alleles that can predispose individuals to autoimmune disease. The predominant MHC associations with autoimmune disease can be generally classified as MHC class I or class II predominant (Table 1). The role of the cell surface MHC molecules is to present peptide antigens to T lymphocytes. Class I and class II MHC molecules are distinguished by their expression and antigen sources. Class I molecules are expressed on all cells, whereas class II expression is restricted to professional APCs such as dendritic cells and B cells. Regarding antigen source, class I antigens are derived from cytosolic sources, whereas class II antigens are derived from extracellular proteins. Associations of the MHC with genetic disease are of primary importance in contrasting class I (psoriatic arthritis, ankylosing spondylitis) with class II (rheumatoid arthritis, juvenile idiopathic arthritis) joint disease (Table 1).

Although there are many loci in the MHC that can predispose an individual to multiple autoimmune diseases and disease subtypes, for the majority of loci, precise causal alleles have not thus far been defined. Within a given locus, causal alleles may be different between diseases, reflecting either genetic differences in antigen recognition (MHC region) or differences in cell-specific enhancers, which may provide precise insights into the pathogenic and protective cell subsets for particular diseases.

TNF

The identification that cytokines (especially proinflammatory cytokines that initiate inflammatory and immune responses) have a central role in autoimmunity and could be individually targeted for therapeutic benefit was a key conceptual advance in the understanding of autoimmune diseases. Studies in tissues associated with autoimmune

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diseases such as the rheumatoid synovium, which was studied owing to its accessibility, helped to identify marked upregulation of many pro-inflammatory cytokines, including TNF, interleukin (IL)-1β, granulocyte macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFN-γ), IL-2 and IL-6 (ref. 17). Crucially, it was subsequently shown in synovial cultures taken from patients with rheumatoid arthritis that monoclonal antibodies against TNF downregulated IL-1β secretion, and subsequently the release of many other pro-inflammatory cytokines (Fig. 2) (refs. 18,19). Rather than suggesting a system of overlapping, highly redundant inflammatory pathways that cause inflammation, these studies supported a model of a delicately balanced, hierarchical cytokine network or cascade dependent on TNF that resulted in inflammation. It is of interest in this context that TNF appears to 'raise the alarm', as it is released rapidly after almost any stressful stimulus, and it acts to recurit the 'firefighters', recruiting leukocytes to sites of stress.

After the success of clinical trials using anti-TNF therapy in rheumatoid arthritis[20], related diseases such as Crohn's disease[21,22] and psoriasis were also tested and shown to respond to this treatment. It was then determined that in this group of diseases, including rheumatoid arthritis, juvenile rheumatoid arthritis, Crohn's disease, ulcerative colitis[23], psoriasis[24], psoriatic arthritis[25] and ankylosing spondylitis[26,27], that TNF expression is an important rate-limiting step in disease pathogenesis, such that anti-TNF therapy is effective in the majority of such patients. Consistent with the beneficial effect of TNF blockade in rheumatoid arthritis and Crohn's disease, mice overexpressing TNF were demonstrated to have gut- and joint-associated immunopathologies[28].

With regard to the importance of genetics and genomics in planning target discovery, it is important to note that defining TNF as a target occurred totally independently of these technologies. Furthermore, in disease tissue microarrays or in GWASs, the TNF pathway does not show any genetic association, even with diseases in which anti-TNF therapy is very effective. This is important because it indicates that the high-throughput technologies based on DNA or RNA sequencing will miss important therapeutic targets. No single approach can be used to address such an important problem as the definition of therapeutic targets.

The IL12/23 pathway

Autoimmunity was long thought to be driven by IFN-γ–expressing $CD4^+$ T helper 1 (T_H1) cells[29]. However, the loss of IFN-γ increased inflammation in a mouse model of multiple sclerosis, as it did in a model of arthritis questioning this role for T_H1 cells in autoimmunity[30], and IFN-γ–specific antibody treatment increases arthritis activity in animal and human studies[31,32].

Subsequent studies implicated $CD4^+$ T_H17 cells in a variety of mouse models of autoimmunity[33,34]; the clinical relevance of these findings was validated by human genetic studies implicating the IL-23 pathway in autoimmune disease pathogenesis[35]; this pathway is essential for amplifying and stabilizing the pathogenic function of T_H17 cells[36]. Among the IL-23 pathway genes, there are multiple associations of SNPs within *IL23R* with multiple immune diseases, such as IBD[37], psoriasis[38,39], ankylosing spondylitis[40] and psoriatic arthritis[41] have been reported. (Of note, the associated *IL23R* polymorphisms in psoriatic arthritis are distinct from those reported in the other diseases.) The most notable

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genetic association of *IL23R* with most of these autoimmune diseases is the coding polymorphism Arg381Gln: the minor glutamine allele (observed in approximately one out of seven individuals with European ancestry) confers a two- to threefold increase in protection, compared to the more-common arginine allele, against developing IBD[37]. This protective glutamine allele is a loss-of-function mutation resulting in decreased numbers of IL-23–dependent $CD4^+$ T_H17 and $CD8^+$ Tc17 cells in human cells[42–44].

Monoclonal antibodies against p40, the cytokine subunit common to IL-12 and IL-23 are approved for the treatment of psoriasis[45] and psoriatic arthritis[46], and phase 2 studies in IBD have shown promising results[47]. Given the protective, loss-of-function allele in *IL23R*, it is possible that selective targeting of IL-23 may be equally or more efficacious than combined IL12/23 targeting. Monoclonal antibodies blocking the IL-23–specific p19 subunit have demonstrated promising results in Crohn's disease[48] and psoriasis[49]. With respect to the interpretation of therapeutic responses to blocking IL-17 across autoimmune diseases, the role of T_H17 cells in autoimmune disease pathology is complex and is discussed later.

PTPN22 association with seropositive autoimmune diseases

In addition to the MHC, a major genetic association with multiple autoimmune diseases identified before the GWAS era involved the Arg620Trp polymorphism in *PTPN22*. Specifically, the less-common tryptophan allele is associated with a large number of seropositive autoimmune diseases such as rheumatoid arthritis, type 1 diabetes, systemic lupus erythematosis and autoimmune thyroid disease[50]. No association is observed with multiple sclerosis, and the opposite Arg620 allele is associated with Crohn's disease[51]. The tryptophan allele disrupts the binding of PTPN22 to CSK (c-Src tyrosine kinase), resulting in alterations in thresholds for T and B cell receptor signaling[52]. CSK normally downregulates T cell receptor signaling, and mice lacking PTPN22 have increased T cell activation[53]. However, the effect of the tryptophan allele on lymphocyte responsiveness in humans remains controversial, with both increased and decreased T cell and B cell receptor signaling reported[54–57].

Understanding heterogeneity in autoimmune disease through therapy response

Heterogeneity in anti-TNF responses. The finding that anti-TNF therapy, while the most profitable drug class and the standard of care in eight diseases is not effective in multiple sclerosis and, in fact, may worsen disease is a clue to the pathogenesis of this disease, the mechanisms of which remain largely unresolved. GWAS results are largely unrevealing in this regard; although the TNF signature in anti-TNF–responsive diseases can be gleaned from some associations (for example, associations with *TNFAIP3*, which downregulates TNF effects[15]), mutations associated with a TNF signature are not as common in autoimmune disease as those associated with other pathways. (Table 1). GWAS-identified TNF association signatures would certainly be an insufficient basis for selecting between alternative therapies for individual patients. GWASs of anti-TNF responses have demonstrated genetic associations with *CD84* (ref. 58), but this finding has not yet been confirmed in independent studies. Furthermore, it is worth pointing out that the dominant

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contribution to anti-TNF nonresponsiveness as determined by this study is not genetic; the *CD84*-associated SNPs accounted for only 2.6% of the variance in anti-TNF responses[58]. Importantly, there is no clear cut boundary between responders and nonresponders to anti-TNF treatment; it is a continuum, and the degree of response depends on the timing of therapy, with the greatest response if therapy commences within 6 months of diagnosis[59,60]. The most telling evidence for the nongenetic basis of low responsiveness is that patients that do not respond at a given point in time, so-called nonresponders, have a 50% chance of responding within 6 months to a different or same anti-TNF therapy. The specific factors that determine TNF responsiveness are not well understood, but the actual presence of TNF in joints in RA at the time of treatment is important for responsiveness[59,60].

Targeting the IL-12/IL-23 pathway in psoriasis

Psoriasis is a major success story in precision therapeutic targeting. This is due to clear GWAS results combined with the fact that that disease status and the response to therapy can be precisely followed (including with serial tissue sampling). Currently approved biologic therapies for plaque psoriasis include, in chronological order of approval, anti-TNF[61], anti-p40 (anti–IL-12/23) (ref. 62) and, most recently, anti–IL-17 therapies[63]. Serial sampling studies of psoriatic skin lesions from patients that responded favorably to anti-TNF treatment have shown that the downregulation of pro-inflammatory cytokines begins with IL-1β and IL-8, with decreases in IL-23 observed later[64].

Because the result of GWASs have associated multiple components of the IL-23 pathway with psoriasis, including, IL23R and IL23A (p19) (ref. 65), one might speculate that an important way in which anti-TNF therapy acts, particularly in psoriasis, is by downregulation of IL-23. With the approval of anti–IL-12/23, a key question is whether therapies that target upstream targets such as TNF or more-focused therapies targeting downstream components would be more effective. In a large randomized, controlled trial of individuals with moderate to severe psoriasis, anti-IL-12/23 (p40) demonstrated superior efficacy to the less-potent anti-TNF therapy in psoriasis (etanercept)[45]. It remains to be determined whether even more focused approaches, such as IL-23–specific therapies (for example, anti-IL-23A or p19), which would not affect IL-12 signaling, will be equally or more efficacious than approaches that block both cytokines. They might be predicted to be safer.

Another issue is whether the targeting of inflammatory mediators produced by IL-23–responsive cells would be effective. In fact, blocking either IL-17A alone[63] or both IL-17A and IL-17F by anti-IL17R (ref. 66) agents is effective in psoriasis in humans. The clinical and molecular response to IL-17 inhibition was rapid compared to anti-TNF or anti-IL12/23 blockade, with near-resolution of symptoms of within six weeks[63,66]. IL-17 acts by enhancing neutrophilia, tissue remodeling and repair and production of antimicrobial proteins[67]. These results suggest an essential and relatively downstream effector role for IL-17 in disease pathogenesis[68]. In all autoimmune diseases, treatment of acute flares and maintenance of disease remission are often conceptually separated. Whether blockade of IL-17 versus IL-23 has differential efficacy in the treatment of flares and maintenance of long-term remission will need to be studied.

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Tissue-specific considerations for therapy

Given its marked efficacy in psoriasis, and the efficacy in IBD of anti–IL-12/23 (ustekinumab) in phase 2 studies[47], it was particularly disappointing that anti–IL-17 treatment not only was ineffective in IBD, but also it demonstrated a trend toward worsened disease compared to placebo[69]. To an extent, this result was predicted by studies in mice lacking IL-17A, which have an accelerated wasting disease in the CD45Rb high-transfer model of colitis[70]. The intestine has a baseline tolerance to resident microbiota (mediated by IL-10 (ref. 71) and TGF-β1 (refs. 72,73), among many mediators), but it also maintains a robust defense capacity against pathogens and against breaching of the usual anatomic and functional containment of intestinal microbiota[74–76]. There is a crucial role for IL-10 secreted by T_H17 cells in the maintenance of intestinal tolerance[71,77], and thus it may be speculated that the worsening of intestinal inflammation observed with anti–IL-17 treatment in IBD[69] might result from impaired function of protective T_H17 cells.

This disparity in therapeutic effectiveness might be explained by the fact that tissue-specific T_H17 cell subsets have evolved to combat specific pathogens. For example, *Candida albicans*–specific human T_H17 cell clones produce IL-17 and IFN-γ, but not IL-10, whereas *Staphylococcus aureus* (a typical skin pathogen)-specific T_H17 cells produce IL-17 and are able to produce IL-10 upon re-stimulation[78]. Thus, tissue-specific autoimmune disease differences may reflect corresponding tissue- or organ-specific differences in typically encountered infectious pathogens (Box 2). Anti–IL-12/23 therapies (ustekinumab) have shown positive results for ankylosing spondylitis in a small, open-label study[79], and have also been approved for the treatment of psoriatic arthritis[80]; both of these are diseases have been linked with mutations in the MHC class I region and the IL-23 signaling pathway. Furthermore, for both psoriatic arthritis[66,81] and ankylosing spondylitis[82], early clinical trials blocking the IL-17 pathway have demonstrated promising results (Table 2) (ref. 83). This therapeutic effectiveness in blocking IL-17 in psoriatic arthritis is despite differences in skin IL-17 and joint IFN-γ expression signatures[84].

Box 2

Evolving host-microbiome relationships

Any increases in the incidence of autoimmune diseases measurable in decades must reflect environmental changes that have evolved relatively recently in human history[115]. The human genetic architecture evolved in response to natural selection. Genetic variation which provides protection against historically significant pathogens may, in a different time and environment confer increased risk to a distinct disease[115,116].

Changes in factors such as diet, sanitation and use of antibiotics can affect the content of the intestinal microbiome[117]. There is increasing evidence that the changing intestinal microbiome can drive increasing incidence of autoimmune diseases[118]. For example, expansion of intestinal Prevotella copri was correlated with newly diagnosed rheumatoid arthritis[119]. Correlational observations in humans are further supported by studies in model organisms which demonstrate how genetic factors (for example, innate immune deficiency in Myd88-deficient mice) can alter the intestinal microbiome, which in turn, modulates risk for the development of autoimmunity (for example, type 1 diabetes)[120]. A

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long-term goal would be to modulate host-microbiome interactions to decrease risk for autoimmune diseases in high-risk individuals.

There is also overlap between genes contained within loci that have been linked to increased risk of developing IBD, and between genes that are implicated in the predisposition to mycobacterial infection[51]. Ashkenazi Jewish individuals have a higher prevalence of IBD, and they have historically been relatively protected against dying from tuberculosis[121]. Thus one might speculate that the higher prevalence IBD in the Ashkenazim is due to positive selection for genetic variants that protect against tuberculosis, but in a different time and environment (for example, distinct intestinal microbiome composition), confer increased risk for IBD.

One might speculate that the plethora of loci identified by GWAS of autoimmune diseases reflects a matching abundance of functional polymorphisms positively selected for in response to historically significant infectious pathogens[122]. While generally well-tolerated with a favorable side-effect profile, blockade of TNF is associated with modestly increased risk for infections generally[123,124]. Of particular note, anti-TNF therapy has been associated with reactivation of latent tuberculosis[125], such that testing for *Mycobacterium tuberculosis*

The success of targeting the IL-23 or IL-17 pathways in these diseases contrasts with the effectiveness of these therapies in rheumatoid arthritis, in which similar positive findings have thus far not been reported. This may reflect the fundamentally distinct genetic architecture of rheumatoid arthritis[85,86], characterized by associations with MHC class II, the absence of associations with *IL23R* and the presence of associations with *PTPN22* (Table 1). The dichotomy between MHC class I– and class II–predominant diseases reflects fundamentally distinct pathogeneses, and thus distinct optimal therapeutic approaches.

Blocking T cell activation: abatacept and autoimmune diseases

Given the dominant role of MHC class II associations across autoimmune diseases, it would seem logical that modulating TCR activation might be useful therapeutically. The outcome of engagement of TCRs with peptide-bearing MHC molecules on APCs is modulated by additional signaling partner interactions. These ‘second signal’ partnerships can activate T cells (for example, CD28 expressed on T cells paired with B7 molecules on APCs) or inhibit T cell activation (for example, CTLA4-B7) in nature. *CTLA4* (encoding cytotoxic T-lymphocyte associated protein 4) is expressed on T cells, and polymorphisms in the *CTLA4* gene region are associated with a variety of autoimmune diseases, notably type 1 diabetes[87], autoimmune thyroid disease[88], rheumatoid arthritis[85], and celiac disease[89] (Table 1). Rare, heterozygous *CTLA4* mutations result in a functional haploinsufficiency, with dysregulation of $FoxP3^+$ regulatory T cells (T_{reg} cells) and systemic autoimmunity, although this results in incomplete genetic penetrance and a wide range of disease manifestations[90,91].

Rheumatoid arthritis is the only autoimmune disease demonstrating an association with CTLA4 in which biologics are routinely administered (Table 1). Interestingly, rheumatoid arthritis is also the major approved indication for treatment with abatacept, a high-affinity CTLA4 fusion protein (comprising the CTLA4 extracellular domain plus an IgG1 Fc

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fragment) that blocks second signals (e.g., CD28 co-stimulation) required for T cell activation[92] (Table 2). In contrast, well-powered studies of IBD demonstrated a lack of efficacy for abatacept in Crohn's disease or ulcerative colitis[93]. It may be speculated that this lack of efficacy occurs because effector memory T cells, predominant in the gut, are less dependent on CD28 for co-stimulation[94].

B cell depletion approaches

Whereas autoantibodies are a characteristic feature of many autoimmune diseases, it is important to distinguish between examples of primary pathogenicity versus autoantibody expression that reflect the secondary effects of increased immune activity (for example, through $CD4^+$ T cell help). GWAS signals are enriched in both B cell gene expression[95] and enhancer[96] landscapes. Among B cell enhancer regions, GWAS signals are most enriched in lupus, followed by rheumatoid arthritis. Germline genetic variation identified by GWASs reflects primary, driving events, and so it may be inferred that B cells are pathogenic in these GWAS-signal-enriched diseases.

Rheumatoid arthritis is the major approved indication for B cell depletion approaches, such as through anti-CD20 (rituximab)[97] (Fig. 2). In relapsing-remitting multiple sclerosis, another GWAS-signal B cell enhancer–enriched disease, rituximab treatment resulted in fewer inflammatory brain lesions and clinical relapses[98] (Table 2), but it has not been approved by the US Food and Drug Administration (FDA) for this use. In addition, ritiuximab has demonstrated modest efficacy in ankylosing spondylitis in anti-TNF–naive patients, but has not been approved by the FDA for this thus far[99,100]. In systemic lupus erythematosus, rituximab, while very effective in some patients, was also only of modest overall efficacy and so was not approved by the FDA. In contrast, no efficacy was observed with rituximab in ulcerative colitis in a phase 2 study[101]. These findings are consistent with the absence of enrichment for ulcerative colitis GWAS signals in B cell enhancer regions[95]. Taken together, this would indicate that the autoantibodies commonly observed in ulcerative colitis (for example, pANCA) are secondary effects and not primary drivers of disease. There is ongoing research on other B cell targets, but none has reached clinical approval apart from Belimumab, an antibody specific to B-lymphocyte stimulator, which is a fully human monoclonal antibody. Belimumab is approved for systemic lupus erythematosus by the FDA, but has shown modest efficacy[102,103].

Conclusions and future directions

Heterogeneity in disease pathophysiology and therapeutic responses is driven by genetic, developmental and environmental factors. Genetic discovery through GWASs over the past several years has identified a striking overlap of genetic loci between autoimmune, chronic inflammatory diseases. The immediate work that needs completion includes a comprehensive dissection of similarities and differences in the precise allelic architecture at these loci, integrated with tissue- and context-specific data on epigenetics and gene expression, all within the larger context of trying to define the effect of the environment on the predisposition to disease, which is poorly understood apart from, for example, smoking. These nongenetic aspects can be explored in a variety of ways, one of the most powerful

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being by epidemiology. Prospective epidemiological studies involving very large patient cohorts followed over the long term will be needed to try to determine which environmental factors might be important. These types of studies are now being designed through efforts such as the Precision Medicine Initiative[104]. Also critical in this regard is the serial sampling of relevant human tissues in the context of therapeutic interventions. It is incumbent that complete and timely reporting of results from therapeutic interventions in humans, both positive and negative, be mandated upon those responsible for clinical trials. Biomedical discovery is classically based on defining unifying principles of broad applicability. Similarly, the practice of medicine has traditionally been based on repeated observations and definitions of similarities between patients that guide treatment decisions on the basis of prior experience. It is increasingly clear, however, that the full realization of the promise of genetic and genomic discovery will require a paradigm shift embracing complexity, heterogeneity, and information-rich decision matrices personalized to individual patients[105], their diets, microbiomes, past medical histories, and other environmental factors.

With regard to drug development, an additional practical consideration is the immunogenicity of biologic agents, exacerbated with intermittent administration, which reduces efficacy and increases adverse side effects[106]. With the changing economic landscape in health care, the costs and long-term efficacy of specific biologic targeting[107] will increasingly be compared with small molecules, which are generally associated with lower rates of immunogenicity, but also variable target specificity; regrettably, they are not necessarily cheaper (e.g., tofacitanib).

Central to this new era of precision medicine will be a long-term, longitudinal view of research partners including, importantly, the patients (Fig. 1). The invaluable medical prescription, *primum non nocere* (first do no harm), has in the past resulted in a symptom-based treatment approach in autoimmune diseases. However, as new more effective therapies are developed, the goals of attaining control of inflammation and preventing structural tissue damage are increasingly being realized. For diseases such as type 1 diabetes, because a substantial amount of structural damage antedates disease presentation, symptom-based treatment (here, application of insulin) remains the cornerstone of therapy. For all autoimmune diseases, future goals involve earlier intervention, induction of immune tolerance, and possibly normalization of immune function. Critical to this progress will be defining how early microbial exposures modulate the immune system, for both early diagnosis and disease prevention. However, the major current hurdle is to consider which therapeutic combinations might be both safe and effective in autoimmune diseases. This is not a trivial task; premature attempts to develop combinations, for example using etanercept and anakinra[108,109] have yielded challenging results, namely no increase in efficacy but a marked increase in infections. But defining safe and effective combinations is possible. In rheumatoid arthritis, more than 50%, and in many reports, almost 70% of patients on TNF blockade are also treated with low-dose methotrexate. Targeting pathways that maintain disease chronicity but that are not involved in host defense against infection might help get us closer to a cure. The multiple clues from GWASs might help progress on this path.

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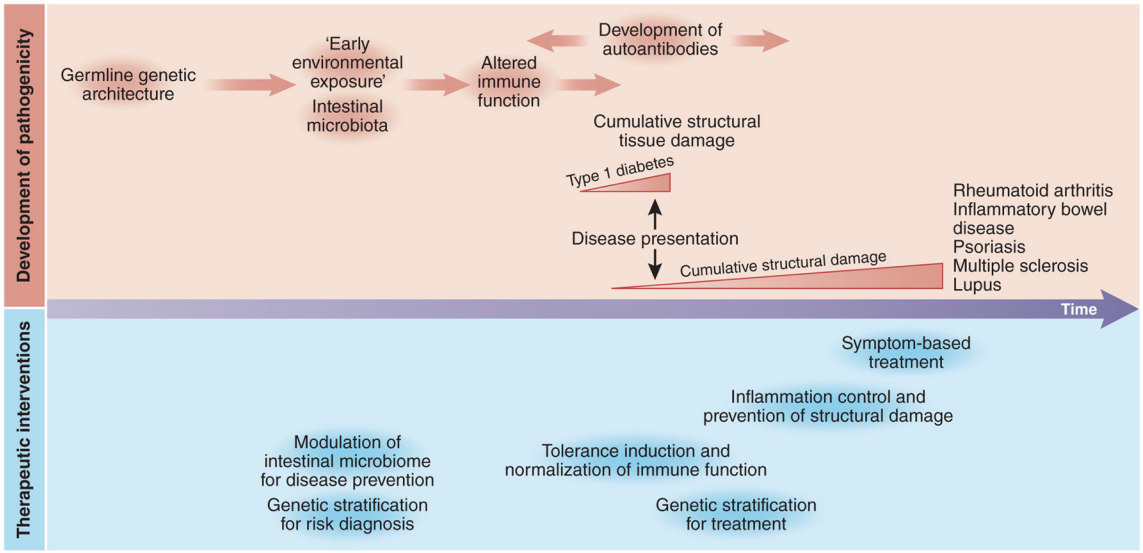

Figure 1.

Timeline of pathogenicity and therapeutic interventions in autoimmune diseases. Altered immune function antedates disease presentation across autoimmune diseases. In some cases, most notably for type 1 diabetes, substantial structural damage has already occurred by the time of disease presentation. In such cases, therapeutic options are restricted to symptomatic treatment, such as hormone replacement (insulin, thyroid hormones). For many other autoimmune diseases, therapeutic paradigms involve earlier treatment, control of inflammation and prevention of structural damage. In the future, induction of immune tolerance, and normalization of immune function may be accomplished, guided by genetic stratification for both treatment and prevention of disease.

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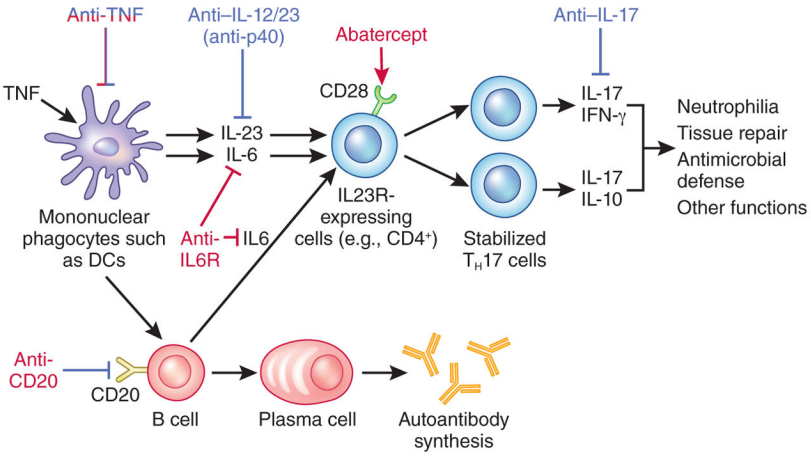

Figure 2.

Levels of therapeutic targeting across autoimmunity. Targetable pathways of rheumatoid arthritis and psoriasis are shown. Therapies that are effective in rheumatoid arthritis are shown in red, and therapies effective in psoriasis are shown in blue. The broad efficacy of anti-TNF therapy across many diseases reflects its central role in the cytokine network. In contrast, a more limited range of diseases have demonstrated positive results to blockade with anti–IL-12/23. IL-23 perpetuates and stabilizes IL23R-expressing pathogenic cells, including $CD4^+$ T_H17 cells. IL-17, as produced by T_H17 cells, promotes neutrophilia, as well as enhances antimicrobial defense and tissue repair. Antagonism of IL6R and CTLA4 fusion proteins preventing CD28 co-stimulation are effective in the treatment of rheumatoid arthritis, as are B cell ablation approaches, such as by CD20-specific antibody administration, which are approved for the treatment of rheumatoid arthritis.

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Table 1

Major genetic association signals across autoimmune diseases

	MHC class	*IL23R*	*PTPN22*	*CTLA4*[a]
Type 1 diabetes	Class II		Arg620**Trp**	Non-coding
Juvenile idiopathic arthritis	Class II		Arg620**Trp**	
Autoimmune thyroid disease	Class II		Arg620**Trp**	Non-coding
Rheumatoid arthritis	Class II		Arg620**Trp**	Non-coding
Multiple sclerosis	Class II			
Celiac disease	Class II			Non-coding
Systemic lupus erythematosis	Class II		Arg620**Trp**	
Psoriatic arthritis	Class I	Distinct alleles		
Psoriasis	Class I	Arg381**Gln**		
Ankylosing spondylitis	Class I	Arg381**Gln**		
Inflammatory bowel disease	Class II	Arg381**Gln**	**Arg**620Trp	

Underlined and bolded codons represent the allele associated with disease. Red color distinguishes the *PTPN22* association with arginine rather than tryptophan.

[a]Non-coding variants associated with the *CTLA4* region may be distinct between diseases.

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Table 2

Efficacy of therapeutic agents across autoimmune diseases

	TNF	IL12/23	IL17	IL6	CTLA4	Anti-CD20
Rheumatoid arthritis						
Juvenile idiopathic arthritis*						
Multiple sclerosis						
Psoriasis						
Psoriatic arthritis						
Ankylosing spondylitis						
Inflammatory bowel disease						
Specific agents	Infliximab, adalimumab, etanercept, certolizumab	Ustekinumab	Secukinumab, brodalumab	Tocilizumab	Abatacept	Rituximab

Dark green cells, approved indications; light green cells, preliminary positive findings; red cells, shown to worsen disease; gray cells, no evidence for efficacy.

[a]Treatment responses are distinct between systemic and polyarticular forms of juvenile idiopathic arthritis