The question of whether autoimmune diseases (AID) have a genetic link has occupied researchers and clinicians for decades. Mendelian inheritance has been demonstrated for some disorders, others are associated with mutations and polymorphisms in susceptibility genes. Mostly, transmission rates were significantly lower than expected. In such cases, and in disorders with no genetic background, environmental factors seem to influence and/or cause disease onset, progression, and outcome.

Monogenic Disorders

For a group of so-called monogenic disorders, Mendelian inheritance has been demonstrated. The group of monogenic periodic fever syndromes (PFS), a subgroup of autoinflammatory diseases, results in recurrent episodes of fevers, localized as well as systemic inflammation. Secondary to the limitations of an editorial, here we focus on disorders resulting in impaired inflammasome activity. The family of NOD-like receptors (NLRs) includes cytosolic trackers of microbial components and controls the assembly of inflammasomes which results in caspase-activation and subsequent IL-1β and IL-18 production [1,2]. Mutations in genes, encoding components of inflammasomes, have been reported in various human diseases. The presumed most common hereditary PFS is familial mediterranean fever (FMF) [3]. It follows autosomal-recessive inheritance and is caused by mutations in the MEFV gene, encoding for pyrin/marenostrin. Pyrin acts as a regulator in IL-1β activation by the NLRP3 inflammasome and MEFV mutations result in impaired protein function. Still, it is not always predictable if mutations will cause severe disease courses and disease associated complications. Mutations in the NLRP3 gene, which encodes cryopyrin, result in over-exaggerated IL-1β expression by monocytes. Mutations cause a clinical continuum of diseases, ranging from familial cold autoinflammatory disease (FCAS), to the more severe Muckle-Wells syndrome (MWS) and NOMID (neonatal onset multi-inflammatory disease), which results in severe complications, including bony overgrowth, aseptic meningitis, hearing loss, and mental retardation [3,4]. Surprisingly, different disorders out of this group can share the same mutations. The mode of inheritance is autosomal-dominant. Further noteworthy PFS are DIRA (deficiency of IL-1 RA) and TRAPS, a dominantly inherited disorder, caused by mutations in the 55 kDa TNF receptor (TNFRSF1A) [3]. Another example is the recessively inherited Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) [3]. This disorder was first described in the Netherlands and is diagnosed most frequently in the Dutch population. HIDS is caused by mutations in MVK, encoding mevalonate kinase.

Besides the group of autoinflammatory disorders, a group of monogenic AID is caused by mutations in single genes and should thus be mentioned here. The different subgroups of autoimmune-lymphoproliferative disorder (ALPS), characterised by nonmalignant lymphadenopathies associated with autoimmune features in children, are caused by mutations in the genes, encoding Fas/Apol, Fas-ligand, caspase 8, and caspase 10 [4]. The X chromosomal immune-dysfunction, polyendocrinopathy, and enteropathy syndrome (IPEX) is caused by mutations in FOXP3, an important regulator of T regulatory cell function [5]. The prototypic and probably most complicated AID, systemic lupus erythematosus (SLE), is a heterogeneous disease with multiple pathophysiological factors. Still, some forms have been explained by mutations in single genes. Complement Clq, C2, and C4 deficiency result in lupus like disorders [6]. Mutations in TREX1, encoding for the 3′–5′ repair exonuclease 1, were shown to result in a dominant phenotype with symptoms of familial chilblain lupus erythematosus, SLE, or Aicardi–Goutières syndrome [7–11].

Genetic Associations in AID

For various autoimmune diseases, associations with MHC variants and polymorphisms in cytokine genes have been reported [12]. Here, we concentrate on sub-forms of juvenile idiopathic arthritis (JIA) and related disorders. The association of specific HLA alleles with JIA suggests an involvement of T cells in the pathogenesis of these disorders. HLA class I (A, B, and C) molecules present intracellular antigens to CD8+ T cells, whereas HLA class II (DR, DP, DQ) molecules present extra-cellular antigens to CD4+ T cells [13]. Even though associations with HLA alleles have been reported, AID do not follow classical inheritance patterns. Polyarticular JIA is associated with HLA-DRB1*08 in cases of early onset under 4 years and the absence of rheumatic factors, whereas it is associated with HLA-DRB1*04 in cases of later disease onset and presence of rheumatic factors. Oligoarticular JIA (oJIA) is associated with MCH class I variants HLA-A2, which increases the risk of uveitis, class II variants DRB1*01 in milder cases, and DRB1*08, DRB1*11, DRB1*11301, DRB1*0201 in more severe “extended” oJIA cases. MHC-II variants DRB1*04, DRB1*07 seem to be protective for the development of JIA. The most well described association is probably HLA-B27 with enthesis associated JIA, and psoriatic arthritis. Further AID and autoinflammatory syndromes are associated with HLA class I, and class II variants (SLE, Sjögrens disease, Behcet disease, etc.). Some subgroups of JIA are in addition (extended oligoarticular JIA) or explicitly (systemic onset JIA/SoJIA) associated with single nucleotide polymorphisms in and around cytokine genes [12]. SoJIA is not associated with HLA variants, but sequence polymorphisms in several pro- and anti-inflammatory cytokines, such as IL-6, TNF-α, IL-1β, IL-1RA, and IL-10, have been reported. This suggests dysregulation of the balance between pro- and anti-inflammatory signals, resulting in systemic inflammation [14–19].

For all forms of JIA, concordance of disease onset in families...
is low. If JIA develops in siblings, subtype concordance is high. Interestingly, patients without any genetic susceptibility factor also develop autoimmune diseases. These findings and the observation that young immigrants from “high risk” areas do exhibit the same risk of developing AID compared to the population in host countries suggest the environment as an important factor in the pathogenesis of AID [12].

“Environmental Factors” and Epigenetic Modifications in AID

While investigating environmental factors, a recently described group of mechanisms in gene regulation has been shown to play an important role. As a result of their binding to specific DNA sequences, transcription factors are responsible for gene activation and/or silencing. The ability of transcription factors to bind to regulatory regions is, next to the DNA sequence, dependent on the state of chromatin [20]. So-called epigenetic patterns are responsible for the compaction and position of nucleosomes. The main and most intensely investigated epigenetic modifications are DNA methylation and post-translational histone modifications [20-24]. Since epigenetic modifications do not affect the DNA sequence, these changes show the potential of plasticity and underlie environmental influences, such as toxins, infections, medication, or diet. Epigenetic mechanisms are essential for gene regulation and changes in epigenetic marks of e.g. cytokine genes may lead to an imbalance of pro- and anti-inflammatory signals, resulting in systemic inflammation and AID. Recent data support the impact of histone modifications in the pathogenesis of systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis and other AID [25-28].

Modifications in cytidine phosphate guanosine (CpG) DNA methylation are a key mechanism in controlling transcription while establishing stable heritable epigenetic marks. DNA methylation in and around promoters and regulatory elements can directly inhibit transcription. A growing amount of data indicates the role of DNA methylation in the regulation of cytokine expression [29-31]. In SLE and Sjögren’s syndrome (SjS), global DNA was shown to be methylated to a lower degree, and DNA methyltransferases showed lower activity compared to healthy controls. Especially the genes encoding for the B cell co-stimulator molecule CD70 (TNFSF7), GADD45a (Growth arrest and DNA-damage-inducible protein), and CD11a (lymphocyte function-associated antigen), a protein involved in cellular adhesion and co-stimulatory signaling, were shown to be de-methylated in SLE/ SjS patients [26, 32-34]. In addition, the promoter regions of IL10 and IL13 were shown to be methylated to a lower degree in SLE patients, compared to healthy controls. IL-10 and IL-13 are contributing to B cell activation and antibody production which are central mechanisms in the pathophysiology of SLE [35].

Histone modifications and nucleosome compositions are more diverse and dynamic than DNA methylation. Nucleosomes can be modified by the addition and/or removal of acetyl-, methyl-, phosphate-, and ubiquitin-groups [20]. The diversity of histone modifications defines the “nucleosome code” hypothesis. Several major histone modifications, such as histone 3 lysine 9 (H3K9) and H3K18 acetylation, H3K4 di- or tri-methylation seem to be able to positively regulate gene expression, while different combinations could allow for “fine-tuning” of transcription [20,24]. Histone modifications play a well established role in cytokine expression and T helper cell differentiation [20,36]. T cells from SLE patients express diverse cytokine patterns as compared to T cells from controls. Cytokine patterns of SLE patients exhibit decreased overall acetylation of both H3 and H4. In addition, the degree of H3 hypoacetylation correlated inversely with SLE disease activity. Thus, decreased histone acetylation might contribute to the pathophysiology of SLE by promoting gene silencing. SLE monocytes express increased H4 acetylation of a multitude of genes, as compared to healthy controls. Consistent with IFN-α overexpression in SLE, interferon regulatory factor 1 (IRF1) binding sequences were hyperacetylated in more than two thirds of the genome. At present, the significance of these findings remains to be investigated [26].

Concluding Remarks: “how this might all go together”

Significant progress has been achieved over the recent years, explaining genomic and epigenetic mechanisms in the pathophysiology of AIDs. Still, we just seem to uncover the tip of the iceberg and a multitude of questions remain to be answered.

In monogenic diseases it remains to be elucidated, why identical mutations in target genes (e.g. MEFV, NLRP3) result in different disease outcomes. Possible targets of research may be disease modifying genes (SAA, cytokine genes, etc.) and environmental factors resulting in modified epigenetic marks.

For a growing number of AID, HLA associations and polymorphisms in cytokine genes have been reported. Polymorphisms with putative function within and around cytokine genes may be in linkage disequilibrium or part of extended haplotypes, possibly including additional genes and loci. This highlights the necessity to characterize molecular and genomic requirements for appropriate cell type-specific cytokine expression in health and disease. Epigenetic marks have become an interesting new target for research focusing on the pathophysiology of AID.

We believe that the answers to many of these questions lie somewhere within the intersection of these models and warrant further investigation (Figure 1). Gene mutations, HLA associations, extended...
haplotypes, and epigenetic patterns may have cumulative effects on disease progression and outcome and should therefore be investigated together.

References