Journal of Genetic Syndromes & Gene Therapy

Hedrich. J Genet Syndr Gene Ther 2011, 2:1
DOI: 10.4172/2157-7412.10000e2

Editorial Open Access

Genetic Variation and Epigenetic Patterns in Autoimmunity

Christian M. Hedrich

Children's Hospital Dresden, Pediatric Rheumatology and Immunology Section, University Medical Center "Carl Gustav Carus", Technical University Dresden, Fetscherstr. 74, 01307 Dresden, Germany

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-1ß 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 mediterranian 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-1ß 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-1ß expression by monocytic cells. 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 mutli-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 syndrome (ALPS), characterized by nonmalignant lymphadenopathies associated with autoimmune features in children, are caused by mutations in the genes, encoding Fas/ApoI, 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 erythematosis (SLE), is a heterogeneous disease with multiple pathophysiological factors. Still, some forms have been explained by mutations in single genes. Complement C1q, 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 (oaJIA) 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, DRB11*1301, DRB1*0201 in more severe "extended" oaJIA 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 enthesitis associated JIA, and psoriatic arthritis. Further AID and autoinflammatory syndromes are associated with HLA class I, and class II variants (SLE, Sjogrens 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

***Corresponding author:** Dr. med. Christian Michael Hedrich, Children's Hospital Dresden, Pediatric Rheumatology and Immunology Section, University Medical Center "Carl Gustav Carus", Technical University Dresden, Fetscherstr. 74, 01307 Dresden, Germany, E-mail: christian.hedrich@uniklinikum-dresden.de

Received February 12, 2011; **Accepted** February 15, 2011; **Published** February 19, 2011

Citation: Hedrich CM (2011) Genetic Variation and Epigenetic Patterns in Autoimmunity. J Genet Syndr Gene Ther 2:0e2. doi:10.4172/2157-7412.10000e2

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 Sjogren's syndrome (SJS), global DNA was shown to be methylated to a lower degree, and DNA methyl-tranferases showed lower activity compared to healthy controls. Especially the genes encoding for the B cell co-stimulatory 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].

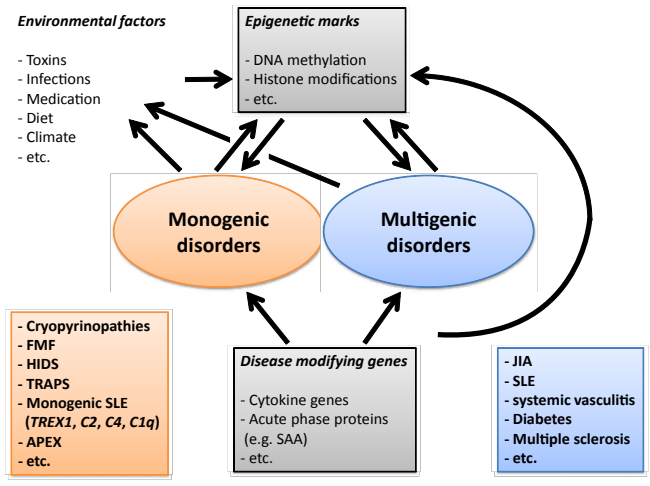

Figure 1: Putative pathophysiological factors in mono- and multigenic autoinflammatory and autoimmune diseases. Monogenic autoinflammatory syndromes and autoimmune diseases (AID) are caused by mutations in single genes. Multigenic disorders are associated with variations in multiple genes, many of which are still unknown. Both groups may be influenced by additional factors which result in varying disease progression and outcomes. Disease modifiers may be variation in further genes (such as cytokine genes, acute phase proteins, etc.) but also environmental factors (such as toxins, medication, infections, etc.) which result in modified epigenetic patterns. Conversely, underlying diseases can also have an influence on epigenetic marks (by changes in diet, medication, new environments, etc.).

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. CD4þ T cells from 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 pathopysiology 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

1. Masters SL, Simon A, Aksentijevich I, Kastner DL (2009) Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease (*). Annu Rev Immunol 27: 621-668.
2. Ryan JG, Kastner DL (2008) Fevers, genes, and innate immunity. Curr Top Microbiol Immunol 321: 169-184.
3. Kastner DL (2005) Hereditary periodic fever syndromes. Hematology Am Soc Hematol Educ Program. 74-81.
4. Rieux-Laucat F, Le Deist F, Fischer A (2003) Autoimmune lymphoproliferative syndromes: genetic defects of apoptosis pathways. Cell Death Differ 10: 124-133.
5. Wildin RS, Ramsdell F, Peake J, Faravelli F, Casanova JL, et al. (2001) X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. Nat Genet 27: 18-20.
6. Meyer O, Hauptmann G, Tappeiner G, Ochs HD, Mascart-Lemone F (1985) Genetic deficiency of C4, C2 or C1q and lupus syndromes. Association with anti-Ro (SS-A) antibodies. Clin Exp Immunol 62: 678-684.
7. Hedrich CM, Fiebig B, Sallmann S, Bruck N, Hahn G, et al. (2008) Good response to IL-1beta blockade by anakinra in a 23-year-old CINCA/NOMID patient without mutations in the CIAS1 gene. Cytokine profiles and functional studies. Scand J Rheumatol 37: 385-389.
8. Lee-Kirsch MA, Chowdhury D, Harvey S, Gong M, Senenko L, et al. (2007) A mutation in TREX1 that impairs susceptibility to granzyme A-mediated cell death underlies familial chilblain lupus. J Mol Med 85: 531-537.
9. Lee-Kirsch MA, Gong M, Chowdhury D, Senenko L, Engel K, et al. (2007) Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 are associated with systemic lupus erythematosus. Nat Genet 39: 1065-1067.
10. Hedrich CM, Fiebig B, Hauck FH, Sallmann S, Hahn G, et al. (2008) Chilblain lupus erythematosus--a review of literature. Clin Rheumatol 27: 949-954.
11. Ramantani G, Kohlhase J, Hertzberg C, Innes AM, Engel K, et al. (2010) Expanding the phenotypic spectrum of lupus erythematosus in Aicardi-Goutières syndrome. Arthritis Rheum 62: 1469-1477.
12. Albert ED, Scholz S (1998) Juvenile arthritis: genetic update. Baillieres Clin Rheumatol 12: 209-218.
13. Frey O, Kamradt T. T-Lymphozyten. In Wagner N, Dannecker GE. Padiatrische Rheumatologie. Springer, 1st edition. September 2007: 11-23.
14. Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, et al. (1998) The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest 102: 1369-1376.
15. Modesto C, Patiño-García A, Sotillo-Piñeiro E, Merino J, García-Consuegra J, et al. (2005) TNF-alpha promoter gene polymorphisms in Spanish children with persistent oligoarticular and systemic-onset juvenile idiopathic arthritis. Scand J Rheumatol 34: 451-454.
16. Rosen P, Thompson S, Glass D (2003) Non-HLA gene polymorphisms in juvenile rheumatoid arthritis. Clin Exp Rheumatol 21: 650-656.
17. Youm JY, Woo JH, Kim TH, Bae SC, Yoo DH (2007) Interleukin-1beta and interleukin-1 receptor antagonist gene polymorphisms in Korean patients with adult-onset Still's disease. Scand J Rheumatol 36: 390-393.
18. Fife MS, Gutierrez A, Ogilvie EM, Stock CJ, Samuel JM, et al. (2006) Novel IL10 gene family associations with systemic juvenile idiopathic arthritis. Arthritis Res Ther 8: R148.
19. Möller JC, Paul D, Ganser G, Range U, Gahr M, et al. (2010) IL10 promoter polymorphisms are associated with systemic onset juvenile idiopathic arthritis (SoJIA). Clin Exp Rheumatol 28: 912-918.
20. Wilson CB, Rowell E, Sekimata M (2009) Epigenetic control of T-helper-cell differentiation. Nat Rev Immunol 9: 91-105.
21. Berger SL (2007) The complex language of chromatin regulation during transcription. Nature 447: 407-412.
22. Kouzarides T (2007) Chromatin modifications and their function. Cell 128: 693-705.
23. Rowell E, Merkenschlager M, Wilson CB (2008) Long-range regulation of cytokine gene expression. Curr Opin Immunol 20: 272-280.
24. Ruthenburg AJ, Li H, Patel DJ, Allis CD (2007) Multivalent engagement of chromatin modifications by linked binding modules. Nat Rev Mol Cell Biol 8: 983-994.
25. Meda F, Folci M, Baccarelli A, Selmi C (2011) The epigenetics of autoimmunity. Cell Mol Immunol
26. Patel DR, Richardson BC (2010) Epigenetic mechanisms in lupus. Curr Opin Rheumatol 22: 478-482.
27. Brooks WH, Le Dantec C, Pers JO, Youinou P, Renaudineau Y (2010) Epigenetics and autoimmunity. J Autoimmun 34: J207-219.
28. Dieker J, Muller S (2010) Epigenetic histone code and autoimmunity. Clin Rev Allergy Immunol 39: 78-84.
29. Chen ZX, Riggs AD (2005) Maintenance and regulation of DNA methylation patterns in mammals. Biochem Cell Biol 83: 438-448.
30. Ooi SK, Bestor TH (2008) The colorful history of active DNA demethylation. Cell 133: 1145-1148.
31. Espada J, Esteller M (2007) Epigenetic control of nuclear architecture. Cell Mol Life Sci 64: 449-457.
32. Zhao M, Wu X, Zhang Q, Luo S, Liang G, et al. (2010) RFX1 regulates CD70 and CD11a expression in lupus T cells by recruiting the histone methyltransferase SUV39H1. Arthritis Res Ther 12: R227.
33. Yin H, Zhao M, Wu X, Gao F, Luo Y, et al. (2010) Hypomethylation and overexpression of CD70 (TNFSF7) in CD4+ T cells of patients with primary Sjögren's syndrome. J Dermatol Sci 59: 198-203.
34. Liu C, Ou T, Wu C, Li R, Lin Y, et al. (2010) Global DNA Methylation, DNMT1, and MBD2 in Patients with Systemic Lupus Erythematosus. Lupus 20: 131-136.
35. Zhao M, Tang J, Gao F, Wu X, Liang Y, et al. (2010) Hypomethylation of IL10 and IL13 promoters in CD4+ T cells of patients with systemic lupus erythematosus. J Biomed Biotechnol 2010: 931018.
36. Schoenborn JR, Dorschner MO, Sekimata M, Santer DM, Shnyreva M, et al. (2007) Comprehensive epigenetic profiling identifies multiple distal regulatory elements directing transcription of the gene encoding interferon-gamma. Nat Immunol 8: 732-742.