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Genetics:

Rare genes for autoimmunity—the new kids on the block

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Abstract

Genome-wide association studies of human diseases have uncovered large numbers of common genetic variants with low effect sizes; however, rare genetic variants with large effect sizes may have greater relevance with respect to disease heritability. The identification and characterization of rare variants such as *SIAE* is, therefore, likely to be a major endeavor in the field in the coming years.

Genome-wide association studies (GWAS) have identified >2,000 common variants associated with various human diseases using technologies that can capture >90% of all common genetic variants.¹ However, these common genetic variants confer relatively small effect sizes, as measured by their estimated odds ratios, and collectively account for only a modest fraction of total disease heritability. This is certainly true with the GWAS-elucidated genes in rheumatic autoimmune diseases.^{2,3} By contrast, rare genetic variants can exhibit considerably larger effect sizes than common genetic variants, and might have a more direct and profound impact on disease pathogenesis. It also seems likely that these rare genetic variants, particularly if highly penetrant, might be more predictive of disease than commonly occurring regulatory variants.

A study by Surolia *et al.*⁵ has identified *SIAE* as the latest addition to the class of autoimmunity genes with rare variants that includes *TREX1* and *IFIH1*. *SIAE*, which encodes sialate O-acetyltransferase⁵ has an autoimmunity-associated odds ratio >8, clearly dwarfing the odds ratios associated with autoimmunity genes previously identified by GWAS.^{2,3} [Sialate O-acetyltransferase deacetylates sialic acid at the 9-OH position and promotes the binding of sialic acids to CD22, a negative regulator of B-cell receptor signaling. CD22 is subsequently phosphorylated by tyrosine-protein kinase Lyn, which is followed by the recruitment and activation of the tyrosine-protein phosphatase non-receptor type 6 (SHP-1). This effect dampens B-cell receptor induced calcium flux, with important consequences for B-cell tolerance.^{6,7} Indeed, mice with mutations in components of this pathway develop lupus-like autoimmunity.^{6–9} Collectively, these studies underline the obligatory role of this molecular pathway in regulating humoral immune responses and preventing humoral autoimmunity.

The role of this sialate-O-acetyltransferase and its associated molecular cascade in autoimmune diseases other than systemic lupus erythematosus is unknown and warrants further study. Indeed, rare loss-of-function *SIAE* variants were predominantly associated with rheumatoid arthritis and type 1 diabetes.⁵ The fact that cell-surface expression of 9-O-acetyl sialic acid

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Competing interests

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is increased on activated B cells from patients with defective *SIAE* variants⁵ suggests that sialate O-acetyltransferase can also act in a B-cell-intrinsic manner in other autoimmune diseases. B-cell depletion therapy is effective in several autoimmune disorders, underscoring the potential pathogenic role of B cells in these diseases. Given that sialate O-acetyltransferase activity has the potential to modulate the threshold for B-cell tolerance and shape the antibody repertoire,⁶ it is conceivable that loss-of-function variants of *SIAE* might have a role in the emergence of specific autoantibody subsets associated with rheumatoid arthritis or type 1 diabetes; however, this hypothesis needs experimental verification. An alternative, but not mutually exclusive, interpretation of the findings of Suolia *et al.*⁵ is that sialate O-acetyltransferase limits autoimmunity through a specific action on non-B-cells. Suolia *et al.*⁵ noted that several patients with an autoimmune disease, but not the healthy controls, were homozygous for a *SIAE* variant that encodes a catalytically-active protein that is unable to be secreted. This observation supports a cell-extrinsic role for sialate O-acetyltransferase in autoimmunity. It will be interesting, therefore, to explore the consequences of *SIAE* mutations on the activation and function of other immune cells.

This work by Suolia *et al.*⁵ has important ramifications on several fronts. It is a clear signal that we should move beyond GWAS, and solely the identification of common genetic variants, towards elucidating the effect that rare genetic variants may have on various autoimmune disorders. Indeed, this effort is likely to dominate the field in the coming years, given the potential of next-generation sequencing.⁴ These findings also affect how we interpret the importance of genes to human disease that are identified in mouse models. Even if a gene fails to emerge as being disease-associated in GWAS of patient populations, the possibility that rare variants of this gene might contribute to human disease must be borne in mind. It is also noteworthy that the track towards identifying common genetic variants using GWAS may also guide us towards the rare disease-causative variants with larger effect sizes. This is perhaps best illustrated by a recent study where resequencing of GWAS-elucidated low-effect size genes for hypertriglyceridemia led to the identification of >150 rare genetic variants with larger effect sizes.¹⁰ As an increasing number of rare genetic variants are deposited in the database of autoimmunity genes (which, at present, are largely populated with GWAS-elucidated genes), the hope is that we will eventually be in a position to account for all of the heritability of autoimmunity.

It is intriguing how some genes, such as *SIAE*, affect multiple autoimmune diseases with respectable effect sizes. Although the cellular and molecular mechanisms that might be altered in each disease setting need to be carefully dissected, these findings suggest that a subset of genes might be operating across multiple autoimmune diseases perhaps by infringing on key checkpoints in immune tolerance to self-antigens. Whether *SIAE* also affects other systemic or end-organ mechanisms leading to autoimmunity remains to be investigated. Our understanding of the molecular basis of autoimmunity is likely to evolve as the rare and common genetic variants underlying autoimmune diseases are discovered and characterized, one by one.

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Biographies

Dr. Anne B. Satterthwaite obtained her PhD from Harvard University in 1993 and pursued postdoctoral studies at UCLA. She is now an Associate Professor in the Departments of Internal Medicine and Immunology at UT Southwestern Medical Center. Dr. Satterthwaite has a long standing interest in defining the signals that regulate B lymphocyte development and activation. Her laboratory is currently engaged in understanding how alterations in these signals result in autoimmunity.

Dr. Chandra Mohan completed his medical studies at the University of Singapore and his doctoral studies in Immunology at Tufts University. He is now a Professor in the Department of Internal Medicine and Immunology at UT Southwestern Medical Center. Dr. Mohan has a long standing interest in the pathogenic mechanisms and genetic origins of systemic lupus erythematosus.

Key points

- Most genes currently associated with autoimmunity have low effect sizes, and account for a modest fraction of disease heritability.
- In contrast, rare genetic variants have large effect sizes, and may be more disease-predictive.
- *SIAE*, *TREX1* and *IFIH1* are 3 examples of rare genetic variants associated with autoimmunity.
- The latest rare autoimmunity gene, *SIAE*, is a member of the CD22/Lyn/SHP1 signaling cascade that thresholds B-cell activation.
- It is likely that the heritability of autoimmunity will be dictated by a few rare autoimmunity genes, bolstered by contributions from several common genetic polymorphisms in other genes.