The Mosaic of Autoimmunity: Genetic Factors Involved in Autoimmune Diseases – 2008

Yehuda Shoenfeld MD[1,2]*, Boris Gilburd PhD[2], Mahmud Abu-Shakra MD[3], Howard Amital MD[4],
Ori Barzilai[2], Yackov Berkun MD[5], Miri Blank PhD[2], Gisele Zandman-Goddard MD[6], Uriel Katz MD, PhD[1],
Ilan Krause MD[7], Pnina Langevitz MD[8], Yair Levy MD[9], Hedi Orbach MD[10], Vitor Pordeus MD[11], Maya Ram[2],
Yaniv Sherer MD[1,2], Elias Toubi MD[12] and Yaron Tomer MD[13]

[1] Department of Medicine B and Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of
   Medicine, Tel Aviv University, Ramat Aviv, Israel

[2] Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel

[3] Rheumatic Diseases Unit, Soroka Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

[4] Department of Medicine D, Meir Medical Center, Kfar Saba, and Sackler Faculty of Medicine, Tel Aviv University, Israel

[5] Department of Pediatrics, Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv
   University, Israel

[6] Department of Medicine C, Wolfson Medical Center, Holon, and Sackler Faculty of Medicine, Tel Aviv University, Israel

[7] Department of Medicine E, Rabin Medical Center (Beilinson Campus), Petah Tikva, and Sackler Faculty of Medicine, Tel Aviv
   University, Israel

[8] Rheumatology Unit, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Israel

[9] Department of Medicine F, Meir Hospital, Sapir Medical Center, Kfar Saba, and Sackler Faculty of Medicine, Tel Aviv University, Israel

[10] Department of Medicine B, Wolfson Medical Center, Holon, Israel

[11] Pro Cardiaco Hospital Research and Training Center-PROCEP, Rio de Janeiro, Brazil

[12] Division of Allergy and Clinical Immunology, Bnai Zion Medical Center and Rappaport Faculty of Medicine, Technion-Israel Institute
   of Technology, Haifa, Israel

[13] Division of Endocrinology, University of Cincinnati College of Medicine, and Cincinnati VA Medical Center, Cincinnati, OH, USA

Thirty years ago we referred to the "Mosaic of Autoimmunity" [1] as the combination of factors associated with the induction of autoimmune diseases. We classified the factors as genetic, immune, hormonal, and environmental. For a specific autoimmune condition to develop, a particular combination of these factors (like the pebbles or small pieces of glass or ceramics that comprise a mosaic) is required. This scheme may explain several phenomena; for example: a) why one patient with systemic lupus erythematosus differs in his/her clinical presentation from another; b) why in the same family the mother may have SLE, her son pemphigus vulgaris, and her daughter juvenile type 1 diabetes mellitus; c) why a patient afflicted with one autoimmune disease is more prone to develop another [2-6]; d) why a "change" in one component of the immune system (splenectomy or thymectomy for example) can ameliorate one autoimmune disease, yet "switch" the patient's condition to another autoimmune disease (known as "the kaleidoscope of autoimmunity") [6-10].

Our knowledge of the mosaic – namely, the factors involved in autoimmunity – has grown extensively over the last three decades. Genetic markers were delineated, involving specific chromosomal aberration and specific genes. Immune factors were revised, adding newly revealed components of the immune system, such as defects in T regulatory cells, the involvement of specific Toll-like receptors (the impact of the innate immunity), and the importance of Th1/Th2 switch in induction of autoimmunity. The hormonal panel, which affects the process leading to autoimmunity, is no longer limited to estrogen and androgens, but also involves prolactin [11] and vitamin D (a hormone and an immunomodulator of the immune system) [12]. The interrelationships between pregnancy (especially the postpartum period) [13] and autoimmune disease induction and exacerbation were more precisely defined. On the other hand, there is a better understanding of autoimmune pregnancy loss, not only in antiphospholipid syndrome but also in other autoimmune diseases [13-17]. Huge progress has been achieved in our understanding of environmental factors, enabling us to both determine the day the disease will erupt and predict the disease that will evolve and even which organs will be affected (i.e., which virus the subject was exposed to, which "infectious burden" he or she is carrying). Certain questions need to be addressed: is it important where one lives (in relation to the equator? sunny area? close to an airport?) [18].

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* Incumbent of the Laura Schwartz-Kipp Chair for Research of Autoimmune Diseases, Tel Aviv University, Israel
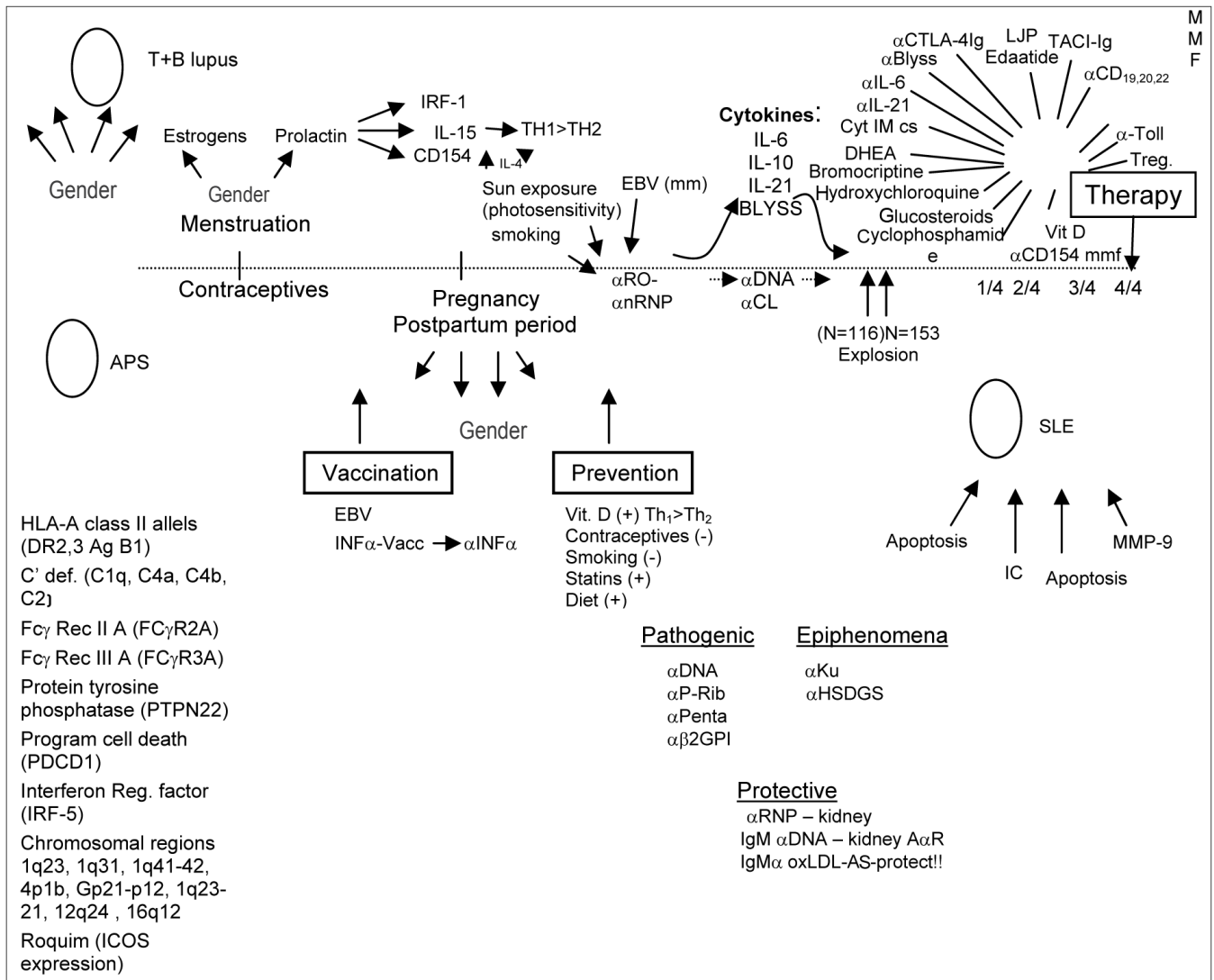SLE = systemic lupus erythematosus

Figure 1. The mosaic of autoimmunity as expressed in SLE

The issue of vaccines (and their diluents, i.e., thimerosal) as inducers of autoimmune disease is still controversial [19-29]. It is conceivable that vaccines may cause autoimmune diseases in susceptible genetically prone subjects. Not only does the vaccine include the infectious agent ingredients ("natural," "weakened," "recombinant"), but its effects are intensified by the "autoimmunologists' trick" – namely, the adjuvant in which the vaccine is incorporated, given to enhance the immune reaction.

In addition, two novel aspects are involved in the conundrum: autoimmune diseases induced by physicians (iatrogenic) employing the new biologics, which are changing "God's order" in the immune system: namely, the suppression of one cytokine may lead to the emergence of another and to a new autoimmune disease [30]. However, the most exciting novel feature is our ability to predict autoimmune disease [17,30] and, consequently, to prevent them [12].

In Figure 1 we depict the diverse mosaic pebbles of one disease – SLE. Since it is a classical and yet so diversified autoimmune condition (SLE is a syndrome rather than a disease), we have omitted several factors in this diagram.

In summary, the "mosaic of autoimmune disease" lists and classifies the different factors involved in the induction of autoimmune conditions and that may induce their exacerbation. With time, more factors will be added, some of which – thanks to our constantly expanding knowledge – will be the result of novel therapeutic interventions. Readers are referred to our previous extensive articles on the various factors involved in the "Mosaic of Autoimmunity" [1-6]. In the present series of papers in this issue of IMAJ we have selected a few topics to expand on – some genetic, some predictive, others pathogenetic, and a few relating to therapy.

Genetics: non-HLA loci, genes and haptotypes

Since in most autoimmune diseases the concordance rate for human leukocyte antigen-identical siblings is significantly lower than the concordance rate for monozygotic (identical) twins, it is clear that other non-HLA genes play a major role in the genetic

HLA = human leukocyte antigen

etiology of autoimmune diseases. Non-HLA genes that have been associated with autoimmunity can be divided into immune regulatory genes and tissue-specific genes.

Non-MHC immune regulatory genes contributing to autoimmunity

The cytotoxic T lymphocyte antigen-4 was the first non-HLA immune regulatory gene to be associated with autoimmunity [reviewed in 32]. CTLA-4 is an important co-stimulatory molecule that plays a key role in the interaction between T cells and antigen-presenting cells in the immunological synapse. Whereas the binding of B7 molecules on antigen-presenting cells to CD28 on T cells co-stimulates T cell activation, CTLA-4 down-regulates T cell activation by competing for the binding of B7 to CD28 and by directly suppressing T cell activation. The suppressive effects of CTLA-4 on T cell activation have raised the possibility that polymorphisms causing reduced CTLA-4 expression and/or function could result in an exaggerated T cell activation and lead to autoimmunity. Indeed, CTLA-4 is associated with many autoimmune conditions, including both B cell-mediated autoimmune diseases (such as Graves' disease) and T cell-mediated autoimmune diseases (e.g., type 1 diabetes). Thus, CTLA-4 is a general autoimmunity gene. However, the relative risk conferred by CTLA-4 is low, demonstrating that other genes must play a role in the development of autoimmunity.

Using a whole-genome linkage study, Tomer and Davies [32] identified a locus on chromosome 20 showing strong linkage with Graves' disease. Further fine mapping identified the CD40 gene as the Graves' disease susceptibility gene in this locus. CD40 is expressed predominantly on B cells and other antigen-presenting cells, and has been shown to play an essential role in the regulation of humoral immunity. Sequencing of the CD40 gene revealed a C/T single nucleotide polymorphism in the 5' untranslated region of the gene that was associated with Graves' disease. Since the 5'UTR region influences the initiation of translation we hypothesized that this CD40 SNP might alter CD40 translation, thereby influencing its expression. Expression studies confirmed this hypothesis. Recently, the same CD40 SNP was found to be associated with high immunoglobulin E levels in asthma.

The protein tyrosine phosphatase gene (PTPN22) is the latest autoimmunity gene to be identified. PTPN22 is associated with rheumatoid arthritis, SLE, type 1 diabetes, and Graves' disease [reviewed in 33]. PTPN22 is an important regulator of T cell receptor signaling in memory and effector T cells, and polymorphisms in the PTPN22 gene might alter T cell receptor signaling and T cell activation.

Tissue-specific genes

More than 20 years ago a polymorphic region near the insulin gene was discovered and shown to confer a risk for type 1 dia-

betes [34]. The disease-associated locus was later fine-mapped, and it is now known that the polymorphism conferring the susceptibility to type 1 diabetes is the presence of a variable number of tandem repeats within a regulatory region affecting insulin gene expression. Therefore, it was postulated that the polymorphism influenced disease disposition through influence on insulin gene expression. More recently, several groups have shown that VNTR alleles, which are protective of type 1 diabetes, are associated with significantly higher insulin mRNA levels in human fetal thymus. Therefore, it is postulated that higher levels of thymic insulin expression in individuals with these alleles promote the negative selection of insulin-specific T lymphocytes, thus facilitating immune tolerance induction and protection from type 1 diabetes. These findings may represent a general principle in autoimmunity and may apply to other autoimmune conditions.

Another important tissue-specific autoimmunity gene is the nucleotide-binding oligomerization domain 2 (NOD2) gene that is associated with Crohn's disease. The C-terminal region of NOD2 contains a leucine-rich repeat that serves as a pattern recognition receptor for many innate signals such as lipopolysaccharide. Interestingly, the three major NOD2 variants that are associated with Crohn's disease are located in the LRR region of the gene, and cause increased activation of nuclear factor-kappa B. Thus, NOD2 SNPs may predispose to Crohn's disease by increasing NF-κB activation.

Two tissue-specific genes have been found in thyroid autoimmunity – the thyroglobulin gene and the thyroid-stimulating hormone receptor gene [reviewed in 33]. Thyroglobulin is the major thyroid protein and we have identified amino acid substitutions within the Tg protein that are strongly associated with thyroid autoimmunity. We postulate that these amino acid variants may alter the degradation of Tg in endosomes, thereby creating more immunogenic Tg peptides that can stimulate the immune response.

Selective IgA deficiency and the mosaic of autoimmunity

IgA is the second most prevalent antibody in serum to IgG and the predominant antibody class in external secretions, playing a key role in immune protection. In humans, there are two subclasses of IgA (IgA1 and IgA2) – each a product of a separate gene. Two different allotypic variants of IgA2 have been described – IgA2m and IgAm [1]. Functionally, IgA1 may interact with two antigen molecules (higher avidity recognition of antigenic structures), while IgA2m [35] has a limited capability in this respect. Many specific receptors to IgA are expressed on different cell types: human FcαRI (CD89) is constitutively expressed on neutrophils, monocytes, eosinophils, some macrophages, and interstitial dendritic cells. The pIgR receptor expressed on epithelial cells is

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MHC = major histocompatibility complex
CTLA-4 = cytotoxic T lymphocyte antigen-4
5'UTR = 5'untranslated
SNP = single nucleotide polymorphism

VNTR = variable number of tandem repeats
LRR = leucine-rich repeat
NF-κB = nuclear factor-kappa B
Tg = thyroglobulin

critical for the transport of polymeric IgA into mucosal secretions. IgA can bind to T cells, B cells and natural killer cells, but the type of receptors involved remains unknown [35]

Selective IgA deficiency is defined as: a) serum IgA levels lower than 5 mg/dl, b) normal levels of all other immunoglobulins, c) normal production of immunoglobulins, and d) normal cellular immunity [35]. SIgAD is the most common primary immunodeficiency in humans. However, there is a difference in frequency between Caucasian and Asian populations (approximately 1 in 700 Caucasians and 1 in 18,500 Japanese being affected). The primary SIgAD may be the result of a defect or blockade at several levels, for example: a) impaired Ig isotype switching, which may be due to the lack of a specific switch recombinase activation-induced cytidine deaminase, polymorphism, or accessibility of the S or I region; b) failure of IgA-bearing B cells to differentiate into plasma cells; and c) a defect at the transcriptional and/or at the post-transcriptional level. Recently, mutations in the tumor necrosis factor receptor family member transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), which mediates isotype switching in B cells, were found to be present in about 5% of patients with SIgAD. Moreover, B cells from individuals with TACI mutations do not produce IgG and IgA in response to the TACI ligand, a proliferation-inducing ligand (APRIL). An additional mechanism involving increased apoptosis of CD20 + IgA + B cells has been described as a basis for primary SIgAD [36]. Secondary IgA deficiency may be caused by drugs such as D-penicillamine, sulfasalazine and gold.

Selective IgA deficiency and autoimmunity

Individuals with SIgAD have numerous autoantibodies [37] that are generally not accompanied by overt disease. However, many autoimmune diseases have been reported to accompany SIgAD, such as SLE (5.2% of children and 2.6% of adults), rheumatoid arthritis (0.3%), juvenile rheumatoid arthritis (2.8%), Still's disease (3.4%), type I diabetes (0.02% adults, 2.2% children), myasthenia gravis (0.7%), celiac disease (2.5%), and Crohn's disease (1.2%). Individual cases of SIgAD associated with many other autoimmune manifestations have been reported [38]. Anti-IgA antibodies can be detected in approximately one-third of patients with complete SIgAD. Although reaction to blood products are uncommon, anti-IgA antibodies increase the risk of severe reactions to blood products [39].

Possible origins of the association between SIgAD and autoimmune diseases

Two theories for these phenomena are known. According to the first, excessive absorption of mucosal antigens leads to an inappropriate response to usually excluded antigens that cross-react with self- and benign antigens. This hypothesis, however, does not explain why only certain patients with IgA deficiency develop an autoimmune disease. The second holds that common genetic factors (HLA-A1, B8, DR3 haplotype) are shared by SIgAD and several other autoimmune diseases. These genetic factors may

SIgAD = selective IgA deficiency

be responsible for an imbalance in the immune system, affecting the regulatory T cells, which can lead to both SIgAD and autoimmunity [35]. In conclusion, autoimmune disorders occur more frequently in individuals with SIgAD than in the general population. The treatment of patients with SIgAD should be directed to the accompanying disease.

In conclusion, IgA has to be determined in every patient with an autoimmune disease and especially in those at risk of developing an autoimmune condition in the future.

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Correspondence: Dr. Y. Shoenfeld, Head, Dept of Medicine B and center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer 52621, Israel.

Phone: (972-3) 530-2652;

Fax: (972-3) 535-2855

email: shoenfel@post.tau.ac.il